Archives Of Volume 3

Breast Cancer

Editor in Chief : A.Kaviani M.D.

2016 Yearbook

KBDI

www.ArchBreastCancer.com

ISSN 2383-0425

Kaviani Breast Diseases Institute

SIT
Sordina Iort Technologies Spa

PSP
339485
Pars Sinuhe Pad P.J.S

LIAC

Linear Accelerator Dedicated for Intra Operative RadioThrapy (IORT)

No.20 , Pakravan St. , Ketabi Sq. , Shariati Ave. , Tehran-Iran
Tel: +98(21)22890996 Fax: +98(21)22897197
Email: info@psptrade.com
www.psptrade.com

Aim and Scope

Archives of Breast Cancer (ABC) is an open access, peer-reviewed journal that publishes articles on all aspects of breast cancer research, including the pathophysiology, prevention, early detection, diagnosis, treatment, molecular and cellular biology, genetics, epidemiology, psychological issues, rehabilitation and quality of life. Although the main focus of the journal is breast cancer, some important topics among benign breast diseases and breast health such as breastfeeding will be considered for publication.

Full Journal Title	*Archives of Breast Cancer*
Frequency	*Quarterly*
Language	*English*
Price	*Open Access*
p-ISSN	*2383-0425*
e-ISSN	*2383-0433*
Public Relations	*Kamelia Davoodzadeh*
Design	*Farahnaz Bayat Nejad*
Publisher	*Kaviani Breast Disease Institute*

Editorial Office:

Kaviani Breast Disease Institute (KBDI), No 3,
Tavaneer Sq., Tehran, 1434888483, Iran
Tel: +98 21 88871785
Fax: +98 21 88871698
Email: office@archbreastcancer.com
Website:
www.archbreastcancer.com

In scientific collaboration with Tehran University of Medical Sciences

Archives of Breast Cancer

Dear colleagues

Archive of Breast Cancer (ABC) is an open access, peer-reviewed journal that publishes articles on all aspects of breast cancer research. Although the main focus of the journal is breast cancer, some important topics among benign breast diseases and breast health such as breast pain, breastfeeding will be considered for publication.

Successful and widespread international distribution of the yearbook 2015 motivated our team to publish the yearbook 2016 including all published articles in this year. In 20116, we did our best to maintain and improve the quality of the published papers into the main focus of the journal. We invited some world-renowned scientific authorities to join the editorial board of the journal and the article processing was even better than the last year, regarding time and quality of feedback. This yearbook contains 30 articles covering multiple aspects of breast cancer from different various academic centers around the world.

In 2017, we are planning join a well-known academic publisher in order to get more visualized and play a more prominent role in dissemination of knowledge regarding breast cancer control throughout the world. We have also planned to publish a special issue on "Medical Ethics and professionalism in Breast Cancer" in which all aspects of this important topic will be explored.

Hereby, I shall invite all the researchers around the world with research lines related to breast cancer to submit their manuscripts to ABC. This would be a special issue; thus, all the submitted manuscripts will be processed fast track.

I hope we can improve the quality of the journal by your contribution to the important field of breast cancer prevention, diagnosis, management and rehabilitation.

Best rergards
Ahmad Kaviani, MD

Announcement for Travel Grant

Archives of Breast Cancer intends to offer an award for young researchers. The investigators who are within their first 5 years from graduation can participate. The selected author (introduced by corresponding author) of the manuscripts that are submitted in the year 2017 will be considered for this exciting award:

• The first rank manuscript will be published in the upcoming issue (with publication time of less than 4 weeks). The selected author will receive an award with the registration fee of an international congress in the year 2017 (up to € 400).

• Two other selected manuscripts will be peer-reviewed with fast-track processing. The first feedback will be sent within 2 weeks and they will be considered for publication in the upcoming issue. The selected authors will be granted with registration fee of an international congress in the year 2017 (up to € 200 each).

For submission of manuscripts, please visit our URL at: http://archbreastcancer.com and in the covering letter, indicate that you are interested to apply for this award.

Contents

EDITORIAL

Breast Cancer Management: Should We Treat Our Patients According to the TNM or the Molecular Classification? 1
R. Salmon

ORIGINAL ARTICLE

Implant Exposure after Immediate Reconstruction for Breast Cancer 3
A. Fitoussi, H. Charitansky, F. Petitperrin, B. Couturaud

Analysis of 6174delT Mutation in BRCA2 Gene by Mutagenically Separated PCR Among Libyan Patients with Breast Cancer 8
L. Elfandi, G. Said, S. Suleiman Saleh, M. Marwan, N. Enattah

Assessment of Dose Delivery to Supraclavicular and Axillary Lymph Nodes in Adjuvant Breast Cancer Radiotherapy, with or without Posterior Axillary Boost in Relation to BMI 14
M. Aghili, P. Seifi, F. Farhan, A.R. Sebzari, E. Mohamadi, V. Vaezzadeh

Can We Create A Reliable and Valid Short Form of Champion Health Belief Model Questionnaire? 19
M. Saadat, R. Ghalehtaki, D. Sadeghian, S. Mohammadtaheri, A. Meysamie

SHORT COMMUNICATION

The Frequency of Breast Cancer Among Women Referred to Hospitals for Biopsy in Birjand, Iran During 2011-2013 24
R. Hoshyar, F. Haghighi, M. Hosseinian, F. Mezginejad, H. Mollaei, N. Fakhr, Z. Beyki

CASE REPORT

Gestational Breast Cancer: Report of A Case and Literature Review 27
F. Paixão-Barradas, D. Pereira, L. Ramalho, I. Marques

Contents

INVITED COMMENTARY

Psycho-oncology: A Common Discipline for All! 32

E. Bo-Gallon

REVIEW ARTICLE

The Effects of Naringenin on Some Human Breast Cancer Cells: A Systematic Review 34

Z. Akbarzadeh, F. Parvaresh, R. Ghiyasvand, M. Miraghajani

ORIGINAL ARTICLE

Measuring Attitude and Practice of Physician toward Breaking Bad News to the Breast Cancer Patients: Development and Validation of a Questionnaire 46

S. Borjalilu, M. Karbakhsh, R. Mirsharifi, K. Davoodzadeh, M. Aghili, A. Kaviani

What Can Computed Tomography Scans of the Thorax Show after Breast Surgery? 52

A. Alikhassi, N. Ahmadinejad, M. Lashkari, H. Akbari

Evaluation of The Value of Core Needle Biopsy in The Diagnosis of a Breast Mass 56

A. S. Fattahi, A. Tavassoli, M. R. Kalantari, S. Noorshafiee, M. Rahmani

SHORT COMMUNICATION

Breast One Stop Clinic – Follow up Experience at Sultan Qaboos University Hospital in the Sultanate of Oman 62

A. Al Jarrah, H. S. Almoqbali, R. Al Shehi, S. Al Aghbari, S. G. A. Rizvi, B. S. Al-Qassabi, R. Lakhtakia

CASE REPORT

Bell's Palsy As a Rare First Presentation of Breast Cancer 66

M. Hosseini, E. Vafaei, A. Asghari, R. Moein Ara, N. Nafissi

Contents

EDITORIAL

The Challenge of Obtaining and Maintaining Expertise 70
D. Krag

INVITED COMMENTARY

Is Endogenous Prolactin, Not Endocrine Prolactin, Responsible for Hyperparathyroidism in Breast Cancer Patients? 74
A. Mohammadnejad, Z. Khorgami

REVIEW ARTICLE

Diagnostic Value of PET/CT in Comparison with Other Conventional Imaging Modalities for the Evaluation of Breast Cancer Recurrence: A Systematic Review of the Literature 77
S. Heydarheydari, A. Haghparast

ORIGINAL ARTICLE

Axillary Reverse Mapping: A Potentially Safe Procedure in Oncology 83
B. Behboudi, M. Neishaboury, F. Elyasinia, M. Najafi, A. Kaviani

Impact of Sitting or Semi-Setting Position of Patients During Breast Surgery on Hemodynamic Indexes 87
K. Karvandian, S. Shabani, J. Zebardast

Relationship between Hardiness and Marital Satisfaction in Women with Breast Cancer 92
F. Nabizadeh, A. Mahdavi

CASE REPORT

Contralateral Axillary Lymph Node Metastasis in Breast Cancer, an Unusual Clinical Scenario: A Case Report and Review of the Literature 139
A.A. Assarian, A. Elahi

Contents

INVITED COMMENTARY

Breast Cancer and Paradigm of Genomic Instability 102
H. Mozdarani

The Effect of Reactive Oxygen Species Threshold on Cancer Cell Fate 106
M. Gardaneh, A. Modirzadeh Tehrani

REVIEW ARTICLE

Electrochemotherapy for Treatment of Cutaneous Breast Cancer Metastases: A Review 108
S. M. Banerjee, M.R.S. Keshtgar

ORIGINAL ARTICLE

Evaluation of Saline Sonohysterography Findings in Patients with Breast Cancer Receiving Tamoxifen Adjuvant Therapy 118
M. Rahmani, L. Farmanbordar, R. Omranipour, M. Malek, S. Zand

Axillary Nodal Examination in Breast Cancer: How Much Is Enough? Evidence for a New Minimum 126
S.G.D Gangadaran

Comparison of the Accuracy of Frozen Section in Morning and Afternoon Working Hours for Axillary Lymph Node Biopsy 130
F. Elyasinis, M.R. Keramati, F. Ahmadi, M. Ashouri, V. Moghadas, F. Elyasinia, M. Yaghoubi, A. Aboutorabi, A. Kaviani

CASE REPORT

Anaplastic Large Cell Lymphoma Associated with Saline Breast Implant 135
G. Ng, R.K. Patel, L. Smith, G. Sclabas

Radioguided Occult Lesion Localisation (ROLL) for Excision of Non-Palpable Breast Lesions, a Personal Experience in a Patient with Multifocal Breast Cancer 139
A. Assarian, S. Zand

Editorial Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.2016311-2

Breast Cancer Management: Should We Treat Our Patients according to the TNM or the Molecular Classification?

Remy Salmon*[a]

[a] *Hôpital des Peupliers, Paris, France*

It is the merit of a French surgeon, Pierre Denoix, the former director of the Gustave Roussy Institute, to have created two major concepts in the breast cancer management: 1) the TNM classification and 2) the multidisciplinary "committees".

The TNM classification described four (in fact five) clinical T classes from T0 (non palpable tumor), T1 (0-2cm), T2 (2-5cm), T3 (over 5cm) and T4 (chest wall or cutaneous invasion). During the years, this initial classification improved separating the main classes in subclasses (T1a or T1b for example) and adding the post-operative classification (pTNM) according to the size in the permanent section of the operative specimen in pathology report.

This classification also included the clinical axillary nodal status N0, 1a, 1b, 2 and 3. The lymph node status in the TNM classification has also been recently upgraded by adding micro-metastatic and IHC characteristics of the lymph node according to post operative assessments. The M status is not any more clinical but is diagnosed on the workup on common metastatic sites. Initially, it was just according to the findings on the radiological analysis of the chest X-ray and the bone scan examination of the ribs, sternum, pelvis, and other common sites. Nowadays, it has become more and more sophisticated by searching the metastatic lesions in other organs, especially visceral organs, and PET scan is becoming a standard approach in some teams.

The immense merit of this classification was first to exist, in order to communicate between surgeons and other physicians about the patients. Moreover, it was useful particularly to schematically separate the operable breast cancer from the metastatic ones and to decide which patients were the best candidates for breast conserving therapy. As all classifications, TNM suffers from its own limitations. As an example, the significance of a small T1 in a large breast is quite different from a T2 lesion in a small breast. Actually, one can discuss the exact significance of a 1.9 cm versus a 2.1 cm lesion which are in different T status, but is there really a great difference between them (T1 or T2)?

Then, if we go back to the beginning of this paper, Pierre Denoix also created the concept of multi-disciplinary committees. In these meetings, next to the surgeons were sitting radiologists, pathologists, and radiation therapists. When he practiced, medical oncologists were not really concerned about breast cancer. Most of them were from hematology discipline and used to consider breast cancer as a minor subject until papers by G. Bonadonna demonstrated the benefits of CMF adjuvant medical treatment on survival in the end of the 70's.[1] We all know the efficacy of medical oncology and the expected improvements in the coming years, since its immense development.

We have to emphasize two points: the discovery of hormonal receptors which led to the creation of Tamoxifen by ICI in England in the 60's, and the analysis of proliferation either by DNA analysis differentiating diploid from aneuploid tumors. Ploidy is associated with the S-phase analysis by flow cytometry as described by Remvikos *et al.* at Curie Institute in 1991 who demonstrated that the most proliferative tumor, the more efficient was the chemotherapy.[2] The proliferation index, whatever technique is used, allows deciding, if a patient is a candidate for an adjuvant hormonal therapy and/or chemotherapy according to its biological profile. Additionally, since 2004, HER2 profile has changed the management of breast cancer in case of the over-expression of the HER2 protein, and Trastuzumab

Address for correspondence:
Remy Salmon, MD
Address: 80, rue de la Colonnie, 75013 Paris, France
Tel: +33 1 44 16 53 54
Fax: +33 1 44 16 56 11
Email: dr.rjsalmon@gmail.com

has completely changed the prognosis of these tumors. All the biological information did not exist when Denoix practiced and the biological classification derived from Sorlie and Perou papers appeared only at the beginning of the 21st century.[3] The biological parameters have led to a molecular classification in which the tumors are separated as Luminal A-B, triple negative, HER2 positive, Claudine-low cancers. That was the initiation of "targeted" therapies, now called "precision" medicine, for the best benefits of our patients.

Let's go back again to the title of the paper and the question of what the best choice is for our patients; TNM or molecular classification.

This is a hard question for surgeons, since they are more familiar with TNM. However, the word "operable breast cancer" does not mean that the surgeon must operate before any other treatments. This is the concept of neoadjuvant treatment.

Due to the biological profile of the tumor, a patient with a small tumor with negative receptors and a high proliferative index could be a good candidate for a primary chemotherapy (neoadjuvant treatment), while a large tumor with a low proliferative index and high hormonal receptors would be a good candidate for a locoregional treatment first and a chemotherapy, if given, will be administered only in the post operative course. The initial purpose of neoadjuvant treatment was to permit a conservative treatment where a mastectomy was initially impossible due to the tumor-breast size ratio, or permit surgery where it was initially technically impossible. In addition, neo-adjuvant treatment represents an *In vivo* test for the efficacy of the medical treatment, and the ultimate benefit is when a complete response is obtained on the surgical specimen. On the other hand, the lack of response or the progression under chemotherapy is the proof of a really aggressive disease and necessitates a protocol modification. Furthermore, the benefits of neoadjuvant treatment versus locoregional benefits have been clearly demonstrated and its impact on the overall survival has been recently demonstrated; the pathologic response has become the "surrogate marker" of the neoadjuvant treatment efficacy.

After the surgery has been performed, adjuvant chemotherapy is mainly administered to prevent distant recurrences and contra-lateral cancers. It can even be given to patients with low proliferative, hormone receptors positive (HR+) cancers according with the size of the tumor and invasion to axillary nodes.

What does that it all mean? How should or can we decide between the two classifications?

Ideally, we should have a good preoperative biopsy specimen before deciding the best treatment choices for a given patient. In a very near future, we will have the whole genome in one week for three hundred Euros! In addition, every classification is always disputable and the exact significance of different parameters can be unclear. For instance, are the prognostic and predictive significance of positive hormonal receptors at the level of 10 identical to 100%? Do positivity of estrogen receptors and negativity of progesterone receptors have the same significance as compared to the time when both hormonal receptors are positive? The cut-off point of Ki67 is another good example. Clearly, a Ki67 at 5% is associated with a good prognosis and at 60% is associated with an aggressive cancer. However, is the cut off between good and bad 14-20% or more than 20%? The recent introduction of tumor-inflitrating lymphocytes (TIL) does not simplify the challenge.

Does that mean that we have to rely on biological parameters which are subject to variations between laboratories and pathologists and should we all send our specimens to highly sophisticated centralized platforms? certainly not!

More recently, commercial molecular signatures have demonstrated their ability to separate low risk from high risk patients. Unfortunately, there is always an intermediate group in which making a medical decision remains difficult.

The only solution for surgeons to survive in this new era is to know the biology and medical treatments similar to the medical oncologists. Ideally, medical oncologists should also know surgical procedures and learn the radiation techniques. Cancer is a continuous disease in which physicians define virtual categories to help them with their medical decisions and to enable them to communicate both with their colleagues and their patients.

From the multidisciplinary teams, will emerge the best treatment options for the patients in which the surgeons should keep their place as long as they know how and when to operate.

Finally, it seems that the old Heraclite sentence "the only thing which does not change is that everything is always changing" remains also true for breast cancer management.

References

1. Bonadonna G, Rossi A, Valagussa P, Banfi A, Veronesi U. The CMF program for operable breast cancer with positive axillary nodes. Updated analysis on the disease-free interval, site of relapse and drug tolerance. Cancer 1977; 39(6 Suppl): 2904-15.
2. Remvikos Y, Vielh P, Padoy E, Benyahia B, Voillemot N, Magdelenat H. Breast cancer proliferation measured on cytological samples: a study by flow cytometry of S-phase fractions and BrdU incorporation. Br J Cancer 1991; 64(3): 501-7.
3. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, *et al*. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001; 98(19): 10869-74.

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.2016313-7

Implant Exposure after Immediate Reconstruction for Breast Cancer

Alfred Fitoussi*[a,b], Helene Charitansky[c], Fabien Petitperrin[b], Benoit Couturaud[b]

[a] Centre Du Sein, Paris, France
[b] Curie Institute, Paris, France
[c] Department of surgery, Centre Claudius Regaud, Toulouse, France

ARTICLE INFO

Received:
21 October 2015
Revised:
10 November 2015
Accepted:
16 January 2016

Keywords:
Immediate breast reconstruction, delayed breast reconstruction, implant removal

ABSTRACT

Background: The technique most frequently employed for breast reconstruction, either immediate (IBR) or delayed (DBR), is the insertion of a prosthesis. The placement of a foreign body always carries the risk, albeit small, of peri-prosthetic infection and exposure of the implant that necessitates its removal, signaling the temporary or permanent failure of the reconstruction.

Methods: We retrospectively analyzed data of 738 consecutive patients immediate implant-only breast reconstructions between 1989 and 2005 in order to evaluate the contributing factors of failure.

Results: Our statistical analysis identified 3 statistically significant risk factors of implant extrusion: irradiation (P = 0.01), post-operative chemotherapy (P = 0.03), and the use of non- Becker expanders (P = 0.02).

Conclusions: It is important, especially for the multidisciplinary breast cancer team members, to be aware of these factors in order to make the optimal decision for immediate reconstruction after mastectomy and the suggested techniques. The patients should also be aware, as part of a shared medical decision, of the risks and their frequency before accepting IBR.

Introduction

Reconstruction, whether immediate or delayed, after mastectomy for breast cancer is most commonly performed using breast prostheses.[1] There are many techniques and improvements, as much on the technical side as with the materials used. However, the risk of infection of the implant and the necessity to remove the implant remains a permanent concern to the surgeons, independent of the psychological impact and medico-legal consequences for the patients.[2,3]

The literature has little on this subject, but confirms that implant-based reconstruction may be occasionally maintained once infection has supervened.[4-7] Further surgical attempts at reconstruction after an infection, in those who agree, tend to require musculocutaneous flaps, which come at the cost of additional donor scars.

We retrospectively analyzed the records of 738 patients between 1989 and 2005 and the different treatments received in order to analyze the possible contributing factors of prosthetic extrusion/removal.

Methods

The records of 738 patients who underwent implant-based immediate breast reconstruction

Address for correspondence:
Alfred Fitoussi, MD
Address: Centre du sein, 18 rue Pierre et Marie Curie, 75005, Paris, France
Tel : +331 44402002
Email : alfred.fitoussi@gmail.com

(IBR) between 1989 and 2005 were analyzed retrospectively. The data collection was consecutive and involved a single institute although the surgeons were of variable experience levels (including trainees and consultants).

Inclusion criteria

All patients who were candidates for mastectomy and immediate breast reconstruction were included in the study. Indications for performing IBR were as follow: 1) primary treatment of breast cancer by mastectomy when adjuvant radiotherapy was not planned post-operatively, according to our institutional protocols. These patients received radio- or chemotherapy, if the final histopathological diagnosis required a change to the original therapeutic plan. 2) Recurrence after breast conserving therapy (BCT), when clinical examination confirmed the indication of implant-based reconstruction without musculocutaneous flaps. All these patients had previously received irradiation as part of their BCT.

Mastectomy was performed with the preservation of the maximal possible skin, whilst being oncologically secure. The reconstruction itself comprised a prosthesis completely covered by muscles; both pectorals and the serratus anterior.[8] In some cases of recurrence following BCT, the quality of the pectoral muscles did not allow complete implant coverage. The use of an abdominal advancement flap is becoming more and more frequent, both to cover the prosthesis and to allow creation of a high quality infra-mammary fold.

Study variables

The study variables included age, menopausal status, clinicopathological variables (surgical indications, histological results, and adjuvant therapy indications, if necessary), surgery-related factors (number of operations on the same breast before reconstruction, scars, skin sparing, type of implant, number of devices change, and complications), and data concerning implant removal (clinical presentation and symptoms, detected microorganisms, biologic abnormality, medical therapy for infection, immediate and later surgical treatments, and possibly the refusal of new reconstruction by the patient).

Statistical analysis

The Kaplan-Meier test was used to analyze the data. The follow-up period was defined from the day of mastectomy and immediate breast reconstruction. The event was considered as the first implant removal due to complications such as fever, threatened or actual extrusion, and suspicion of peri-prosthetic infection. Patients who experienced no events were censored, if the implant was preserved. A desired event was defined as the implant removal only in patients who were operated without using the flap. Curves were compared with univariate analysis by Logrank test. The role of successive prosthesis number on the removal device risk for complication was studied by Cox model.

A Cox model with Forward method was used to study the independent role of each clinical and non-clinical variables, in particular, surgical techniques, on the device removal risk due to complications.

Results

Patient demographics

A total of 738 patients were enrolled in the current study. The median age of the patients was 48 years (range: 21 – 75 years) with a median follow-up of 75 months (69-83). The majority of the patients were pre-menopausal (68.4%) and the body mass index (BMI) was less than or equal to 20 kg/m^2 in 202 (28.6%) participants. A total of 700 (94.8%) patients who underwent reconstruction were newly diagnosed with breast cancer and the rest of the participants (38) had previously undergone BCT and were diagnosed with recurrence. The median hospital stay was 7 days (range: 4 – 37 days).

Histopathological findings

The most common histological type of the tumor was DCIS (69.8%). According to the TNM classification, a total of 501 (71.8%) patients were diagnosed with in situ (T0) tumor, 94 (13.5%) had a tumor less than 2cm in diameter (T1), 57 (8.2%) had T2 tumors, and 11 (6.6%) patients were diagnosed with tumors larger than 5cm (T3). Details could not be found for 35 (4.7%) patients. The nodal status was known in 692 of the 700 patients treated for a newly-diagnosed cancer of whom 646 (93.3%) were classified as N0, 42 (6.1%) as N1a, and 4 (0.6%) as N1b.

Overall, taking into account the patients with recurrent tumors, 489 (66.3%) had some forms of surgical procedure prior to breast reconstruction. A change in the status between the pre-operative biopsy and definitive histopathological result caused a modification (upgrade) in the planned therapeutic strategy in 125 patients. All of the patients received radiotherapy and 85 (68%) of them received chemotherapy.

Reconstructive technique

In 486 (65.8%) mastectomy cases, the surgeons were able to preserve the breast skin and additional plastic surgical techniques were employed in 138 (18.6%). The plastic techniques were the round block (57%) and inverted-T incision pattern (63%). A synchronous symmetrizing procedure was performed on the contra-lateral breast in 512 (69.4%) patients.

Axillary node harvest was performed during the

reconstruction procedure in 660 patients (89.5%) with a mean node number of 10 (range: 0 – 40). Four implant types were used during the study period: saline (n = 289), silicone filled prostheses (n = 244), and Becker (n = 140) and non-Becker expander-prostheses (n = 65).

Adjuvant therapy

Forty-two patients had previously received radiation therapy before IBR (5.7% of the patients), predominantly for recurrence of the initial cancer (n = 38) and for hematological malignancy (lymphoma). Adjuvant radiotherapy to the chest wall and/or nodal fields was given to 125 patients (16.9%). Neoadjuvant chemotherapy was used either during the primary treatment of those with recurrence (n = 34; 4.6%) or in cases with *de novo* cancers (n = 85; 11.5%). Overall, 78% of the patients received no radiotherapy and 85.4% received no chemotherapy before and after surgery.

Implant removal

Implant removal was necessary in 29 cases (3.9%) for either infection or extrusion. It occurred mostly within 2 months of surgery in 17 patients (57%). The implants were removed for the other 12 cases in different times after the operation beyond 8 weeks. The last one was done 121 months after surgery.

Reasons for implant removal included pyrexia (14 patients), abscess (10 patients), and lymphatic collection (5) with some patients experiencing a combination of symptoms.

The implant was exposed in 15 cases, of whom 9 were secondary to cutaneous necrosis and 6 secondary to delayed healing.

All in all, implant removal was required in 29 patients: for skin necrosis or delayed healing (20), in which, 6 had signs of associated infection. In seven patients, the implants were removed due to infection without skin necrosis. Two remaining patients underwent implant removal due to hematomas.

Clinical features of infection included pain, erythema and local heat, pyrexia, and purulent discharge.

Through univariate analysis, three factors (implant type, radiotherapy and chemotherapy) were identified as being associated with implant removal which remained significant in multivariate analysis. The use of a non-Becker expander gave a relative risk (RR) of removal of 3.2 (P = 0.02). Either pre- or postoperative radiotherapy was a statistically significant risk factor for implant removal (P = 0.01) and the risk was greater when irradiation was administered after reconstruction (P = 0.004 in multivariate analysis) with an RR of 3.2. Postoperative chemotherapy also appeared to affect implant removal (P = 0.03) (Table 1). On the other hand, postoperative chemotherapy also appeared to affect implant removal (P = 0.03) (Table 2).

Table 1. Rate of prosthesis removal for complications with respect to irradiation

	Rate (%) at 1 year	Rate (%) at 5 years
No radiotherapy	2.09 (0.91-3.25)	2.59 (1.22-3.93)
Pre-operative radiotherapy	4.76 (0-10.99)	4.76 (0-10.99)
Post-operative radiotherapy	5.83 (1.54-9.93)	7.64 (2.7-12.31)

Table 2. Rate of implant removal for complications with respect to chemotherapy.

	Rate (%) at 1 year	Rate (%) at 5 years
No chemotherapy	2.39 (1.18-3.57)	2.84 (1.48-4.18)
With chemotherapy	5.56 (1.13-9.78)	7.50 (2.36-12.38)

The factors which were not associated with an increased risk of implant removal included age (P = 0.7), a BMI of less than 20 (P = 0.2), the incision pattern (P = 0.6), skin conservation (P = 0.6), synchronous axillary dissection (P = 0.6), prior surgery (P = 0.6) and implant exchange (P = 0.6).

In 276 patients whose implants were removed, another implant was inserted in the same operation. The number of implant changes was not found to be significantly related to implant removal (P > 0.6). The majority, i.e. 463 patients (62.7%), with only one implant and those with multiple implants are summarized in Table 3.

Table 3. Total prosthesis per patient according to the number of the implants at the time of complication

	Number of prosthesis at the time of complication				
Total prostheses per patient	0	1	2	3	Total
1	443	20	0	0	463
2	219	4	3	0	226
3	39	1	0	1	41
4	7	0	0	0	7
5	1	0	0	0	1

Surgical management of patients that underwent implant removal

A total of 29 patients had their prostheses removed for non-aesthetic complications. Preservation of the reconstruction was performed in 7 (24%) cases either through immediate exchange of the prosthesis (n = 3), autologous flap alone (n = 2), or combined implant-flap conversion (n = 2). A total of 22 (76%) patients underwent implant removal, simple lavage and drainage without immediate replacement or flap reconstruction. Of these, 7 underwent further reconstruction as a delayed procedure: implant-based (n = 2), autologous flap alone (n = 4), latissmus dorsi flap (n = 3), and one transverse rectus abdominis myocutaneous flap (TRAM flap) or combined implant-flap conversion (n = 1). Thus, 15 remained ultimately without a reconstruction (15/728 = 2.1%), 7 patients refused to undergo further surgery and in 8 patients the data were not available.

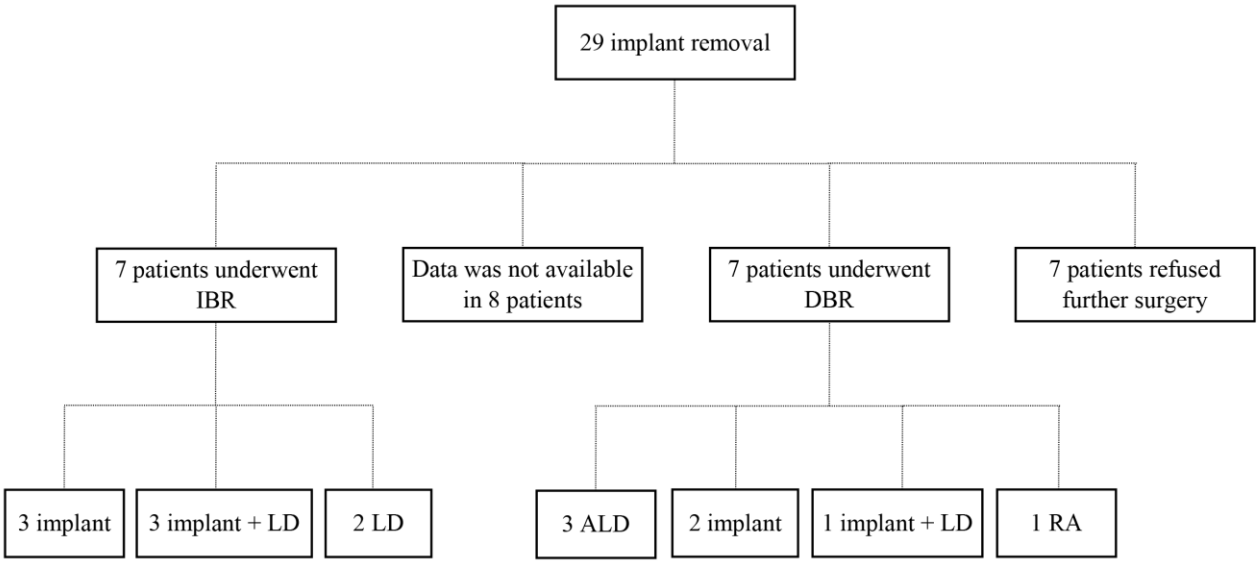


Figure 1. Summary of ultimate outcome of patients who required implant removal (IBR; immediate breast reconstruction, DBR; delayed breast reconstruction, LD; latissimus dorsi flap, ALD; autologous latissimus dorsi flap, RA; rectus abdominis flap)

Discussion

Our institutional protocols recommend an IBR in all circumstances where adjuvant therapy is not expected postoperatively. This is based on two fundamental principles: 1) avoiding a delay in adjuvant therapy as a consequence of either delayed healing or any other surgical complications and 2) the desire to not compromise the aesthetic result of reconstruction through irradiating a prosthesis due to the well-known risk of capsular contracture. Immediate implant-based breast reconstruction comprises approximately 50% of IBR at our institution.

In the current study, definitive histological results differing from preoperative diagnoses caused the unplanned addition of adjuvant therapy in 38.5%: chemotherapy in 15.6% and irradiation in 22.9% of cases after implant reconstruction. Patients must therefore be informed of this potential. In our series, 38 patients with recurrence accepted implant-only IBR, refusing any flap because of the additional donor scar. Clearly, the risk of postoperative complications, including delayed healing, implant extrusion, and ACC must be clearly explained to the patients.

Adjuvant treatment is occasionally required, even if the preoperative diagnosis indicates the contrary. This does not signify that one should not perform implant-based IBR. The patients in whom this type of reconstruction is destined, must, on the contrary, be clearly informed of the risk encountered in such circumstances.[9] It is the same for women previously irradiated who have a local recurrence of their breast cancer and choose implant reconstruction. For the patients who are very likely to receive adjuvant treatments before reconstruction, it is possible to make a choice of not reconstructing with an implant immediately. Delayed reconstruction after completing the radiotherapy protocol seems to minimize the risk of complications.[10,11]

We also analyzed and compared different types of prostheses (pre-filled with saline, silicone, Becker and other expanders) used in our study population. The use of non-Becker expanders was significantly associated with implant removal. Similar results have been reported by other authors previously.[12] One may therefore suggest that these expanders have been used for poor indications of implant-based reconstruction (breast with excessive volume, irradiated tissues) and we have progressively abandoned the use of these expanders.

A link between synchronous axillary clearance and later implant removal has been suggested in the literature.[2] Neither harvest nor the number of nodes appeared to be related to implant removal in our series. Among our study group, obesity defined by the BMI was not associated with a higher risk of implant removal. However, McCarthy *et al.* reported that obesity could increase the risk of both complications and implant failure.[3]

In our series, 29 prostheses were removed either for infection, extrusion, or a combination of the two; 17 of them occurred in the first 3 months after surgery. One may therefore consider that these events have occurred early in the life of a prosthesis. All patients underwent surgical management of their complications. When a simple healing delay was the cause (4 cases), in the absence of the signs of associated infection, the implant pocket was cleaned and a new prosthesis was inserted with a drain. Some recommend dual drainage to allow postoperative saline irrigation.[7] We have no experience in this regard, but were able to preserve the implant reconstruction in the absence of signs of infection (n = 7). Three other patients in whom reconstruction could be preserved had a 'conversion', either by autologous latissimus dorsi alone or in combination with a prosthesis. Such management was considered to be adapted for the cases in whom skin necrosis with signs of infectious was the cause. Any secondary tissue defect necessitated importing 'fresh' tissue. In 7 patients with implant removal, delayed reconstruction was selected, particularly for those with infection. Then, according to the state of the thoracic tissues and wounds/scars, some could have preservation of their reconstruction by the prosthesis alone whereas others required a flap.[5]

In conclusion, this retrospective study of 738 patients undergoing IBR by retro-pectoral prosthesis allowed us to study the risk factors for prosthesis removal either due to infection or extrusion. There were three factors that proved to be statistically significant: 1) postoperative radiotherapy, 2) postoperative chemotherapy, and 3) non-Becker type expanders.

Of the 3.9% of our patients that required removal of an implant, reconstruction was ultimately possible in 75.9%. Salvage was equally distributed between immediate and delayed and musculocutaneous flaps were a precious resource. However, for a quarter of the patients, this episode was sufficient and they had no desire to pursue further reconstruction.

Conflicts of interest

None

References

1. Gurunluoglu R, Gurunluoglu A, Williams SA, Tebockhorst S. Current trends in breast reconstruction: survey of American Society of Plastic Surgeons 2010. Ann Plast Surg 2013; 70(1): 103-10.
2. Nahabedian MY, Tsangaris T, Momen B, Manson PN. Infectious complications following breast reconstruction with expanders and implants. Plast Reconstr Surg 2003; 112(2): 467-76.
3. McCarthy CM, Mehrara BJ, Riedel E, Davidge K, Hinson A, Disa JJ, *et al.* Predicting complications following expander/implant breast reconstruction: an outcomes analysis based on preoperative clinical risk. Plast Reconstr Surg 2008; 121(6): 1886-92.
4. Spear SL, Onyewu C. Staged breast reconstruction with saline-filled implants in the irradiated breast: recent trends and therapeutic implications. Plast Reconstr Surg 2000; 105(3): 930-42.
5. Krueger EA, Wilkins EG, Strawderman M, Cederna P, Goldfarb S, Vicini FA, *et al.* Complications and patient satisfaction following expander/implant breast reconstruction with and without radiotherapy. Int J Radiat Oncol Biol Phys 2001; 49(3): 713-21.
6. Disa JJ, Ad-El DD, Cohen SM, Cordeiro PG, Hidalgo DA. The premature removal of tissue expanders in breast reconstruction. Plast Reconstr Surg 1999; 104(6): 1662-5.
7. Yii NW, Khoo CT. Salvage of infected expander prostheses in breast reconstruction. Plast Reconstr Surg 2003; 111(3): 1087-92.
8. Gruber RP, Kahn RA, Lash H, Maser MR, Apfelberg DB, Laub DR. Breast reconstruction following mastectomy: a comparison of submuscular and subcutaneous techniques. Plast Reconstr Surg 1981; 67(3): 312-7.
9. Mortenson MM, Schneider PD, Khatri VP, Stevenson TR, Whetzel TP, Sommerhaug EJ, *et al.* Immediate breast reconstruction after mastectomy increases wound complications: however, initiation of adjuvant chemotherapy is not delayed. Arch Surg 2004; 139(9): 988-91.
10. Tran NV, Chang DW, Gupta A, Kroll SS, Robb GL. Comparison of immediate and delayed free TRAM flap breast reconstruction in patients receiving postmastectomy radiation therapy. Plast Reconstr Surg 2001; 108(1): 78-82.
11. Rogers NE, Allen RJ. Radiation effects on breast reconstruction with the deep inferior epigastric perforator flap. Plast Reconstr Surg 2002; 109(6): 1919-24; discussion 25-6.
12. Armstrong RW, Berkowitz RL, Bolding F. Infection following breast reconstruction. Ann Plast Surg 1989; 23(4): 284-8.

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.2016318-13

Analysis of 6174delT Mutation in BRCA2 Gene by Mutagenically Separated PCR Among Libyan Patients with Breast Cancer

Lamia Elfandi[a], Ghada Said[b], Saleh Suleiman Saleh[b], Mohamed Marwan[c], Nabil Enattah*[b]

[a] School of Biological Sciences, The Libyan Academy, Tripoli, Libya
[b] Department of Genetic Engineering, Biotechnology Research Center (BTRC), Twisha, Tripoli, Libya
[c] Faculty of Sciences, Tripoli University, Tripoli, Libya

ARTICLE INFO

Received:
1 November 2015
Revised:
23 January 2016
Accepted:
13 February 2016

Keywords:
BRCA2 gene, breast cancer, polymorphisms, 6174delT

ABSTRACT

Background: Breast cancer is the most common malignancy among women. It is estimated that 1 in 10 women worldwide is affected by breast cancer during their lifetime. In 5 to 10% of breast cancer patients, the disease results from a hereditary predisposition, which can be attributable to mutations in either of two tumor suppressor genes, BRCA1 and BRCA2 to a large extent. BRCA2 6174delT mutation constitutes the common mutant alleles which predispose to hereditary breast cancer in the Ashkenazi population with a reported carrier frequency of 1.52% . In this study, we investigated the presence of the 6174delT mutation of the BRCA2 gene in Libyan woman affected with breast cancer and compared the results with those of other population groups.

Methods: Eighty- five Libyan women with breast cancer in additions to 5 relatives of the patients (healthy individuals) were recruited to this study. We obtained clinical information, family history, and peripheral blood for DNA extraction and analyzed the data using multiplex mutagenic polymerase chain reaction (MS-PCR) for detection of 6174delT mutation in the BRCA2 gene .

Results: The 6174delT of the BRCA2 gene was not detected either in the 85 patients with breast cancer (18 with familial breast cancer and 67 with sporadic breast cancer) nor in the 5 healthy individuals.

Conclusions: The present study showed that the 6174delT of the BRCA2 gene was not detectable using mutagenic PCR in the Libyan patients with breast cancer and can be considered to be exceedingly rare.

Introduction

Cancer is a major public health problem throughout the world. It is considered to be the second most common cause of death in developed countries and the fourth most common in developing nations. In Arab countries, within the years 1982–1987, cancer deaths comprised more than 10% of all deaths in Bahrain, Iraq and Kuwait.[1,2] Cancer was responsible of 8.7 percent of all deaths in Benghazi Municipality within the 6-year period 1991–96. This can be compared to 2.0% in 1970–73 and 3.9% in 1980–83. Among women, the proportional cancer mortality ratio per 1000 deaths was 83.3 for females.[3] Cancer registries in North Africa (Morocco, Algeria, Tunisia, Libya, Egypt) increased in number within the past few years from 1 to 9%, and now cover 13 percent of the region population.[3] The incidence rates of breast cancers per 100,000 population in

Address for correspondence:
Nabil Enattah, M.D., PhD.
Address: Department of genetic engineering, Biotechnology Research Center (BTRC), Twisha, Tripoli, Libya.
P.O.Box 30313
Tel: +218 21 5805998
Fax: +218 21 5680035
Email: nabil.enattah@btrc.ly

North African countries ranged between 23.3 in Benghazi, Libya (the year 2004) to 60.5 in Algiers (the year 2006).[3]

Hereditary breast cancer is considered to account for a small proportion of all breast cancer cases.[4] However, a positive family history for breast cancer is a very important risk factor for the development of this malignancy. About 4–5 percent of breast cancer cases are considered to be related to inheritance of a dominant cancer-predisposing gene.[5] In the other 5 to 10% of breast cancer patients, the disease results from a hereditary predisposition, which can be attributable to mutations in either of two tumor suppressor genes, BRCA1 and BRCA2 to a large extent.[6-8] Currently, hundreds of BRCA1 and BRCA2 mutations are known. Most of these mutations are nonsense or frameshift mutations, which can be detected throughout the entire gene sequence and produce truncated proteins. The prevalence of BRCA1 and BRCA2 mutations varies in different populations due to founder effects and other geographical and environmental factors.[9-15] Founder mutations are known to be mutations detected frequently in a particular population due to geographic, cultural, or ethnic isolation. Individuals of Ashkenazi Jewish community have an especially high carrier rate for three mutations, which predispose them to hereditary breast and ovarian cancer syndrome: the 185delAG and the 5382insC in BRCA1 and the 6174delT in BRCA2 with a prevalence of about 2.5 percent in that population.[15-19]

The BRCA2 6174delT mutation constitutes the most common mutation alleles predisposing to hereditary breast cancer in the Ashkenazi population with a carrier frequency of 1.52%.[15] Yet, the calculated contribution of the BRCA2 6174delT mutation to breast cancer diagnosed in Ashkenazi women before the age of 50 is about 8 percent.[16-18]

Few mutations have been described in BRCA1 and BRCA2 in high-risk non-Ashkenazi Jews population. In a family from Libya, the 1100delAT BRCA1 mutation was found and the 8765delAG BRCA2 mutation was previously described in two Jewish Yemenite-families.[20] Moreover, 185de1AG BRCA1 mutation has been detected in Moroccan Jewish women.[21]

The history of the Libyan population reflects a heterogeneous genetic pool of Arabs, Amazighs (Berbers), Romans, Tuaregs, Tebus, Africans, Turks, Greeks, and Jews.[22, 23] Here, we investigated the 6174delT mutation in BRCA2 by mutagenically separated PCR for Libyan women diagnosed with breast cancer and compared the results with those of other population groups.

Methods

Study Samples

The patients enrolled in this study were selected from the patients in Breast Cancer Follow-Up Clinic in Tripoli Central Hospital and African Oncology Institute "Sabratha". Informed consent was obtained from all participants and the study was approved by the Board of the Libyan Academy for Higher Studies, School of Biological Sciences. A total of 90 samples were included in this project, of whom 85 were diagnosed as patients, complaining of breast cancer, while 5 were diagnosed as normal (control group). The study patients were 26-70 years old. Three to five milliliters blood samples were collected in vacutainer tubes with EDTA as the anticoagulant and transported to the Laboratory of Genetic Engineering Department (Biotechnology Research Center) and frozen at -20 °C until needed for DNA extraction and subsequently, PCR analysis.

DNA extraction

A total number of 90 DNA samples were extracted according to Sambrook *et al.*[24] The frozen blood samples were thawed, treated with 1X SSC buffer, Na Acetate, 10% SDS and 5 µl protinase K, and vortexed briefly and incubated for 1 hour at 55 °C. The DNA was isolated using the phenol/chloroform method and precipitated with Ethanol as described by Sambrook *et al.*[24] The DNA quantity and quality were determined according to Sambrook *et al.*[24] using a spectrophotometer and agarose gel electrophoresis. All chemicals used in this study were of the molecular grade.

Multiplex Mutagenically Separated PCR method (MS-PCR)

A simple and rapid method for detection of commonly analyzed mutation (6174delT) in BRCA2 were used as described in a previously published article.[25] In general, three primers designed for the mutation (one common, one specific for the mutant, and one specific for the wild-type allele). The competing mutant and wild-type primers were designed to differ by ~20 bp in size, in order to allow easy detection of the PCR products by routine electrophoresis and ultraviolet illumination after ethidium bromide staining. The sequences of the primers were designed as described elsewhere.[25] The primers sequences, annealing temperatures and the sizes of PCR products are demonstrated in Table 1.

Table 1. Nucleotide sequences of the primer set

Primer	Primer sequence	Size of amplicon
Common reverse (PI)	5'-agctggtctgaatgttcgttact	151 bp
Wild-type forward (P2)	5'-gtgggatttttagcacagctagt	171 bp
Mutant forward (P3)	5'- cagtctcatctgcaaatacttcagggatttttagcacagcatgg	

In general, the genotype of the 6174Tdel was determined using a mutagenically separated PCR method as described.[25] The final volume used for the PCR assay was 25 µl, in which 25ng genomic DNA was amplified with 0.9 µl 20mM of the three primers included in the reaction, 0.125µl 5 Go Taq® Flexi DNA Polymerase, 5µl 5X Green Go Taq® Flexi Buffer (Promega), 4µl 25Mm MgCl Solution and 0.5 µl 10mM dNTP were employed using an Applied Biosystem Thermocycler. PCR amplification comprised of an initial denaturation step at 95 °C for 5 minutes followed by 30 cycles of denaturation at 94 °C for 1 minute, annealing at 59 °C for 30 seconds, extension at 72 °C for 1 minute, and a final extension step at 72 °C for 7 minutes. The PCR products for the mutagenically separated PCR were analyzed by electrophoresis on a 3% agarose gel, stained with ethidium bromide and visualized using a UV transilluminator for the presence of wild or mutant allele.

Results

The mean age of the patients included in this study was 44 ± 9 years (range: 26 – 70 years). Breast cancer was detected in 14% of the patients (12 patients) in the age group 25-34 years and 25% of the patients (21 patients) in the age group 45-54 years old, reach a maximum of 47% (40 patients) in the age group 35- 44 years, and declined to 13% (11 patients) in the age group 55-64 years, and was detected in 1% of the patients (one patient) in the age group 65-74 years (Figure 1). This study showed that 51% of the patients (43 patients) had breast cancer in the right breast and 49% (42 patients) had breast cancer in the left side. The pathology reports revealed that types of breast cancer in our study were ductal carcinoma in-situ (1%, 1 patient), infiltrating lobular carcinoma (24%, 20 patients), and infiltrating ductal carcinoma (75%, 64 patients) (Figure 2). The types of breast cancer were infiltrating ductal carcinoma in 36% (n = 31), infiltrating lobular carcinoma in 12% (n = 10)

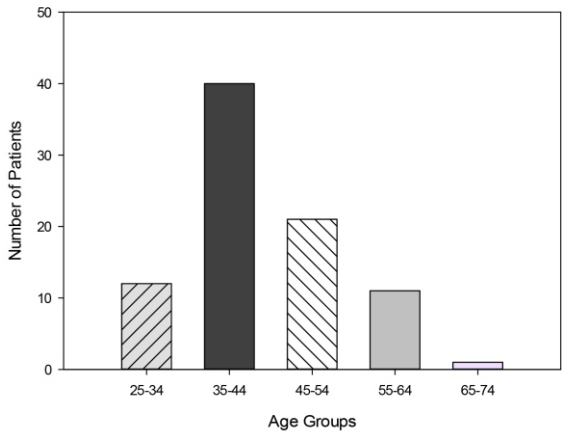


Figure 1. The correlation between age and the incidence of breast cancer among Libyan women

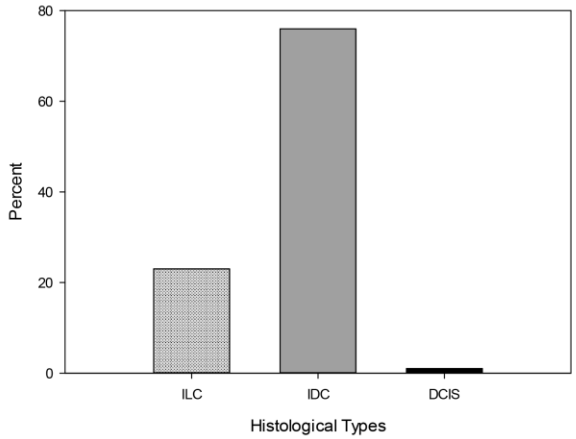


Figure 2. The histological types of breast cancer among Libyan women (ILC; invasive lobular carcinoma, IDC; invasive ductal carcinoma, DCIS; ductal carcinoma in-situ)

and ductal carcinoma in-situ in 1% (n=1) of the patients in the left breast and infiltrating ductal carcinoma in 39% (n=33), and infiltrating lobular carcinoma in 12% (n=10) of the patients in the right breast (Table 2). A family history can always play an important role in developing any medical disease, including breast cancer. In this study, we focused on first and second degree family relationships, including parents, children, siblings, grandparents, and aunts. Regarding positive family history of breast cancer, 21% (18 patients) had a past history of breast cancer in the family. Fourteen percent (12 patients) of the patients had a positive history of breast cancer in the first degree relatives and 7% (6 patients) in the second degree family members (Table 3). Moreover, the data showed that 40% of the patients (n=36) had a family history of cancer and 27% (14 patients) had a family history of other cancers except breast cancer. Nine percent of the patients reported a family history of other cancers except breast cancer (n=8) in first degree relatives and 18% (16 patients) in the second degree relatives (Table 3)

Mutagenically separated PCR (MS-PCR) was done for all DNA from 85 cases for the 6174delT mutation in the BRCA2 gene and 5 controls (All 85 cases were negative for 6174delT) with the

Table 2. The laterality and the histological type of breast cancer

Histological type	N (%)
Left breast	
Infiltrating ductal carcinoma	31 (16%)
Infiltrating lobular carcinoma	10 (12%)
Ductal carcinoma in-situ	1 (1%)
Right breast	
Infiltrating ductal carcinoma	33 (39%)
Infiltrating lobular carcinoma	10 (12%)

Table 3. Family history of breast cancer and other cancers

Family history	Breast cancer	Other cancers
Negative	67 (79%)	66 (73%)
Positive (first degree)	12 (14%)	8 (9%)
Positive (second degree)	6 (7%)	16 (18%)

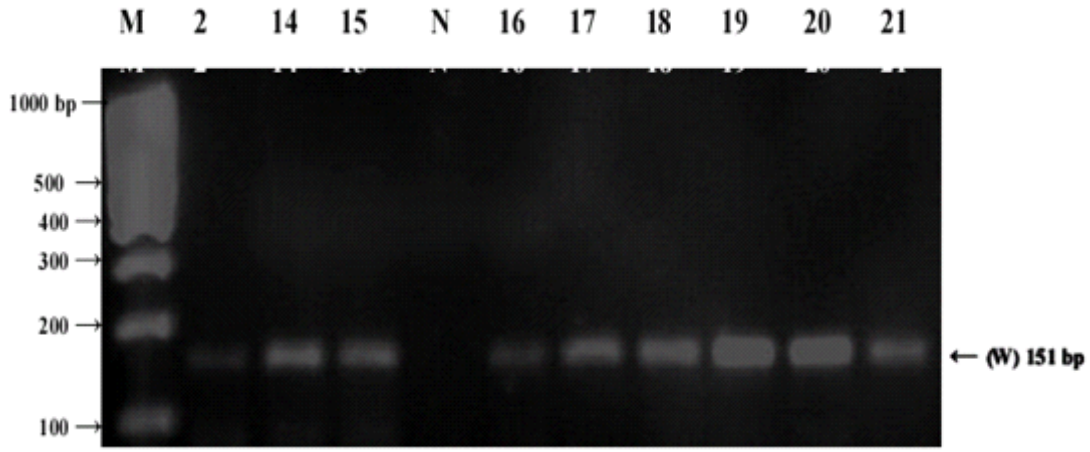


Figure 3. Electrophoretogram of multiplex mutagenic PCR (MS-PCR) products on the 3% agarose gel. Lane M: molecular size of the DNA marker. Lane N: negative control. Lane 2: PCR products of a normal individual. Lanes 14 to 21: PCR products of breast cancer patients. W: Wild – type product.

appearance of one band (151bp) on agarose gel electrophoresis indicating no mutation in any allele in exon11 (Figure 3).

Discussion

The risk of breast cancer in Libya is highest among women younger than 50 years of age, which is 10 years younger than reported in other countries.[3] Almost all women diagnosed with breast cancer had history of breastfeeding to one or more children. The present results indicated that the mean age of our patients was 44 ± 9 years (range: 26-70 years), which is in agreement with the results of previous study that reported that the median age of 46 years (range: 21–76 years) for breast cancer patients in National Cancer Institute in Egypt between 1994 and 1998.[26] Another study from Victorian Cancer Registry reported the mean age of 43.5 ± 8.2 years (range:23-60 years).[27] One study reported that the median age at diagnosis was 52.5 years in Lebanese breast cancer females.[28] The present study revealed that the rate of breast cancer was 14% in the age group 25-34 years and 25% in the age group 45-54 years, reached a maximum of 47% in the age group 35- 44 years, then declined to 13% in the age group 55-64 years, and was 1% in the age group 65-74 years. This finding is in agreement with another study which showed that the frequency of breast cancer was 14% in the age group 26-34 years, 30% in the age group 45-54 years, reached a maximum of 45% in the age group 35- 44 years, and then declined to 11% in the age group 55-60 years.[27] There was an increase in the incidence of breast cancer in young women under 40 years of age in France.[29-31] On the other hand, frequency of breast cancer was 8% in the age group 25-34 years, 27% in the age group 35- 44 years, 35% in the age group 45-54 years, 22% in the age group 55-64 years, and 9% in the age group 65-70 years.[32] The present study showed that 51% of the patients had cancer in the right breast and 49% of them had cancer in the left breast; this finding is compatible with the results of another study.[33]

A large number of distinct mutations in the BRCA1 and BRCA2 genes have been reported through the world, and many methods have been reported for the study of BRCA mutations, including allele-specific oligonucleotide hybridization, allele-specific PCR, PCR-mediated site-directed mutagenesis, heteroduplex analysis (HDA), single-strand conformation polymorphism, and the protein truncation test.[14] Identification of BRCA1 and BRAC 2 mutations carriers is an important focus in prevention and early detection of the breast cancer risk. In this study, we used the Mutagenically Separated PCR method to detect the 6174delT mutation in BRCA2 gene among Libyan patients with breast cancer; this method is considered to be a simple and reliable, and can be considered for routine use, but it needs high-resolution electrophoresis to detect this mutation. We observed in our study that neither the patients (67 cases with sporadic breast cancer and 18 familial breast cancer patients) nor the 5 healthy individuals had the 6174delT mutation in the BRCA2 gene by this simple method which requires high-resolution electrophoresis; however, the 6174delT mutation of the BRCA2 gene was not present in these samples which might be due to the small number of samples or the fact that the samples

were not taken from families carrying the BRCA2 susceptibility gene mutations. In addition, this mutation is present mostly in certain ethnic groups such as Ashkenazi Jews. However, our results are consistent with several studies that did not detect a 6174delT mutation in the BRCA2 gene in other populations, although they used deferent methods for detecting mutations in BRCA genes (data not shown).

In conclusion, the study indicated the absence of the 6174delT mutation of the BRCA2 gene in Libyan breast cancer patients and in controls. A complete BRCA2 gene sequence analysis might be necessary for identification of specific mutations in Libya, a country with an ethnically diverse population.

Acknowledgment

The authors wish to thank the Genetic Engineering Department at Biotechnology Research Center, Tripoli, Libya for supplying genetic analysis facilities.

Conflicts of interest

The authors state that no conflicts of interest exist.

References

1. Singh R, Al-Sudani OE. Cancer mortality in Benghazi, Libyan Arab Jamahiriya, 1991-96. East Mediterr Health J 2001; 7(1-2): 255-73.
2. Bodalal Z, Azzuz R, Bendardaf R. Cancers in Eastern Libya: first results from Benghazi Medical Center. World J Gastroenterol 2014; 20(20): 6293-301.
3. Zanetti R, Tazi MA, Rosso S. New data tells us more about cancer incidence in North Africa. Eur J Cancer 2010; 46(3): 462-6.
4. Keen JC, Davidson NE. The Biology of Breast Carcinoma. . Amer Cancer Soc 2003; 97(3): 825-33.
5. Mavaddat N, Pharoah PD, Blows F, Driver KE, Provenzano E, Thompson D, *et al.* Familial relative risks for breast cancer by pathological subtype: a population-based cohort study. . Breast Cancer Res 2010; 12: R10.
6. Claus EB, Schildkraut JM, Thompson WD, Risch NJ. The genetic attributable risk of breast and ovarian cancer. Cancer 1996; 77(11): 2318-24.
7. Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, *et al.* Linkage of early-onset familial breast cancer to chromosome 17q21. Science 1990; 250(4988): 1684-9.
8. Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, *et al.* Identification of the breast cancer susceptibility gene BRCA2. Nature 1995; 378(6559): 789-92.
9. Loman N, Johannsson O, Kristoffersson U, Olsson H, Borg A. Family history of breast and ovarian cancers and BRCA1 and BRCA2 mutations in a population-based series of early-onset breast cancer. J Natl Cancer Inst 2001; 93(16): 1215-23.
10. Kim BY, Lee DG, Lee KR, Han SH, Surendran S, Han CW, *et al.* Identification of BRCA1 and BRCA2 mutations from Korean breast cancer patients using denaturing HPLC. Biochem Biophys Res Commun 2006; 349(2): 604-10.
11. Bergman A, Flodin A, Engwall Y, Arkblad EL, Berg K, Einbeigi Z, *et al.* A high frequency of germline BRCA1/2 mutations in western Sweden detected with complementary screening techniques. Fam Cancer 2005; 4(2): 89-96.
12. Palomba G, Pisano M, Cossu A, Budroni M, Dedola MF, Farris A, *et al.* Spectrum and prevalence of BRCA1 and BRCA2 germline mutations in Sardinian patients with breast carcinoma through hospital-based screening. Cancer 2005; 104(6): 1172-9.
13. Gorski B, Jakubowska A, Huzarski T, Byrski T, Gronwald J, Grzybowska E, *et al.* A high proportion of founder BRCA1 mutations in Polish breast cancer families. Int J Cancer 2004; 110(5): 683-6.
14. Fattahi MJ, Mojtahedi Z, Karimaghaee N, Talei AR, Banani SJ, Ghaderi A. Analysis of BRCA1 and BRCA2 mutations in southern Iranian Breast cancer patients. Arch Iran Med 2009; 12(6): 584-7.
15. Neuhausen S, Gilewski T, Norton L, Tran T, McGuire P, Swensen J, *et al.* Recurrent BRCA2 6174delT mutations in Ashkenazi Jewish women affected by breast cancer. Nat Genet 1996; 13(1): 126-8.
16. FitzGerald MG, MacDonald DJ, Krainer M, Hoover I, O'Neil E, Unsal H, *et al.* Germ-line BRCA1 mutations in Jewish and non-Jewish women with early-onset breast cancer. N Engl J Med 1996; 334(3): 143-9.
17. Couch FJ, Farid LM, DeShano ML, Tavtigian SV, Calzone K, Campeau L, *et al.* BRCA2 germline mutations in male breast cancer cases and breast cancer families. Nat Genet 1996; 13(1): 123-5.
18. Oddoux C, Struewing JP, Clayton CM, Neuhausen S, Brody LC, Kaback M, *et al.* The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. Nat Genet 1996; 14(2): 188-90.
19. Roa BB, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. Nat Genet 1996; 14(2): 185-7.
20. Gal I, Gershoni Baruch R, Haber D, Dagan E, Eisenberg-Barzilai S, Zidan J, *et al.* The 1100delAT BRCA1 and the 8765delAG BRCA2 mutations: occurrence in high-risk non-Ashkenazi Jews and haplotype comparison of Jewish and non-Jewish carriers. Fam Cancer

2004; 3(1): 11-4.
21. Kreiss Y, Barak F, Baruch RG, Levy-Lahad E, Pras E, Friedman E. The founder mutations in the BRCA1, BRCA2, and ATM genes in Moroccan Jewish women with breast cancer. Genet Test 2000; 4(4): 403-7.
22. Halima AB, Bahri R, Esteban E, Aribia MH, Moral P, Chaabani H. Ethnic composition and genetic differentiation of the Libyan population: insights on Alu polymorphisms. Ann Hum Biol 2014; 41(3): 229-37.a
23. Danubio ME, Martorella D, Rufo F, Vecchi E, Sanna E. Morphometric distances among five ethnic groups and evaluation of the secular trend in historical Libya. J Anthropol Sci 2011; 89: 127-38.
24. Sambrook J, Frisch EF, Maniatis T. Molecular cloning. A laboratory manual. 2nd ed: Cold spring Harbor laboratory; 1989.
25. Chan PC, Wong BY, Ozcelik H, Cole DE. Simple and rapid detection of BRCA1 and BRCA2 mutations by multiplex mutagenically separated PCR. Clin Chem 1999; 45(8 Pt 1): 1285-87.
26. Omar S, Khaled H, Gaafar R, Zekry AR, Eissa S., El-Khatib O. Breast cancer in Egypt: a review of disease presentation and detection strategies La Revue de Santé de la Méditerranée orientale 2003; 9(3): 448-63.
27. Osborne RH, Elsworth GR, Hopper JL. Age-specific norms and determinants of anxiety and depression in 731 women with breast cancer recruited through a population-based cancer registry. Eur J Cancer 2003; 39(6): 755-62.
28. Lakkis NA, Adib SM, Osman MH, Musharafieh UM, Hamadeh GN. Breast cancer in Lebanon: incidence and comparison to regional and Western countries. Cancer Epidemiol 2010; 34(3): 221-5.
29. Molinie F, Vanier A, Woronoff AS, Guizard AV, Delafosse P, Velten M, *et al.* Trends in breast cancer incidence and mortality in France 1990-2008. Breast Cancer Res Treat 2014; 147(1): 167-75.
30. Leclere B, Molinie F, Tretarre B, Stracci F, Daubisse-Marliac L, Colonna M. Trends in incidence of breast cancer among women under 40 in seven European countries: a GRELL cooperative study. Cancer Epidemiol 2013; 37(5): 544-9.
31. Colonna M, Delafosse P, Uhry Z, Poncet F, Arveux P, Molinie F, *et al.* Is breast cancer incidence increasing among young women? An analysis of the trend in France for the period 1983-2002. Breast 2008; 17(3): 289-92.
32. Dey S, Soliman AS, Hablas A, Seifeldein IA, Ismail K, Ramadan M, *et al.* Urban- rural differences in breast cancer incidence in Egypt (1999-2006). The Breast 2010; 19(5): 417-23.
33. Prehn A, Clarke C, Topol B, Glaser S, West D. Increase in breast cancer incidence in middle-aged women during the 1990s. Ann Epidemiol 2002; 12(7): 476-81.

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163114-18

Assessment of Dose Delivery to Supraclavicular and Axillary Lymph Nodes in Adjuvant Breast Cancer Radiotherapy, with or without Posterior Axillary Boost in Relation to BMI

Mahdi Aghili*[a], Parisa Seifi[a], Farshid Farhan[a], Ahmad Reza Sebzari[a], Ehsan Mohamadi[a], Vahid Vaezzadeh[a]

[a] *Department of Radiation Oncology, Radiation Oncology Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Received:
12 December 2015
Revised:
2 February 2016
Accepted:
28 February 2016

Keywords:
Dosimetry,
breast cancer,
posterior boost,
axillary lymph nodes,
supraclavicular lymph nodes

ABSTRACT

Background: The axillary and supraclavicular nodal volume treatment results in improvement of local control and survival after breast conserving surgery (BCS) or modified radical mastectomy (MRM). Studies on the depth of these nodes have questioned the consistent use of standard fields for all patients. This study was done to assess the dose delivery to these lymph nodes with conventional treatment techniques according to body mass index (BMI).

Methods: Twenty six patients with breast cancer undergoing breast surgery were included and computed tomography (CT) simulation was done. Their axillary and supraclavicular nodal volumes were contoured for planning target volume (PTV). Supraclavicular and posterior axillary fields were generated for each patient with digital reconstruction radiography (DRR) technique. Then the dose distribution of the two conventional methods - anterior-posterior field (AP), and anterior field with posterior boost (AP+PA boost) - for total dose of 5000 cGy, was examined with radiotherapy dose plan program. An AP planned field suitable for PTV, was designed and compared to AP+PA boost. The diameter of axilla was measured at the center of AP field in CT scan. Data were analyzed in relationship to BMI.

Results: PTV coverage and excessively irradiating normal tissues (hot points), proved to have significant differences in each method ($p < 0.001$ to 0.01). Axillary and supraclavicular LNs were in 1.6 to 10 and 0.5 to 6.3 cm depth, respectively. Depth of the prescribed dose, which was gained from planned field, had a significant statistical association with BMI ($p < 0.05$).

Conclusions: Current standard fields are not appropriate for all patients, because of poor coverage of PTV. To sum up, 3D CT planning is strongly recommended for patients with high BMI.

Address for correspondence:
Mahdi Aghili MD, AFSA
Address: Radiation Oncology Research Center, Cancer Institute , Imam Khomeini Hospital Complex, Keshavarz Blvd., Tehran, 1419733141, Iran.
POB :13145-158.
Tel: +98 21 66948679
Fax: +98 21 66581633
E-mail: aghili@tums.ac.ir

Introduction

Breast cancer with annually 1.5 million new cases, is the most common cancer among women all over the world.[1] In early stages, tumor will be resected and depending on the stage of the disease and lymph node involvement, adjuvant radiation therapy might be necessary. Adjuvant radiation in patients with lymph node involvement, would increase local control and survival in patients who

have sustained either breast conserving surgery (BCS) or modified radical mastectomy (MRM).[2-4] Since 2012, American Society of Clinical Oncology (ASCO) highly recommends radiotherapy in lymph node positive patients even with less than 3 positive nodes. In a systematic review by Veronesi *et al*. and a recent study by van Wely *et al*. it has been shown that radiation of nodes decreases recurrence rate, even in patients with clear nodes.[5, 6] These data show the importance of adequacy of dose distribution for the lymph nodes in this region. On the other hand, radiation side effects like upper limb lymph edema, brachial plexopathy, radiation-induced pneumonitis, cardiac complications and radiation-induced malignancies necessitate reduction of normal tissues dose delivery.[3,4,7]

Some studies have shown variability in depth of these groups of nodes, which raise doubt regarding application of a unique and standard method for all patients. In fact, level 3 axillary lymph nodes depth varies between 14 to 76 mm. Meanwhile, some have shown a relation between body mass index (BMI) and depth of axillary nodes.[8-10] Thus, inappropriate field or depth of dose prescription for treatment planning, leads to higher or lower dose delivery than optimal leading to inadequate dose in tumoral site or excessive dose delivery in normal tissues that in turn might lead to higher recurrence rate and side effects, respectively.

Most of these problems can be overcome by computed tomography planning. Treatment planning software can calculate and choose appropriate field and assay dose distribution in each part.[7, 8, 11, 12] Today, for almost all patients in advanced radiotherapy centers, application of a treatment planning software and computed tomography rather than a unique clinical delineation is accepted as the standard practice. Recent studies have focused on details of CT planning. An important issue that should be taken into consideration is that, sometimes clinicians do not contour lymph nodes as planning target volume (PTV) and still use the standard clinical fields, without computerized planning. In this state, the overall organs dose intake cannot be accurately assessed. Posterior axillary field is one of the most common fields used in breast cancer adjuvant radiotherapy, in order to improve dose delivery, especially in patients with multiple nodes involvement or extra-capsular extension. This study aims to assess the dose delivery to axillary and supraclavicular lymph nodes with conventional treatment techniques according to body mass index (BMI).

Methods

Patients treated with breast conserving surgery (BCS) or modified radical mastectomy (MRM) and referred for adjuvant radiation to Cancer Institute of Tehran University of Medical Sciences, were included from March to November 2011 and a CT simulation for treatment planning was performed. Patients lied down in supine position on a flat board and a specific breast board was used with ipsilateral hand rise up and head tilt to contralateral site of involvement. CT scanning was carried out from the angle of mandible bone to 5 cm below infra-mammary fold and in 5 mm intervals of slices.

For determination of fields and delineation of nodes, RtDosePlan (Math Resolution, LLC 5975 Gales Lane, Columbia, MD 21045) program was used. An assistant delineated supraclavicular and axillary nodes as a PTV; from cricothyroid notch to lower border of head of clavicle according to radiotherapy oncology group RTOG criteria and two radiation oncologists supervised and corrected it.[13]

A physicist planned the field which was desired by the radiation oncologist as a supraclavicular and axillary field with digital reconstruction radiography (DRR) technique base on skeletal and skin landmarks which was used in our clinic without attention to PTV. Supraclavicular field borders in DRR planning are medial border (lateral border or head of ipsilateral clavicle), lateral border (axillary fold), inferior border (lower border of head of clavicle), superior border (cricothyroid notch), and posterior axillary field in posterior, designed similar to supraclavicular field, with a limitation in medial border as only 2 to 3 cm of lung would be in the field.

Dosimetry

According to planned DRR, with RtDosePlan treatment planning software, for linear accelerator and energy of 6 mv, three methods were applied. The first one was AP method. In this method, an anteroposterior field for 50Gy/25f in the center of supraclavicular field and in depth of 3 cm was used. The second one was AP-Boost method. In this method, an AP field for 50Gy/20f in depth of 1.5 cm (d max) was applied, with a posterior axillary field to compensate dose up to 50Gy/25f in depth of 5.5 cm (point we spot as middle of axilla in conventional fields). In the third method (3D CT planning method) a plan was designed to irradiate breast tissue, skin folds, lung, cricothyroid cartilage, etc according to PTV and ignoring skeletal markers such as the humorous head. In this plan, a field was designed to cover PTV with 1-cm margin, by multi-leaf collimators. The treatment planning program chose the suitable depth of the prescribed dose, automatically, and according to isodoses coverage this point was corrected manually to achieve for PTV coverage by 90% of the prescribed dose. This point is known as the depth of prescribed dose. Dose calculations were done for 50Gy/25f in the depth of prescribed dose. In all plans after drawing the Dose Volume Histogram (DVH), the following dosimetric parameters was defined and measured:

V45: Volume which receives 45 Gy or 90% of the prescribed dose.

V45 body: Volume of body and normal tissue which receive 45 Gy in cc

D100: The isodose which covers all of PTV.

Hot point: The volume (cc) of the body that receives more than 107% of the prescribed dose (the dose that is known as the unfavorable).

Hot point Minimum 2cc: The maximum dose which is more than 107% and covers more than 2 cc of tissue in the body.

Global Max: The maximum dose delivery, regardless of the volume.

Axillary diagonal: The anteroposterior diagonal, measured in the center of axillary field in CT scan.

Supraclavicular nodes depth: The maximum depth of supraclavicular nodes from the skin in the center of AP field in sagittal view measured in CT scan according to PTV.

Axillary nodes depth: The highest depth of axillary nodes from the skin in the center of AP field in axial view of axilla in CT scan, according to PTV.

Results

Twenty six breast cancer patients treated in the Cancer Institute of Tehran University of Medical Sciences were recruited in this study. Eleven patients had left sided and 15 had right sided breast cancer. MRM was performed for 10 patients and 16 were treated by BCS. Lymph node dissection was performed for 21 patients, 3 others underwent SLNB and the remaining 2 patients no surgical assessment for lymph nodes was performed. In patients receiving lymph node dissection, the number of involved lymph nodes ranged from 0 to 27 (N0 to N3).

The average, Min, and Max of axillary diameter, axillary and supraclavicular nodes depth for patients are demonstrated in Table 1.

The min, max and mean of BMI and depth of dosed description is demonstrated in Table 2. These two variables showed a significant association and in regression curve analysis this formula was obtained: Depth of prescribed dose = 0.117 x BMI + 0.551

Table 1. Axillary diameter, axillary (AX) nodes depth and supraclavicular (SC) nodes depth (cm)

	Mean±SD	Minimum	Maximum
Axillary diameter	1.56±14.9	12	18
SC node depth	0.8±4.71	3.2	6.3
Ax node depth	1.2±7.2	5.0	9.7

Table 2. Body mass index (BMI) and depth of dose prescription (DEPTH in cm)

	Mean±SD	Minimum	Maximum
BMI	26.96±3.71	20.76	33.98
DEPTH	4.78±0.88	3.5	6.4

In AP method and AP+Boost method, patients' contribution curve about dose sufficiency was similar. There was a significant difference between the mean volume of PTV that receives 90% of prescribed dose in AP and AP+Boost method, which was 72.2% and 87% and the minimum volume of PTV covered by 90% isodose was 30% and 60%, respectively (figures 1 and 2).

In Table 3, dosimetry findings in three methods were compared.

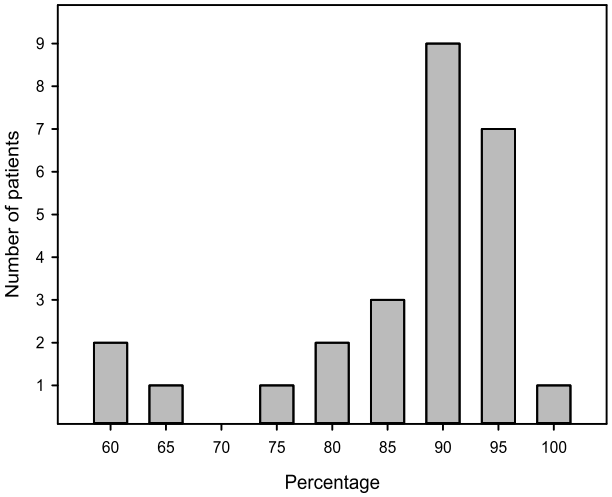


Figure 1. V90 coverage percentage in AP method

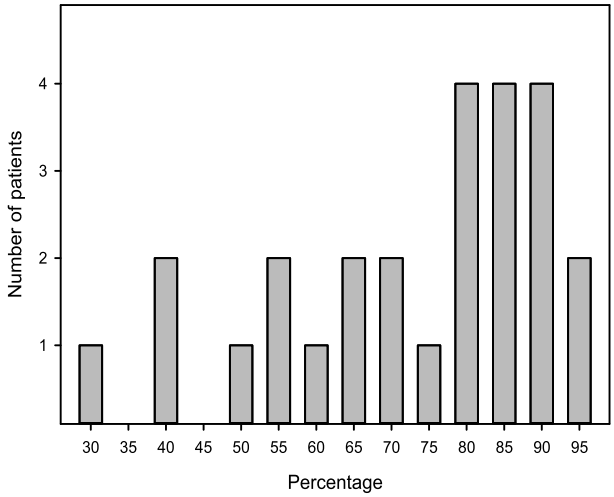


Figure 2. V90 coverage percentage in AP +Boost method

Table 3. Comparison of dosimetry findings in 3 methods

RT technique	Mean±SD	P-value
V45PTV (%)		< 0.001
AP+Boost	87.8±11.26	
AP	72.25±18.35	
PLAN	97.59±3.99	
V45BODY (cc)		< 0.01
AP+Boost	608.3±149.27	
AP	434.5±105.07	
PLAN	613.7±274.77	
D100 (cGy)		< 0.001
AP+Boost	1578.85±1421.74	
AP	1330.58±1190.237	
PLAN	4047.35±810.13	
Hot point > 107% (cc)		< 0.001
AP+Boost	104.08±81.22	
AP	24.12±17.12	
PLAN	181.26±78.48	
Hot point (min 2cc cGy)		< 0.001
AP+Boost	5666.15±133.23	
AP	5462.31±55.41	
PLAN	6027.31±272.45	

Discussion

Radiation is an integral part of nodal treatment in breast cancer. Efficacy of dose delivery and avoiding excessive does are the most important criteria for planning an appropriate field; and in this regard, the position and depth of axillary and supraclavicular nodes are important determinants. The depth of axillary nodes is variable in patients, Kirova *et al*. reported it to be between 19 to 64 mm.[8] Liengsawangwong *et al*. found that level III axillary nodes and supraclavicular nodes depth to be between14 to 67 mm, and it is related with BMI. In that study in patients with higher BMI, the prescribed dose for these nodes were targeted deeper.[10] Bentel *et al*. showed an association between depth of these nodes and the axillary diameter.[14] Goodman evaluated dose and location of posterior axillary nodes and recommended that if we have no 3D planning, axillary nodes should be identified by CT scanning at first.[15] In this study, the depth of supraclavicular nodes ranged from 3.2 to 6.3 cm and axillary nodes in supra clavicular field was from 5 to 9.7 cm.[15] This variation in depth of nodes, leads to variation in dose delivery; however method of treatment influences dose delivery, as well.

Very low amount of D100 in both AP and AP+Boost method shows lack of coverage in these two methods indicating that a part of PTV is out of the treatment field. It could be due to two reasons according to the review of the plans. Head rotation to the contralateral direction might put part of supraclavicular nodes out of treatment field. The other reason could be due to the deep location of level II and III axillary lymph nodes.

According to these findings, it seems that conventional radiotherapy methods are not suitable for satisfactory lymph nodes coverage in treatment of breast cancer. In AP+Boost method, more patients can receive sufficient dose. However in this approach, volume is significantly larger than AP method. After assessment of CT scan of 60 patients with breast cancer, Wang *et al* mentioned that AP+Boost method is an unfavorable method. In comparison, oblique supraclavicular field with Posterior Axillary Boost (PAB) or anterior axillary boost with intensity modulated radiotherapy (IMRT), the latter method had better dose distribution. In that study, the authors found that part of treatment volume that receives 105% of dose has a linear relation with maximum depth of PTV.[16] Jephcatt *et al*. evaluated CT scans of 10 patients with 4 types of fields in 2004 which included AP field alone, AP-PA field, AP field+post axillary boost (PAB), and AP + PAB with tissue compensator.[4] In that study, AP field alone had PTV coverage in only 60% of cases and the overall results were unsatisfactory. AP+Boost method had a good coverage and minimal hot spot; but, posterior neck and lung tissue were exposed to a very excessive dose. In the third method, dose of PTV was sufficient and dose of posterior neck and lung was low. In all methods, hot spot was less than 120%, and hot spot in AP+PAB technique was more than AP alone, too.[4]

According to our findings, regarding use of conventional techniques and the association between depth of prescribed dose and BMI, and considering that the diameter of axilla varies in different patients, use of a unique and fixed field with consistent depth of prescribed dose in all patients is not a suitable technique. This is due to the fact that a part of lymph nodes will not receive the sufficient dose and on the other hand, single AP field (usually 6 mv photon, in the depth of 4cm or less of prescribed dose), creates hot spots with high volume and dose leading to normal tissue injury and acute or chronic side effects. In the 3D planning method, higher depth of the prescribed dose was equivalent to more and larger hotspots. This effect is more distinctive with low energies.

Based on the study findings, 3D planning and if not possible, defining the suitable depth of prescribed dose with CT scan or using the formula is highly recommended. According to the location of axillary lymph nodes which are deep located, especially in patients with high BMI, use of high energy beams for prevention of side effects and delivering sufficient dose to breast regional lymph nodes is recommended. Indications to use posterior axillary boost need more assessment. Since many patients are not planned to undergo any types of surgery for axillary area and radiation therapy is the sole treatment modality for this region, this decision regarding the prescribed dose would be of utmost importance.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65(1): 5-29.
2 Reed DR, Lindsley SK, Mann GN, Austin-Seymour M, Korssjoen T, Anderson BO, *et al*. Axillary lymph node dose with tangential breast irradiation. Int J Radiat Oncol Biol Phys 2005; 61(2): 358-64.
3. Huang CJ, Hou MF, Chuang HY, Lian SL, Huang MY, Chen FM, *et al*. Comparison of clinical outcome of breast cancer patients with T1-2 tumor and one to three positive nodes with or without postmastectomy radiation therapy. Jpn J Clin Oncol 2012; 42(8): 711-20.
4. Jephcott CR, Tyldesley S, Swift CL. Regional radiotherapy to axilla and supraclavicular fossa for adjuvant breast treatment: a comparison of four techniques. Int J Radiat Oncol Biol Phys 2004; 60(1): 103-10.
5. Veronesi U, Galimberti V, Paganelli G, Maisonneuve P, Viale G, Orecchia R, *et al*. Axillary metastases in breast cancer patients with negative sentinel nodes: a follow-up of 3548 cases. Eur J Cancer 2009; 45(8): 1381-8.
6. van Wely BJ, Teerenstra S, Schinagl DA, Aufenacker TJ, de Wilt JH, Strobbe LJ. Systematic review of the effect of external beam radiation therapy to the breast on axillary recurrence after negative sentinel lymph node biopsy. Br J Surg 2011; 98(3): 326-33.
7. Recht A, Edge SB, Solin LJ, Robinson DS, Estabrook A, Fine RE, *et al*. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001; 19(5): 1539-69.
8. Kirova YM, Servois V, Campana F, Dendale R, Bollet MA, Laki F, *et al*. CT-scan based localization of the internal mammary chain and supra clavicular nodes for breast cancer radiation therapy planning. Radiother Oncol 2006; 79(3): 310-5.
9. van Beek S, De Jaeger K, Mijnheer B, van Vliet-Vroegindeweij C. Evaluation of a single-isocenter technique for axillary radiotherapy in breast cancer. Med Dosim 2008; 33(3): 191- 8.
10. Liengsawangwong R, Yu TK, Sun TL, Erasmus JJ, Perkins GH, Tereffe W, *et al*. Treatment optimization using computed tomography-delineated targets should be used for supraclavicular irradiation for breast cancer. Int J Radiat Oncol Biol Phys 2007; 69(3): 711-5.
11. Mansur DB, Kong FM, El Naqa I, Taylor ME, Zoberi I, Bradley JD, *et al*. CT localization of axillary lymph nodes in relation to the humeral head: significance of arm position for radiation therapy planning. Radiother Oncol 2005; 77(2): 191-3.
12. Krasin M, McCall A, King S, Olson M, Emami B. Evaluation of a standard breast tangent technique: a dose-volume analysis of tangential irradiation using three-dimensional tools. Int J Radiat Oncol Biol Phys 2000; 47(2): 327-33.
13. White J, Tai A, Arthur D, Buchholz T, MacDonald S, Marks L, *et al*. Breast cancer atlas for radiation therapy planning: Consensus definitions. https://www.rtog.org/LinkClick.aspx?fileticket=vzJFhPaBipE= (accessed 12 November 2015).
14. Bentel GC, Marks LB, Hardenbergh PH, Prosnitz LR. Variability of the depth of supraclavicular and axillary lymph nodes in patients with breast cancer: is a posterior axillary boost field necessary? Int J Radiat Oncol Biol Phys 2000; 47(3): 755-8.
15. Goodman RL, Grann A, Saracco P, Needham MF. The relationship between radiation fields and regional lymph nodes in carcinoma of the breast. Int J Radiat Oncol Biol Phys 2001; 50(1): 99-105.
16. Wang X, Yu TK, Salehpour M, Zhang SX, Sun TL, Buchholz TA. Breast cancer regional radiation fields for supraclavicular and axillary lymph node treatment: is a posterior axillary boost field technique optimal? Int J Radiat Oncol Biol Phys 2009; 74(1): 86-91.

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163119-23

Can We Create A Reliable and Valid Short Form of Champion Health Belief Model Questionnaire?

Mohammad Saadat[a], Reza Ghalehtaki[b], Dorsay Sadeghian[c], Saead Mohammadtaheri[d], Alipasha Meysamie*[e]

[a] *Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran*
[b] *Department of Radiation Oncology, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran*
[c] *Department of Pathology, Cancer Institute, Tehran University of Medical Science, Tehran, Iran*
[d] *Shahid Beheshti University of Medical Science, Tehran, Iran*
[e] *Department of Community Medicine, Tehran University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Received:
12 January 2016
Revised:
5 February 2016
Accepted:
15 February 2016

Keywords:
Breast cancer, health belief, reliability, validity

ABSTRACT

Background: We aimed to create a shortened form of the Champion Health Belief Model instrument which is a widely used questionnaire about breast cancer screening behaviors with acceptable validity and reliability.

Methods: The Persian version of the Champion Health Belief Model (CHBM) instrument consists of 57 items in 8 concepts. The subjects of the study were 40 female faculty members and 34 nurses of Tehran University of Medical Sciences in 2014. Based on the results, the most influential questions in each concept were chosen and then analyzed for internal consistency and the mean scores of the concepts were compared to the original questionnaire. Next, the original form was delivered to a different population. The mean scores of each concept were compared between original and short forms. At last, the same second population was asked to fill in the shortened form in a two-week interval and a test re-test comparison was done.

Results: In the first step, out of 57 items in the original questionnaire, 28 items were selected based on their influence on the mean score of each concept. In 40 female faculty members who were all above 40, all of the Cronbach's alphas for all subscales were above 0.6 (ranging from 0.624 to 0.830) in the shortened form questionnaire; although they were lower than the original form. There were no significant differences between short and original questionnaires in terms of mean subscale scores. In the second step, in the second population including 34 female nurses aged over forty years in a university medical center, there was again no significant statistical difference between the 28-item and 57-item instruments. In the third step, two weeks later, the completed shortened questionnaire among 20 subjects of the same population of the nurses showed similar results, indicating the reliability of the newly design shortened form of the questionnaire.

Conclusions: The shortened 28-item form of the CHBM instrument seems to be both valid and reliable, and less time-consuming. Its results can be comparable to other studies that used the standard form.

Address for correspondence:
Alipasha Meysamie, MD, MPH
Address: Department of Community Medicine, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 88962357
Email: Meysamie@tums.ac.ir

Introduction

Breast cancer is the most common malignancy among women and is the second fatal cancer only after lung cancer.[1,2] Approximately half of the breast cancer incidence and the attributed mortality occurs in developing countries.[3] In our country, breast cancer takes place about 10 years earlier than

developed countries and comprises 19% of all cancer incidences.[4,5]

Considering effective treatment strategies and the indolent course of the disease, screening is a necessary tool to decrease the incidence of advanced diseases.[1] The most effective screening method with a proven role in improving the overall survival is mammography.[6] There is a wide gap in the rate of regular women who undergo regular mammography between developed and developing nations. For example, while about 66.8% of women in the United States[7] and 76% in England[8] undergo regular mammography, multiple studies show that less than 5% of Iranian women get a regular mammogram.[9-14]

There are many causes for such low rates of regular mammography among women in Iran. Among different tools to evaluate these causes, the Champion Health Belief Model[15] has been used extensively in Iran and other parts of the world.[9-14] This standard questionnaire was introduced in the 60s to evaluate the potential causes of breast cancer screening participation. It has been validated in many languages, such as Spanish[16], Turkish[17]and also Persian.[18] In the majority of these studies, women reported "lack of knowledge" and "not being recommended by their physicians" as the main causes for not undergoing regular mammography. In some studies among female physicians, only 11.8% of the women aged over 40 years had undergone regular mammography.[13]

Considering the low rate of regular screening among Iranian women, in order to change this paradigm, new breast cancer screening policies are needed. To achieve an evidence based policy, there is a need to further study the causes of such low participation in different countries and subpopulations. For this reason, the Champion Health Belief Model, which is widely accepted as a valid and reliable tool and is already available in Persian[18], seems to include too many questions and takes a long time for people to fully answer.

This could be an obstacle for participation in future studies, especially when this questionnaire is combined with many other questions on various issues like demographic characteristics, screening habits, knowledge, etc. In this study, we decided to create a short form of the Champion Health Belief Model with similar validity and reliability that could replace the available standard questionnaire to be readily used in preventive practice and clinical practice..

Methods

Developing the Instrument

In this cross sectional study, the Persian version of the standard Champion Health Belief Model (CHBM) questionnaire (developed by Parvaneh Taymoori[18]) was first distributed among 40 women selected from the female faculty members of Tehran University of Medical Sciences in 2014. These members were randomly selected using the names enlisted in different departments at the university official website (accessed as medicine.tums.ac.ir). The questionnaires were delivered in closed non-transparent envelopes. The Persian version of the CHBM standard questionnaire consists of 8 concepts and 57 items selected out of various versions from 1993 to 1999 based on their appropriateness to Iranian women culture and society.[15] These items include: 1) perceived susceptibility to breast cancer (3 items), 2) perceived seriousness of breast cancer (7 items), 3) perceived benefits of breast self-examination (BSE) (6 items), 4) perceived barriers for BSE (9 items), 5) confidence in ability (10 items), 6) health motivation (7 items), 7) perceived mammography benefits (6 items), and 8) perceived mammography barriers (9 items).

Each item is scored from 1 to 5 based on a Likert scale: "I strongly disagree" (1 point), "I disagree" (2 points), "I am not sure" (3 points), "I agree" (4 points), and "I strongly agree" (5 points). The score of each subscale is treated separately and is not merged into a single overall score of all the subscales. Then, the filled questionnaires were collected and analyzed. Next, apparently repeated and similar questions were removed and the items which had a higher agreement with the total concept score were selected. So, the selected questions were entitled as the short form questionnaire. Then, for the second time, the standard 57-item CHBM questionnaire was distributed among a different population comprising 34 female nurses of the teaching hospitals of the same university. After collecting the completed questionnaires, the scores of the selected items were compared to standard items. After that, in the test/re-test step, the shortened questionnaire was delivered to the same population of the female nurses and the results were compared with the earlier ones.

Statistical Methods

In order to evaluate the reliability of the shortened questionnaire as compared to the concept score of the standard questionnaire, Cronbach's Alpha was used to evaluate the internal consistency. To compare each concept score between original and shortened questionnaires and in order to compare the results of the answers between the two times the questionnaires were completed by the same population, paired samples T test was utilized on the mean score in each concept. SPSS software version 20 was used for all the statistical tests, and alpha was considered 0.05.

Results

Step1. Comparison of concept internal consistency between shortened and original questionnaires

At first, after collecting the standard 57-item CHBM questionnaire from the randomly selected 40 female faculty members of our university, 28 items were selected (about half of the original questionnaire) that had the highest impact on the score of each concept (or subscale) and the items that their removal did not influence the subscale score were removed (Table 1). Then, the internal consistency of the items in each concept was assessed using Cronbach's Alpha. As shown in Table 2, despite a decline in the shortened form, none of the concepts had a Cronbach's Alpha less than 0.6.

Table1. Selected 28 items in 8 concepts out of standard 57 item CHBM instrument

Susceptibility
1 It is likely that I will get breast cancer
2 My chances of getting breast cancer in the next few years are great
Seriousness
1 The thought of breast cancer scares me
2 If someone had breast cancer, her whole life would change
BSE Benefits
1 When I do self-examination, I feel self-satisfied
2 When I complete monthly breast self-examination I don't worry as much about breast cancer
3 Completing BSE each month may decrease my chances of dying of breast cancer
BSE Barriers
1 Doing breast examination will make me worry about what is wrong with my breast
2 BSE takes too much time
3 It is hard to remember to do breast examination
4 BSE is not necessary if you have a routine mammogram
Confidence in BSE efficacy
1 I could find a breast lump by performing BSE
2 I am able to tell something is wrong with my breast when I look in the mirror
3 I can perform BSE correctly
Health Motivation
1 I exercise at least 3 times a week
2 I eat well-balanced meals
3 I have regular checkup even when I am not sick
4 Maintaining good health is extremely important to me
Mammography Benefits
1 If I find a lump through a mammogram, my treatment for breast cancer may not be as bad
2 Having a mammogram is the best way for me to find a very small lump
3 Having mammogram will decrease my chances of dying from breast cancer
4 When I get a recommended mammogram, I feel self-satisfied
Mammography Barriers
1 I have other problems more important than getting a mammogram
2 Having a mammogram is too painful
3 I don't know how to go about getting a mammogram
4 I am too old to need a routine mammogram
5 Having a mammogram is too embarrassing
6 Having a mammogram takes too much time

Table 2. Internal consistency and result of comparing the mean score of each concept item in original and shortened form of CHBM instrument

Fields of Questions	Original Form of Questionnaire				Short Form of Questionnaire				Paired Differences		
	Num of Questions	α	Mean	SD	Num of Questions	α	Mean	SD	Mean	SD	P-Value
Total Questions	57	0.83	-	-	28	0.74	-	-	-	-	-
Susceptibility	3	0.86	1.93	0.86	2	0.79	1.94	0.93	0.00	0.20	0.90
Severity	7	0.82	2.83	0.82	2	0.68	2.73	1.15	0.10	0.48	0.20
BSE Benefits	6	0.80	3.68	0.58	3	0.80	3.70	0.70	-0.03	0.21	0.45
BSE Barriers	9	0.81	2.49	0.58	4	0.63	2.47	0.67	0.03	0.29	0.58
BSE Self Efficacy	10	0.93	2.73	0.90	3	0.83	2.70	1.06	0.03	0.37	0.61
Health Status	7	0.83	4.00	0.76	4	0.75	4.03	0.85	-0.03	0.23	0.43
Mammography Benefits	6	0.80	3.95	0.55	4	0.73	3.92	0.59	0.03	0.17	0.26
Mammography Barriers	9	0.77	2.42	0.63	6	0.62	2.44	0.64	-0.03	0.18	0.38

Step 2. Comparison of the concept scores between original and shortened CHBM instruments

In order to compare the mean acquired score of each concept (subscale), paired samples T test was used. As it is shown in Table 2, no statistical difference were found in the mean score of each concept between original and shortened questionnaires and all of P-values were more than 0.05.

Step3. Comparison of the mean score of each concept between shortened and original questionnaires in a different population

As selection of the desired items for our shortened form was performed based on the results of the standard 57-item CHBM questionnaire, further evaluation of the validity of the new questionnaire had to be performed. Thus, the original questionnaires were distributed among a different population (34 female nurses) and again, the mean scores in each concept were compared between the shortened and standard instruments. There was no significant difference in the mean score of the concepts between the original and the shortened questionnaire.

Step4. Testing the reliability of the shortened form

In order to test the reliability of the new shortened 27-item instrument, we again distributed only the shortened form of the questionnaire among 20 subjects of the same population of nurses (step 3). Next, we compared the mean score of each concept between questionnaires completed two weeks apart. Our study did not show significant difference in any of the concept mean scores, indicating the reliability of our designed shortened instrument.

Table 3. Results of the paired samples T test for comparison of mean concept score between shortened and original forms of the CHBM instrument in nurses population

Concept	Mean	SD	P-Value
Susceptibility	0.00	0.12	0.81
Severity	-0.01	0.38	0.87
BSE Benefits	0.03	0.23	0.47
BSE Barriers	-0.05	0.24	0.22
BSE Self Efficacy	-0.05	0.28	0.26
Health Status	0.02	0.32	0.66
Mammography Benefits	0.03	0.21	0.41
Mammography Barriers	0.02	0.21	0.62

Table 4. Results of the paired samples T test for comparison of concept mean scores of the shortened forms filled out two weeks apart

Concept	Mean	SD	P-Value
Susceptibility	0.10	0.48	0.36
Severity	0.08	0.47	0.48
BSE Benefits	0.02	0.43	0.86
BSE Barriers	0.05	0.61	0.72
BSE Self Efficacy	0.05	0.69	0.75
Health Status	-0.08	0.60	0.58
Mammography Benefits	-0.15	0.52	0.21
Mammography Barriers	-0.06	0.32	0.42

Discussion

Breast cancer survival rates vary widely in different parts of the worlds and this variation is in agreement with rates of screening by routine mammography.[3] Previous studies among different populations in Iran, although not nationally representative, have indicated very low levels of women's participation in screening mammography, even in educated individuals.[13] Among different studied instruments, the Champion Health Belief Model instrument seems to be widely accepted throughout the world based on which a number of studies in Iran have been carried out investigating the causes of such a low participation rate. Some authorities recommend to establish appropriate policies to encourage women to pay more attention to breast cancer early detection by means of screening mammography. In this regard, extensive investigation of the cause(s) of low participation in all parts of the country using a short and less time-consuming instrument is needed. The standard Persian version of the CHBM instrument with 57 items in 8 concepts seems too long and time-consuming and could have a negative impact on the participation of the individuals when investigating the causes, especially when it is combined with many other questions on various issues like demographic characteristics, screening habits, knowledge, etc. So we decided to develop a shortened form of the standard CHBM instrument with comparable results to the original form.

Our study showed that our 28-item questionnaire had acceptable internal consistency within each covered concept (all Cronbach's alphas were >0.6) despite being lower than its original counterpart. In the next step, we found no significant difference between the shortened and original forms of the instrument in terms of concept scores (Table 2). In the third step, we found a good agreement between the results of the shortened form and the original form in a different population which indicated the validity of our brief instrument. Finally, in the fourth step, in order to show the reliability of the shortened newly-designed 28-item questionnaire, we found

no statistically significant difference in the mean score of each subscale (concept) in the same population, when they were asked to complete the short form with an interval of 2 weeks.

A good agreement was found between the shortened and original CHBM instrument; thus, the results of the causes of not undergoing routine mammography screening using the short form are comparable to other studies using the standard CHBM questionnaire. Based on the results of this study, it could be concluded that the shortened 28-item questionnaire which is less time-consuming is a valid and reliable instrument to investigate the underlying cause(s) of the low participation of Iranian women in large population-based studies.

References

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011. CA Cancer J Clin 2011; 61(4): 212-36.
2. Parkin DM, Fernández LM. Use of statistics to assess the global burden of breast cancer. Breast J 2006; 12(s1): S70-S80.
3. WHO Breast Cancer Detection. http://www.who.int/cancer/detection/breastcancer/en/index1.html (accessed 10 November 2015).
4. Harirchi I, Karbakhsh M, Kashefi A, Momtahen AJ. Breast cancer in Iran: results of a multi-center study. Asian Pac J Cancer Prev 2004; 5(1): 24-7.
5. Jazayeri SB, Saadat S, Ramezani R, Kaviani A. Incidence of primary breast cancer in Iran: Ten-year national cancer registry data report. Cancer Epidemiol 2015; 39(4): 519-27.
6. CDC Breast Screening Information. http://www.cdc.gov/cancer/breast/basic_info/screening.htm (accessed 12 November 2015).
7. Health, United States, 2014. http://www.cdc.gov/nchs/hus/contents2014.htm#076 (accessed 12 November 2015).
8. UK Breast cancer statistics. http://www.cancerresearch.uk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/screening (accessed 12 November 2015).
9. Farshbaf K, Shahnazi M, Ghahvehchi A, Torabi S. Performance conditions of breast cancer screening methods and its efficient factors among women referring to health centers of Tabriz. Iran J Nurs Res 2009; 4: 27-38.
10. SalimiPormehr S, Kariman N, Sheykhan Z, AlaviMajd H. Investigation of breast cancer screening tests performance and affecting factors in women referred to Ardebil's health and medical centers, 2009. J Ardabil Univ Med Sci 2010; 10(4): 310-8.
11. Abedian K, Shah Hosseini Z, Adeli M. Survey of health beliefs of women about performing mammography in the health service centers of Sari. J Mazandaran Univ Med Sci 2006; 16(54): 90-8.
12. Charkazi A, Samimi A, Razzaghi K, Kouchaki G, Moodi M, Meirkarimi K, et al. Adherence to recommended breast cancer screening in Iranian Turkmen women: the role of knowledge and beliefs. ISRN Prev Med 2013; 2013: 581027.
13. Alavi G, Hoseininejad J, Masoom A, Shakeri M. Evaluation of prevalence of cervical and breast cancer screening programs between gynecologists. Iran J Obstet Gynecol Infertil 2010; 13(1): 1-6.
14. Aflakseir A, Abbasi P. Health Beliefs as Predictors of Breast Cancer Screening Behaviour in a Group of Female Employees in Shiraz. Iran J Cancer Prev 2012; 5(3): 124-9.
15. Champion VL. Instrument development for health belief model constructs. ANS Adv Nurs Sci 1984; 6(3): 73-85.
16. Medina-Shepherd R, Kleier JA. Spanish translation and adaptation of Victoria Champion's health belief model scales for breast cancer screening-mammography. Cancer Nurs 2010; 33(2): 93-101.
17. Yilmaz M, Sayin YY. Turkish translation and adaptation of Champion's Health Belief Model Scales for breast cancer mammography screening. J Clin Nurs 2014; 23(13-14): 1978-89.
18. Taymoori P, Berry T. The validity and reliability of Champion's Health Belief Model Scale for breast cancer screening behaviors among Iranian women. Cancer Nurs 2009; 32(6): 465-72.

Short Communication Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163124-26

The Frequency of Breast Cancer Among Women Referred to Hospitals for Biopsy in Birjand, Iran During 2011-2013

Reyhane Hoshyar*[a], Fatemeh Haghighi[b], Mahdiyeh Hosseinian[c], Fatemeh Mezginejad[c], Homa Mollaei[d] , Negar Fakhr[c], Zahra Beyki[c]

[a] [b] Department of Clinical Biochemistry, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[c] Department of Pathology, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[d] Department of Medical Lab Technology, Faculty of Paramedical, Birjand University of Medical Sciences, Birjand, Iran
Department of Genetics, Faculty of Natural Sciences, University of Tabriz, Tabriz, Iran

ARTICLE INFO

Received:
14 December 2015
Revised:
20 December 2015
Accepted:
26 February 2016

Keywords:
Breast Cancer,
pathology,
biopsy,
Birjand

ABSTRACT

Background: This study aims to demonstrate the frequency of malignant breast cancer (BC) according to pathologic findings in Birjand during 2011-2013 years.

Methods: For this cross-sectional study, the sample consisted of pathologic records from 229 breast biopsies of two hospitals in Birjand.

Results: Most of the biopsies in women were malignant cases which nearly 90% of them were detected after lymph node involvement. The mean age of women with malignant BC was 48.8 years.

Conclusions: A notable proportion of our cases were diagnosed in metastatic stages as advanced BC. It further highlights the importance of screening and diagnosis at earlier stages.

Introduction

Several studies in Iran have shown that breast cancer (BC) is the most common cancer among Iranian women.[1, 2] Most of breast lesions are of the benign nature with two types of progressive and non-progressive. Non-progressive types do not lead to BC ;but, progressive types increase the relative risk of BC.[2] In addition, benign BC can be divided into three groups including lesions without hyperplasia such as simple fibrocysts, hyperplasia without atypia and hyperplasia with atypia such as ductal and lobular tumors which the latter increases the chance of BC.[3] Early detection of benign or malignant lesions helps to use more effective therapies for the patients.

As many patients with early BC have no symptoms; effective prevention and early detection is one of the priorities of health practitioner. Thus, a key strategy for successful therapy of BC will be early recognition of patients in population. This study compares the distribution of benign vs. malignant cases of BC patients in relation to age and pathological characteristics.

Methods

In this cross-sectional study, data were obtained from patients who were referred by departments of pathology of Emam Reza and Shahid Rahimi hospitals for biopsy, as a diagnostic test, located in Birjand during 2011 to 2013. According to the pathologic findings in these hospitals, about 229 women were inculded to examine the frequency of malignant BC. The data (age and pathologic results of breast biopsies) were retrieved and analyzed by

Address for correspondence:
Reyhane Hoshyar, M.Sc., Ph.D.,
Address: Birjand University of Medical Sciences, Birjand, 9717853577, Iran.
Tel: 098 561 8825420
Fax: 098 56 32433004
E-mail: hooshyar@bums.ac.ir

SPSS statistical software (version 18, SPSS Inc., Chicago, IL, USA). The descriptive statistics (mean and standard deviation) was used to assess the frequency of BC.

Results

During three years, 229 breast biopsies were performed in pathology departments of the study hospitals. Considering age groups, the highest (39.8%) and lowest (1.3%) frequencies of malignancies were observed in the 40-50 and less than 20 years age groups, respectively (Table 1).

Table 1. Distribution of malignant BC cases according to age (N = 146)

Age (Years)	N (%)
<20	2 (1.3%)
20-30	13 (9.0%)
30-40	25 (17.2%)
40-50	58 (39.8%)
50-60	34 (23.2%)
60-70	11 (7.5%)
<70	3 (2.0%)

In fact, 63.9 % of biopsies resulted in diagnosis of malignancy and 12.2%, 17.4% and 6.5% were normal, cyst fibrosis and fat, respectively (Table 2).

Table 2. Pattern of biopsy results (N = 229)

Pathologic results	N (%)
Normal	28 (12.2%)
Fat	15 (6.5%)
Cyst fibrosis	40 (17.4%)
Malignant	146 (63.9%)

In addition, 59% of malignant samples contained some features of hyperplasia. Overall, 4% and 6% of malignant cases had tumours in stage 0 or in-situ and I carcinomas, respectively. In fact, 90% of them were detected after lymph node involvement as metastatic cases (II, III and IV stages).

Discussion

BC is one of the most important women's health problems which its incidence is rising every year in Iran.[1] There are various risk factors for BC, including low age of menarche, late age at first pregnancy, fewer pregnancies, lack of breastfeeding, late menopause, obesity, and hormone replacement therapy. Female breast cancer incidence is strongly related to age.[4, 5] In this study we reported the age distribution of women who were diagnosed with BC in Birjand within three years. According to the surveillance and health service research reports of the United States, most cases of BC are older than 70 years of age.[6] In Iran, BC is diagnosed in women who are at least one decade younger compared to their counterparts in other part of the world.[7] In our study similar to some previous investigations, a considerable proportion of breast cancer cases were between the age of 40 and 50 (39.8%).[8]

Although breast lesions might be of a benign nature such as fibrocystic changes, they can also be warning signs of malignancy. The mean age of benign lesions is generally one to two decades lower in comparison with malignant tumors, almost one to two decades.[3] Therefore, a breast mass especially in an elderly woman should be considered a warning sign of cancer and appropriate diagnostic approaches should be implemented.

In this context, our pathology records showed that the malignancy rate was 63.9% among all of the breast biopsies. In addition, hyperplasia was most commonly observed in patients with malignancy. Our results indicated that 12.2%, 17.4% and 6.5% of biopsy results were normal, cyst fibrosis and fat, respectively. So far, several studies investigated the epidemiology of BC in different regions of Iran such as Isfahan[9], Golestan[10], Tehran[11] and Ardabil[12] and our results were consistent with them indicating that malignant tumors comprised a considerable proportion of the specimens. Since breast cysts may exist from small to large sizes which occur most often after the age 40, early detection of breast cysts may suppress BC initiation and development.[8, 13]

A limitation of this study was the relatively small number of included patient records which were available in 2 hospitals in Brjand within three years.

Another limitation was that the clinical symptoms and data regarding delay in diagnosis could not be retrieved from the pathology reports. Thus, the relative frequency of malignancy in biopsy specimens can be the dependent upon various factors such as prevalence of delay and referral patterns.

Overall, the results further mandate a national breast cancer detection program involving effective public education and encouragement of women for participation in screening programmes. For developing effective awareness programs, it's mandatory that main themes are recognized according to the studies that reveal knowledge gaps.[14]

Acknowledgment

This study is the result of research project number of 910 which was approved by the research committee of Birjand University of Medical Sciences and complied with the terms of its Ethics Committee.

References

1. Fazeli Z, Fazeli Bavand Pour FS, Abadi A, Pourhoseingholi MA, Akbari A, Salimian J. Trend analysis of breast cancer mortality in Iranian women. Sci J Ilam Univ Med Sci 2013;20(4):246-51.
2. Jazayeri SB, Saadat S, Ramezani R, Kaviani A.

Incidence of primary breast cancer in Iran: Ten-year national cancer registry data report. Cancer Epidemiol 2015; 39(4): 519-27.
3. Guray M, Sahin AA. Benign breast diseases: classification, diagnosis, and management. Oncologist 2006; 11(5): 281-308.
4. Kashfi F, Nikoofar AR, Mohammadi R. Fertility risk factors causing breast cancer. J Reprod Infertil 2002; 9(3): 38-45.
5. Yavari P, Mosavizadeh MA, Sadrolhefazi B, Khodabakhshi R, Madani H, Mehrabi Y. Reproductive characteristics and the risk of breast cancer: a casecontrol study. Iran J Epidemiol 2006; 2(1): 119.
6. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. CA Cancer J Clin 2008; 58(2): 71-96.
7. Khadivi R, Harrirchi I, Akbari ME. Ten year breast cancer screening and follow up in 52200 women in Shahre-Kord, Iran (1997-2006). Iran J Cancer Prev 2012; 1(2): 73-7.
8. Harirchi I, Karbakhsh M, Kashefi A, Momtahen AJ. Breast cancer in Iran: results of a multicenter study. Asian Pac J Cancer Prev 2004; 5(1): 24-7.
9. Tazhibi M, Fazeli Dehkordi Z, Babazadeh S. Trends in breast cancer incidence rates by age and tumor characteristics of women in the city of Isfahan for the period 2001-2010: An application of join point analysis. J Res Med Sci 2014; 19: 319-25
10. Taheri NS, Bakhshandehnosrat S, Tabiei MN, Kashani E, Rajaei S, Besharat S, *et al*. Epidemiological pattern of breast cancer in Iranian women: is there an ethnic disparity? Asian Pac J Cancer Prev 2012; 13(9): 4517-20.
11. Sadjadi A, Nouraie M, Ghorbani A, Alimohammadian M, Malekzadeh R. Epidemiology of breast cancer in the Islamic Republic of Iran: first results from a population-based cancer registry. East Mediterr Health J 2009; 15(6): 1426-31.
12. Fouladi N, Pourfarzi F, Amani F, Ali-Mohammadi H, Lotf I, Mazaheri E. Breast cancer in Ardabil province in the north-west of Iran: an epidemiological study. Asian Pac J Cancer Prev 2012; 13(4): 1543-5.
13. HoussamiN, Irwig L, Ung O. Review of complex breast cysts: implications for cancer detection and clinical practice. ANZ J Surg 2005; 75(12): 1080-5.
14. Karbakhsh M. ABC of Breast Cancer Awareness. Arch Breast Cancer 2014; 1(3): 77-8.

Case Report Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163127-31

Gestational Breast Cancer: Report of A Case and Literature Review

Filipa Paixão-Barradas*[a], Daniela Pereira[a], Lurdes Ramalho[b], Isabel Marques[b]

[a] *Department of Obstetrics and Gynecology, Centro Hospitalar Barreiro-Montijo, Barreiro, Portugal*
[b] *Senology Department, Centro Hospitalar Barreiro-Montijo, Barreiro, Portugal*

ARTICLE INFO

Received:
30 December 2015
Revised:
20 January 2016
Accepted:
31 January 2016

Keywords:
Breast neoplasms, pregnancy

ABSTRACT

Background: Gestational or pregnancy-associated breast cancer is defined as breast cancer diagnosed during pregnancy, within the first postpartum year, or during lactation. Breast cancer is one of the most common cancers in nonpregnant and pregnant women.

Case presentation: A 29-year-old pregnant woman presented at eight weeks gestational age with a palpable breast nodule. On breast ultrasound evaluation, only probably benign findings were detected. The pregnancy was uneventful until the third trimester when she started to have a severe back pain which became gradually resistant to medical therapy. Therefore, at 33 weeks, she was assisted at an emergency care facility and a highly suspicious breast mass was detected. A core biopsy was performed that revealed an invasive ductal carcinoma grade 3 with lymph node metastasis.

After several imaging studies, it was diagnosed as a stage 4 breast cancer with bone, liver, and pulmonary metastasis. At thirty four weeks gestation, the pregnancy was terminated by C-section and she started to receive palliative radiation therapy one week later. She also received several cycles of palliative chemotherapy. Nineteenth months after C-section, progression of the disease was observed and a cerebellar metastasis was found. Unfortunately, two months later, her clinical condition deteriorated and the patient died.

Conclusion: Gestational breast cancer represents a clinical situation of utmost important in which the health of both the mother and the fetus should be taken into account. Diagnosis is difficult due to the physiological changes of the mammary glands during pregnancy and lactation, and it usually occurs at an advanced stage.

Introduction

Gestational breast cancer (GBC) is defined as breast cancer diagnosed during pregnancy, in the first postpartum year, or during lactation.

Address for correspondence:
Filipa P.M. Paixão-Barradas
Address: Rua Provedor Nuno Álvares Pereira, número 105, 1º esquerdo, 2870-122 Montijo, Portugal.
Tel: +351 965 880 361
Email: filipapaixaobarradas@hotmail.com

Although breast cancer is one of the most common cancers related with pregnancy, GBC is a rather uncommon event. The incidence of GBC is approximately 15 to 35 per 100,000 deliveries and accounts for about 2% of all newly diagnosed breast cancers.[1, 2] It increases with the age of the pregnant woman and appears to have an increasing trend due to older age of women at the time of the first childbirth. The age of the patients in the majority of the case series ranges from 26–49 years, with most of them diagnosed at 30–40 years of age.[3]

A diagnosis of GBC is more difficult than its diagnosis in nonpregnant woman; moreover, it

usually occurs at an advanced stage, requiring a high level of suspicion. Treatment methods and the treatment onset, as well as the eventual need for pregnancy termination, are not consensual, requiring a multidisciplinary approach.

GBC can potentially have a deleterious effect on both mother and child, presenting a challenging clinical situation that requires a balance between the health of both the mother and the unborn child.

Case Presentation

A 29-year-old multiparous pregnant woman, with no family history of malignancy, presented at eight weeks gestation with a palpable nodule in her left breast detected on breast self-examination. It was a painless movable lump approximately 1.5 cm in size. No associated breast tenderness or skin changes were noted.

On evaluation by breast ultrasound, only probably benign findings (Bi-RADS 3) were detected in the left breast. Nevertheless, two months later, she underwent another ultrasound which only revealed benign findings.

The pregnancy was uneventful until the third trimester when she started to have a severe back pain. Therefore, at 28 and 31 weeks gestation, she went to an emergency care facility and received analgesics. Her pain ameliorated until 33 weeks gestation, when she was assisted because of an incapacitating back pain resistant to medical therapy. At that time, she had a solid mass in her left breast which was about 5cm in diameter and highly suspicious, and had multiple ipsilateral lymph nodes.

A core biopsy was performed that showed an invasive ductal carcinoma G3 (Fig. 1) with positive lymph nodes. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) were positive.

Spinal radiography showed pathological collapses of D8, D12, and L4 (Fig. 2) and the abdominal ultrasound reported liver metastasis (Fig. 3). Chest radiography revealed pulmonary metastasis.

She was then hospitalized with a stage 4 breast cancer and received fetal lung maturation and analgesic therapy. An obstetric ultrasound examination revealed a cephalic fetus (50th percentile) with oligohydramnios.

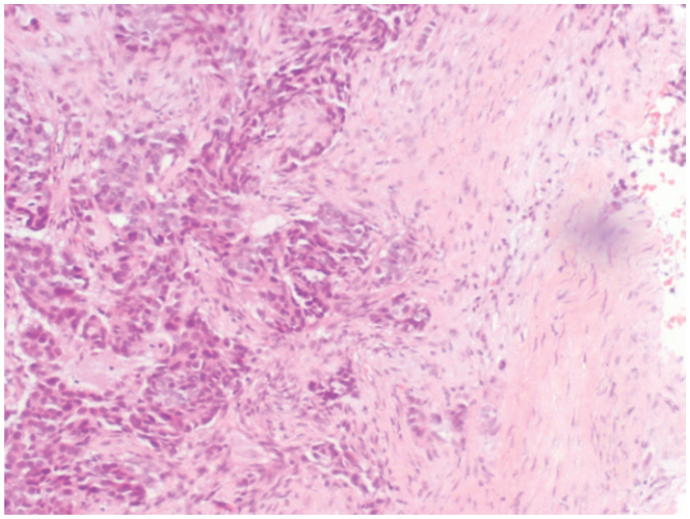


Figure 1. The Core biopsy was performed at 33 gestational age, revealing an Invasive ductal carcinoma grade 3.

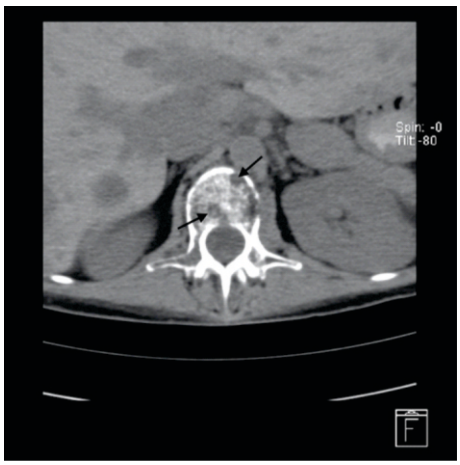


Figure 2. Spinal computed tomography showing diffuse vertebral metastasis (arrow) at D8, D12 and L4.

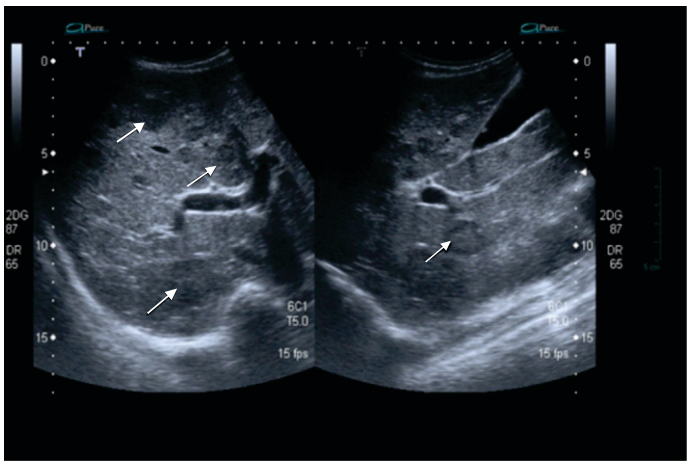


Figure 3. Abdominal ultrasound with an enlarged liver filled of metastasis (see arrows).

At 34 weeks gestation, a healthy neonate (female, 4.8 pounds) was delivered by C-section. No placental metastasis was noted.

One week after C-section, she started the first of ten cycles of palliative radiation therapy with a poor response. Then, she received six cycles of palliative chemotherapy (FEC - Fluorouracil, Epirubicin, and Cyclophosphamide) with a better response, starting an accompanied gait six months after C-section. Later, she also received three cycles of Docetaxel chemotherapy. Then, she underwent treatment with Letrozole, Trastuzumab, and Zoledronate for several months. Finally, she also tried Lapatinib plus Capecitabine.

Nineteenth months after C-section, progression of the disease was observed and a cerebellar metastasis was found (Fig. 4). She underwent surgery. Liver function tests worsened one month later and an abdominal ultrasound showed bigger liver metastases (Fig. 5). She was then admitted with tension ascites (Fig. 6). Unfortunately, two months later (1 year and 10 months after GBC diagnosis), her clinical condition deteriorated and the patient died.

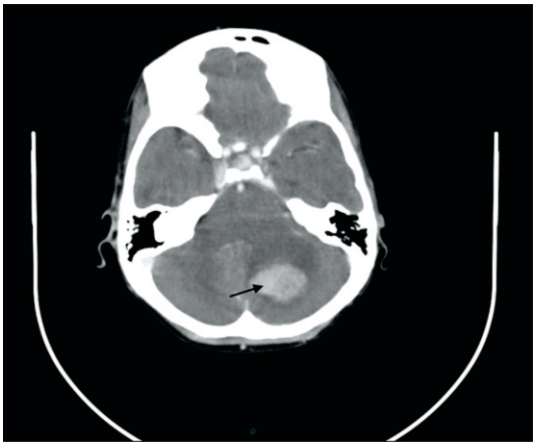


Figure 4. Nineteenth months after C-section, Computed tomography imaging of cerebellar metastasis (see arrow).

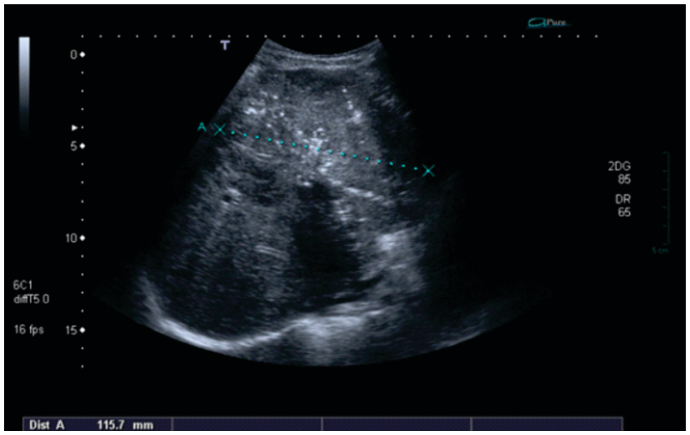


Figure 5. Abdominal ultrasound showing larger liver metastasis.

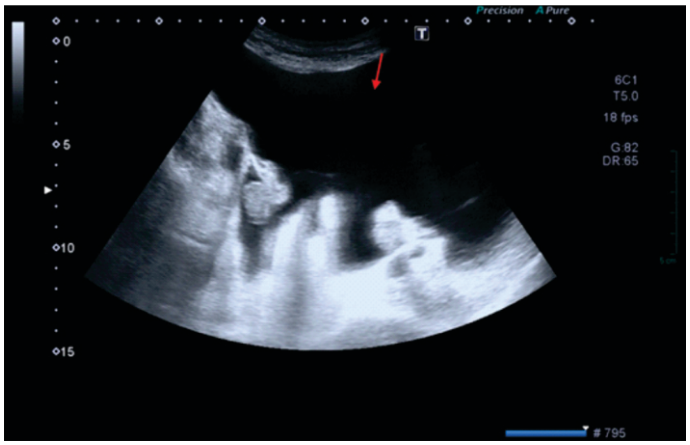


Figure 6. Ascites detected by abdominal ultrasound.

Discussion

Breast cancer can be more successfully treated in case of timely diagnosis; therefore, avoiding a delay in diagnosis is vital. Unfortunately, GBC is more probable to be diagnosed late mainly due to the physiological changes (enlargement, angiogenesis) in the breast during the pregnancy, which makes physical examinations less sensitive. Other factors may also contribute, like the absence of self-examinations on pregnant women as well as low attention to proper breast examination by gynecologists who mainly focus on the developing fetus and pregnancy surveillance.[4]

The protocol to investigate a breast mass in pregnant women is the same as the protocol in nonpregnant women. An ultrasound is the first step to assess a mass in pregnant women since its sensitivity and specificity are not changed by pregnancy.[5] On the other hand, although the results of mammography can be affected by physiological breast changes in pregnancy, it is still recommended. It has a sensitivity of about 86% during pregnancy and the exposure of the fetus to the radiation (with abdominal shielding) rather low (0.004 Gy). However, a negative mammogram in the setting of a palpable mass should not prohibit the physician from performing a biopsy.[3]

Regarding biopsy procedures, a core biopsy is preferred in pregnancy. Fine needle aspiration may be more technically difficult to perform due to the engorgement during pregnancy and it is unreliable due to hyperproliferative cellularity.[6]

Therefore, the index of suspicion for cancer must be higher in pregnant women. A clinically suspicious breast mass requires a biopsy for a definitive diagnosis, despite negative mammographic or ultrasound findings.

The majority of breast cancers in pregnant women are invasive ductal carcinomas (IDC), as in nonpregnant women, and the steroid receptor content (estrogen and progesterone receptor), HER-2 status, proliferation rate, and the presence of the p53 mutation do not differ remarkably from those of age-matched nonpregnant patients.[7]

GBC has many similar histologic and prognostic features with breast cancer in young women. The age of the patients with GBC is probably the factor that affects the biologic characteristics of the tumor, not the pregnancy itself.

According to the guidelines, management of breast cancer in pregnant women is generally similar to nonpregnant patients, with some modifications in order to protect the unborn child. Termination of pregnancy might be sometimes considered during treatment planning, it has not been shown to have a survival benefit and it is a decision that should be individualized.[3]

Consequently, the treatment of choice is surgery. During any trimester of pregnancy, surgery of breast and lymph nodes seems to harbor a minimal risk to the fetus.[1] Chemotherapy in the treatment of GBC is possible after the first trimester of pregnancy and should be administered according to the same principles applied in non-pregnant patients. Radiation therapy should be avoided and delayed whenever possible until after delivery because of its toxic impact on the fetus.[4]

All patients with gestational breast cancer should be assessed for distant metastases according to guidelines developed for non-pregnant patients.[6] A mammogram (with abdominal shielding) of the unbiopsied breast is recommended to exclude contralateral involvement.[3] Systemic staging can include a chest radiograph with fetal shielding (0.0001 Gy) and a liver ultrasound. To evaluate bone metastases, an MRI of the spine without contrast can be done, particularly if the patient is symptomatic.

In our case, the initial presentation of the GBC was missed. The index of suspicion should have been higher, and a biopsy could have been performed immediately, even if the mass did not appear suspicious on imaging. Unfortunately, there was no further evaluation about it. However, given her tumor type and size at diagnosis plus her poor response to initial treatment, she did exceptionally well to survive nearly two years post diagnosis.

We conclude that GBC presents a clinical situation of utmost important which requires a multidisciplinary approach to ensure optimal care for both the mother and the baby. While protecting the interests of mother and the unborn child, breast cancer can be best diagnosed, staged and managed within pregnancy with favorable outcomes for both. The prognosis in GBC, similar to breast cancer in other women, depends mainly on the stage of the disease as soon as the diagnosis was made.

Conflicts of Interest

None

References

1. Woo JC, Yu T, Hurd TC. Breast cancer in pregnancy: a literature review. Arch Surg 2003; 138(1): 91-8; discussion 9.
2. Andersson TM, Johansson AL, Hsieh CC, Cnattingius S, Lambe M. Increasing incidence of pregnancy-associated breast cancer in Sweden. Obstet Gynecol 2009; 114(3): 568-72.
3. Cardonick E. Pregnancy-associated breast cancer: optimal treatment options. Int J Womens Health 2014; 6: 935-43.
4. Jakubik J, Gottwald L, Kukulska M, Góra E, Korczyński J, Bieńkiewicz A, *et al*. Breast cancer in pregnant women: report of two cases and review of the literature. Arch Med Sci 2008; 4(2): 204-7.
5. Ahn BY, Kim HH, Moon WK, Pisano ED, Kim HS, Cha ES, *et al*. Pregnancy- and lactation-associated breast cancer: mammographic and

sonographic findings. J Ultrasound Med 2003; 22(5): 491-7; quiz 8-9.
6. Amant F, Deckers S, Van Calsteren K, Loibl S, Halaska M, Brepoels L, *et al*. Breast cancer in pregnancy: recommendations of an international consensus meeting. Eur J Cancer 2010; 46(18): 3158-68.
7. Middleton LP, Amin M, Gwyn K, Theriault R, Sahin A. Breast carcinoma in pregnant women: assessment of clinicopathologic and immunohistochemical features. Cancer 2003; 98(5): 1055-60.

Invited Commentary Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163232-33

Psycho-oncology: A Common Discipline for All!

Elise Bo-Gallon*[a]

[a] *Psychology and Psychopathology Clinic, Department of Psycho-oncology, Sainte Catherine Institute, Avignon, France*

Psycho-Oncology is a discipline that has emerged in the early 1970s in response to growing interest in the psychological, behavioral and social issues, related to the occurrence of cancer in an individual.[1] Known as psychosocial oncology throughout most of Europe, Psycho-oncology deals with two psychological aspects of cancer: (1) psychosocial: the emotional responses of patients, their families and caregivers; (2) psychobiological: the psychological, behavioral and social factors influencing mortality and morbidity among cancer patients.[2]

The objectives are twofold: integration of psychological care into the total care of cancer patients and their families at all stages of the disease, and progress in understanding psychological, social and behavioral factors that may influence disease progression and survival through research and education.[2,3]

Besides, its name by itself refers to its position of interface among oncology, psychiatry and psychology. Doctors, nurses, social workers, psychiatrists and clinical psychologists are all players of care that are concerned in the field of Psycho-Oncology, bringing their specific clinical and therapeutic skills.[4] Similarly, the research interests are common to all stakeholders of Psycho-Oncology, and are mainly focused on understanding the psychological mechanisms involved in the course of cancer screening, detection, management and rehabilitation of patients and their families.

Psycho-oncology is important to be integrated in care of all cancers; nevertheless, due to the high burden and potential stigma and embarrassment of being diagnosed with breast cancer, implementation of this discipline is of utmost importance in these patients.[5] Providing the supportive care as early as the clinicians' suspicion of breast cancer may lead to better coping with the disease and improve quality of life.[6]

Still booming, Psycho-Oncology today is an international concern, since many countries have developed national associations responsible for the organization and development of this discipline. In addition, International Psycho-Oncology Society (IPOS, founded in 1984) brings together about thirty countries that are organized around the subject of Psycho-Oncology (such as Canada, Japan, Australia, Nigeria and England). The main tasks of IPOS are promoting the effective psycho-oncological care of patients suffering from cancer across the world, through partnerships, public health policy, research and education.[7] In addition to many events organized regularly by each country involved in Psycho-Oncology, IPOS offers a world congress every year. In 2016, Ireland will host the event, while the USA, Portugal and Australia organized previous meetings; a sign of certain worldwide concern about discipline.

While Psycho-Oncology aims to incorporate the psychosocial dimension into the care of cancer patients, the international dynamic reflects the fact the entire scientific community are concerned about the psychological aspects, beyond the strictly inherent characters that a culture, a society or a religion might endorse. Indeed, the common notion among all of us is the patient that we support; the concern which is universal. Therefore we can argue that Psycho-Oncology is a common discipline for all and without borders!

Address for correspondence:
Elise Bo-Gallon, PhD
Address: Equipe psycho-oncologie Institut Sainte Catherine, 250 Ch. Baigne pieds – CS 80005, 84918 Avignon Cedex 9, France
Tel: +33 490276161
Fax: +33 490276180
Email: e.gallon@isc84.org

References

1. Holland JC. History of psycho-oncology: overcoming attitudinal and conceptual barriers. Psychosom Med 2002; 64(2): 206-21.
2. Holland JC. Psycho oncology: Overview, obstacles and opportunities. Psychooncology 1992; 1: 1-13.
3. Herschbach P, Book K, Brandl T, Keller M, Marten-Mittag B. The Basic Documentation for Psycho-Oncology (PO-Bado): an expert rating scale for the psychosocial experience of cancer patients. Onkologie 2008; 31(11): 591-6.
4. Turner J. The changing landscape of cancer care - the impact of psychosocial clinical practice guidelines. Psychooncology 2015; 24(4): 365-70.
5. Neishaboury M, Davoodzadeh K, Karbakhsh M. Does Embarrassment Contribute to Delay in Seeking Medical Care for Breast Cancer? A Review. Arch Breast Cancer 2015; 2(3): 75-8.
6. Kaviani A, Mehrdad N, Yunesian M, Shakiba B, Ebrahimi M, Majidzadeh K, *et al.* Psychosocial Care for Breast Cancer: Physicians' Perspective. Iran J Cancer Prev 2012; 3(1): 23-7.
7. Grassi L, Watson M. Psychosocial care in cancer: an overview of psychosocial programmes and national cancer plans of countries within the International Federation of Psycho-Oncology Societies. Psychooncology 2012; 21(10): 1027-33.

Review Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163234-40

The Effects of Naringenin on Some Human Breast Cancer Cells: A Systematic Review

Zahra Akbarzadeh[a, b], Farnaz Parvaresh[a, b], Reza Ghiasvand[a, b], Maryam Miraghajani*[c]

[a] *Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran*

[b] *Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran*

[c] *Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Received:
5 March 2016
Revised:
16 March 2016
Accepted:
16 May 2016

Keywords:
Naringenin,
systematic review,
breast cancer cells

ABSTRACT

Background: Breast cancer is the most common cancer in women worldwide. Recently, natural remedies such as Naringenin (Nar) - a kind of flavonoids which can be found in grapefruits, oranges, and tomatoes - seem to be interesting. They play a useful role in treatment and chemoprevention because of having pleiotropic molecular mechanisms of action on breast cancer cells.

Methods: We performed a PRISMA-directed systematic review to investigate the effects of Naringenin on some human breast cancer cells (MCF-7, T47D, and MDA-MB-231). Tumor size, apoptosis, estrogenic properties, and cytotoxicity were assessed as primary outcomes. The systematic search without restriction was conducted in electronic databases, including PubMed, Scopus, Google scholar, and Cochrane Library.

Results: Initially, 6445 articles were identified. After screening their titles and abstracts, 32 studies were selected for text appraisal. Finally, 6 articles which met the inclusion criteria were evaluated. Based on the evaluation, Nar could inhibit both cell proliferation and tumor growth at different concentration. Moreover, it could induce apoptosis.

Conclusions: Due to anticancer properties of Nar, some probable mechanisms of these effects are induction of alteration in aromatase and caspase enzymes, and suppression of oestrogen signal transduction pathways. However, more investigations are necessary in the future to decide whether Nar consumption is recommendable as part of breast cancer treatment and control. Also, some clinical trials should be designed to determine the optimal dose for the therapeutic use.

Introduction

Breast cancer is the most common cancer in women worldwide and accounts for nearly 20% of the new cancer diagnosed cases.[1, 2] As about 14% of the total deaths are related to this cancer, it threatens the physical and mental health of women throughout the world.[3,4]

Recently, natural remedies are being widely used and accepted as established treatments for some disorders.[5] Indeed, the continuing worldwide effort is to discover new anticancer agents from medicinal plants. Some researchers have concluded that natural products are protective factors against breast cancer cells.[6, 7] Among them, dietary components such as flavonoids are generally known to have potential protective roles against cancers. Beside the effectiveness of these ingredients in the reduction

Address for correspondence:
Maryam Miraghajani, PhD
Address: Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences,Isfahan, Iran
Tel: +98 31 36688487
Fax: +98 31 36682509
Email: ms.miraghajani@yahoo.com

of malignancy risk and treatment, they have a much wider safety margin than do some drugs.[8]

Naringenin (Nar) belongs to the flavanone family, which is found abundantly in grapefruit juice, citrus fruits, and tomato skin.[9] This flavone possesses diverse biologic effects such as anti-carcinogenic, anti-inflammatory, and anti-oxidant activities.[10] Also, this phytochemical appears to have anti-proliferative effects in many cancer cell lines, especially breast cancer cells.[11, 12] This food component exhibits anti-estrogen effects in estrogen rich states, and estrogenic activity in reduced estrogen states in breast cancer cells. Since more than 60% of breast cancers are estrogen receptor positive (ER+), (a polymorphism in the human estrogen receptor gene that is sensitive to estrogen and may respond to hormone therapy), and on the other hand Nar can inhibit proliferation via this pathway and reduce the number of estrogen receptors in positive cells, these compounds might play a useful role in breast cancer chemoprevention and treatment.[13-16]

However, the effectiveness of this dietary ingredient in breast cancer cells has not yet been reviewed. We conducted this systematic review to evaluate the effect of biologic activities of Nar on the tumor size, apoptosis (by assessment of caspase), estrogenic properties (by assessment of the activation of aromatase enzyme which is a key enzyme in the biosynthesis of steroids), and cytotoxicity (by MTT staining as described by Mosmann) among four types of main human breast cancer cells, including MCF-7, T47D, and MDA-MB-231.

Methods

This literature reviews was designed and presented in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines .

Search strategy

The following databases were searched in June 2015: Scopus, Google Scholar, ProQuest, PubMed, and Cochrane Library. The search terms used were: "Naringenin 7-O-methyltransferase" [Mesh] OR"7-O-xylosyl Naringenin" [Mesh] OR "Naringenin" [tiabs] OR, "Isoflavone " [tiabs] OR "naringenin-7-O-glucoside" [TW], AND "breast cancer" [tiabs] OR "breast neoplasms" [tiabs] OR "breast tumors" [tiabs]. No restriction was applied.

Study inclusion and exclusion criteria

Two researchers independently rated each paper to conclude their inclusion eligibility using defined inclusion and exclusion criteria. The study was included if it had the following criteria: 1) reporting the association between Naringenin as an exposure and breast cancer cells; 2) considering the effect of Naringenin on tumor size, apoptosis (by assessment of caspase 9 or luciferase), estrogenic properties (by assessment of the activation of aromatase enzyme) and cytotoxicity (by MTT staining as described by Mosmann) as primary outcomes.

The exclusion criteria were animal studies and all other breast cancer cell researches which did not include MCF-7, T47D, and MDA-MB-231 cells.

Study selection

The selection process had three stages that were conducted by two authors independently. The first and the second stages included screening the titles and then abstracts, respectively. The final step was to screen the full text of the articles according to the inclusion criteria. A third author arbitrated any unresolved disagreements arising during any stage in the selection process. A PRISMA flow diagram (Figure 1) was used to report the number of studies that were included and excluded in each stage of the selection process.

Data extraction

The following information was extracted from each paper: the name of the first author, type of study, duration, sample size, dose of Naringenin, outcome, mechanism, P-value, and results.

Results

A total of 6445 studies were initially recognized in these databases: 154 in Scopus, 6220 in Google Scholar, 20 in ProQuest, 1 in Cochrane, and 50 in PubMed. After we excluded duplicate studies on the basis of title or abstract, 50 studies were retrieved for more investigation. Studies that were conducted on animal cells and not related to mentioned breast cancer cells were excluded. A total of 47 studies were intended for more assessment. After reading 47 full texts, 6 studies were eligible for inclusion.

Main study characteristics

In one study conducted by Kim *et al*., the T47D-KBluc and MDA-MB-231 human breast cancer cells were treated with Naringenin for 24 hours. Then, the effect of Naringenin on luciferase as a screen for estrogen receptor activity and pS2 protein expression which have a correlation with estrogen receptor positivity in both cells were measured. InT47D-KBluc cells, Naringenin increased the luciferase activity in a concentration-dependent manner, especially at 10μM, via an estrogen receptor-dependent mechanism. The highest significant effect of Nar on the expression pS2 mRNA in T47D-KBluc cells was at10μM. So, it was concluded that Nar could act as a new selective estrogen receptor modulator, with the ability to increase deficient estrogen activity while disrupting excessive estrogen activity (Table 1).[17]

In one study by Filho, the colony size and number,

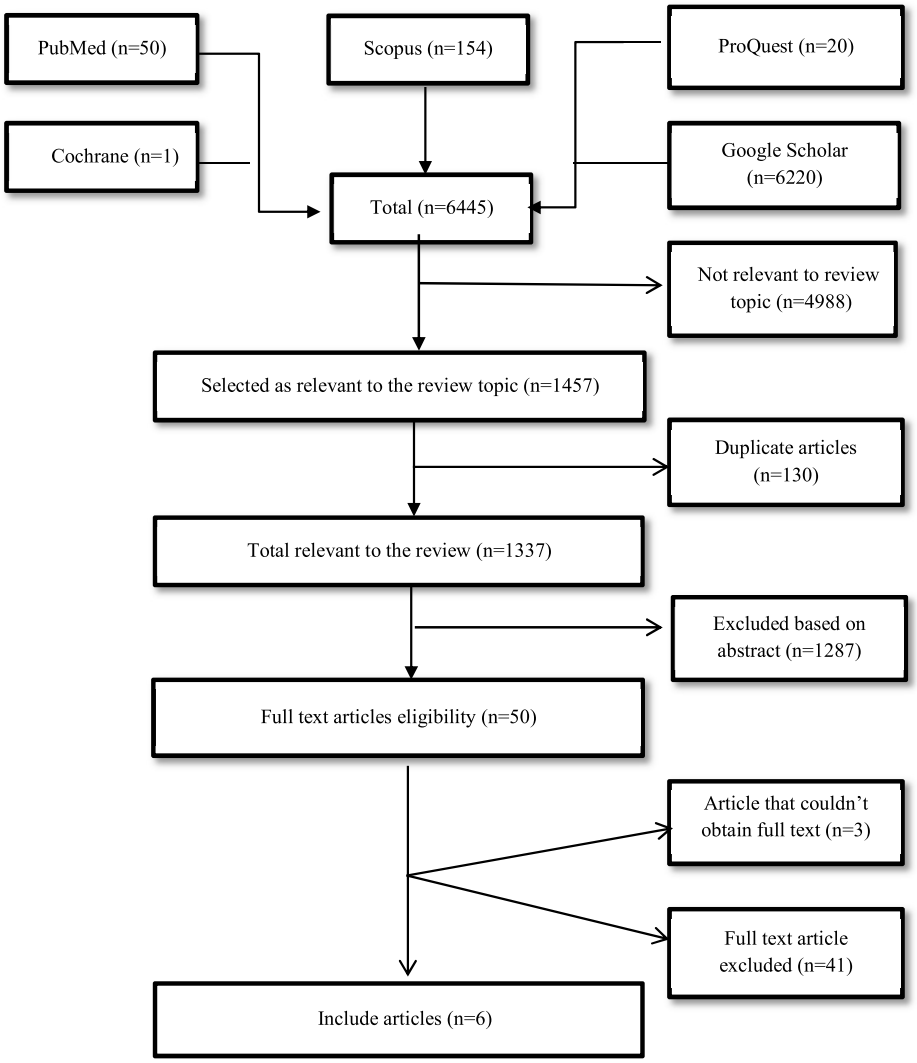


Figure 1. Flow diagram of study selection

apoptotic gene activity, apoptosis, and proliferation of MDA-MB-231 tumor cells were defined after Nar administration. It was illustrated that the colony size in these cells treated with Nar was significantly decreased as compared with untreated cells. Naringenin was found to inhibit the proliferation of MDA-MB-231 cells at concentrations of 500 and 1000 mM. Also, 100 mM Nar could induce about 65% of apoptosis although 1 mM Nar made no significant difference in the expression of caspase 8 and 9 (as an initiator of apoptosis) (Table 1).[18]

In addition, the effect of exposing MCF-7, MDA-MB-231, and T47D human cancer cells to Nar (at $1\times10^{-9}\times10^{-6}$µM to $1\times10^{-4}\times10^{-6}$µM concentration) for 24 hours has been studied. According to the results, Nar decreases the number of MCF-7 and T47D breast cancer cells significantly at $1\times10^{-6}\times10^{-6}$µM concentration. Nar concentrations ranging from $1\times10^{-7}\times10^{-6}$ µM to $1\times10^{-4}\times10^{-6}$ µM reduce only MCF-7 and T47D cells numbers. No similar results have been obtained in MDA -MB-231 cells. In contrast to MDA -MB-231 cells, caspase-3 activation could be detected in both MCF-7 and T47D cells treated with Nar. Also, it has been found that Nar acts as a selective inhibitor of ERα which mediates proliferation in breast cancer cells. Although Nar can modulate ERα signaling pathways, it could not modify the number of ERα among MDA-MB-231(ERα -) cells.[19]

Another study showed that the cytotoxicity effects of Nar were not different with flow cytometric analysis in both cell lines, MCF-7 as the ER positive (+) and MDA-MB-231 as the ER negative (-).[20]

Van evaluated cell proliferation, aromatase inhibition, and estrogenic properties of Nar in MCF-7 adenocarcinoma cells. The proliferative potency of Nar in the MCF-7 cells derived from their EC50s (half maximal effective concentration) and IC50s (half maximal inhibitory concentration) were 287 and 315 nM, respectively. Aromatase activity was very low in MCF-7 cells. In this study, Nar could induce cell proliferation and inhibit aromatase in a concentration range of 1–10 µM.[21] Treatment with Nar (at a concentration ≥ 1 µM) after 6 days did not affect cell proliferation. Also, Nar did not show cytotoxic effects in the MCF-7 cells at estrogenic concentrations ($<1\times10^{5}$µM) but it could induce cell proliferation and significantly inhibit the aromatase

activity. Estrogenic property of Nar is quantitatively more sensitive than aromatase inhibition. In contrast to other reports, this finding did not show the cytotoxic effects of Nar on MCF-7 cells.[20,21]

In a study by Stapel J, although Naringenin could diminish the proliferation MCF-7 cells in a concentration range of 5 to 50 µg/ml, it had not cytotoxic effect by LDH- assay.[22]

Table 1. Details of studies investigated the association between Naringenin and some human breast cancer cells

Author (Year)	Type of Study	Duration	Sample size	Dose of Naringenin	Outcome	Mechanism	Results	P-value
Kim S[17] (2013)	Experimental	24 hours	1×10^5 T47D-Kbluc cells	Concentrations of (0.001,0.1, 1, and 10 µM) (to 1)	Measuring the effect of Nar on proliferative and estrogen receptor activity in T47D breast cancer cells.	Nar acts by an estrogen receptor-dependent mechanism in T47D-KBluc cells.	Naringenin was a weak estrogen agonist that exhibits anti-estrogenic effect in T47D-KBluc breast cancer cells. Nar significantly repressed the luciferase activity. it has no effect on cell proliferation. Nar can modulate the transcription of *pS2 mRNA expression.	P< 0.05
Filho JCC[18] (2014)	Experimental	48 hours for measuring Cell proliferation 24 hours for measuring apoptosis	5×10^4 cells/plate for measuring cell proliferation in MDA-MB-231 cells. 0.1×10^6/plate for measuring apoptosis in MDA-MB-231 cells/	(1 to 1000 mM)	Studying the effect of different concentrations of Nar on colony size, apoptotic activity, apoptosis and proliferation of MDA-MB-231tumor cells.	Apoptosis was induced by Nar via activation of caspase-3 and -9 but not caspase-8 pathways. Higher concentration (1 mM) of Nar caused death via necrosis in this cell line.	Colony size significantly decreases. Nar can inhibit cell proliferation at concentrations of 500 and 1000 µM. Higher concentration (1 mM) of Nar caused death via necrosis in this cell line and inducing apoptosis in MDA-MB-231 breast tumor cells.	P < 0.01
Bulzomi P[19] (2012)	Experimental	48 hours	1×10^{-7}M to 1×10^{-4} M Nar expose to carcinoma cell lines (MCF7, TD7D, and MDA-MB-231)	1×10^9M, 1×10^4M Nar expose to carcinoma cell lines (MCF7, T47D, and MDA-MB-231)	Measurement cell growth, proliferation and the number of MCF7, T47D, and MDA-MB-231 cells when they were exposed to different concentration of Nar.	Nar impairs cell proliferation by activating caspase-3 in MCF-7 and T47D cells, not in MDA-MB-231 cells.	Nar (at 1×10^{-6}M) reduces number and inhibits growth and impairs proliferation in MCF-7 and T47D cells. Nar only decreases the number of Er α-positive cells (MCF-7 and T47D).	P < 0.001
Kanno S[20] (2005)	Experimental	For determining cytotoxicity: 48 hours	For determining cytotoxicity 4×10^5 MCF7 and MDA-MB231 cells.	100, 250, 500 or 1000m M	Determining cytotoxicity (by MTT**) in MCF-7, MDA-MB-231cells.	The mechanism of cytotoxicity which induced by Nar is independent of p53 and has not been cleared yet.	Nar induced cytotoxicity in both MCF-7, and MDA-MB-231 cells. The cytotoxicity of Nar is not different in both of cells.	NR***
Van Meeuwen[21] (2007)	Experimental	For cell proliferation 6 days. For cytotoxicity measurement in MCF-7 cells(by MTT**): 48h. For measurement aromatase activity in MCF-7 cells: 24h.	For cytotoxicity measurement in MCF-7 cells :1×10^5cells/well For measurement aromatase inhibitory in MCF-7 2×10^5 cells/well (24 wells plate).	1-10µM Nar was used. The best result was at concentration 287µM for MCF-7	Nar expose to human epithelial estrogen sensitive breast tumor cells (MCF-7). Aromatase inhibition, cell proliferation, cell cytotoxicity was measured	Inhibition tumor cells by inhibiting aromatase	Nar at concentration range (1–10 µM) can induce cell proliferation or inhibit aromatase. Estrogenicity of Nar is quantitatively more sensitive than aromatase inhibition. Cytotoxicity at concentration ($>1\times10^5$) were observed inMCF-7 cells. The potential of Nar for inhabitation tumor cells (by inhibit aromatase) are higher than proliferative potency	NR***
Stapel J[22] (2013)	Experimental	For measuring MCF-7 cell proliferation: 24h.	For measurement cell proliferation: 5×10^5 cells/ml	5-50 µg/ml	The effect of Nar on cytotoxic potential and cell proliferation of MCF-7.	NR***	Nar was not cytotoxic (by LDH- assay). In the concentration 5 µg/ml Nar can inhibit cell proliferation.	P < 0.05

** pS2 expression was used as a measure for estrogenic response in MCF-7 cells*
*** MTT: 3-(4,5- dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide*
**** NR: Not reported*

Discussion

Flavonoids, polyphenolic compounds, have a broad spectrum of biological activities, including anticancer properties. They have been proved to potentiate the effectiveness of existing drugs in cancer therapy.[23-25]

Therefore, in the present systematic review which is the first review in this field to our knowledge, we evaluated the results of 6 articles that assessed the effect of Nar on the tumor size, apoptosis, estrogenic properties, and cytotoxicity on some breast cancer cells.

In general, among these investigations, two and three studies revealed the beneficial effects of Nar on cell proliferation in MDA-MB-231 cells and inMCF-7 cells, respectively.[7,9,10,18,19] Also, two studies showed that this flavanone could induce apoptosis in MDA-MB-231 and exert proapoptotic functions in MCF-7 and T47D cells.[18, 19] Moreover, 2 studies revealed the antitumor function for Nar.[18,21]

The cancer protective effects of NAR have been attributed to a wide variety of mechanisms.

The effects of Naringenin on estrogen receptor activity

Over 60% of breast cancers are estrogen receptor positive (ER+), which means they are sensitive to estrogen and may respond to hormone therapy.[26] Estrogen via receptors participates in signaling pathway leads to growth cells. Emerging evidence suggests flavonoids could have protective roles against tumors by modulating the activity of estrogen receptors α (ER α) and β (ER β) in some malignant cells.[17,18,27] Nar exhibits anti-estrogenic properties in ERα+ cells by modulating the signaling pathways through inducing specific shape changes in the receptor.[19] Also, estrogen receptor dependent mechanisms in T47D cells can change the expression of pS2 as one of the estrogen target tumor suppressor genes.[17,20]

Further, Naringenin might have anti-estrogenic activities in T47D cells through estrogen receptor modulation.[17] Overall, the results showed that Naringenin is a weak estrogen that also exhibits partial antiestrogenic activities.[28, 29] So, Nar is not an efficient antagonist for activating estrogen receptors but is a sectional agonist which can act as a competitive antagonist.[17]

The effects of Naringenin on aromatase activity

Aromatase is the key-limiting enzyme in production of estrogens and testosterone conversation to estrogens.[30]

The activity of aromatase is higher in the breast cancer adipose tissue when compared with the healthy adipose tissue.[31] In the breast tumor tissue, a promoter switching leads to elevated aromatase gene expression.[32] So, the mechanisms modulating the tumor growth could be via interaction with the estrogen receptor and inhibition of aromatase.[21] Some studies have reported that phytochemicals such as Nar act as aromatase inhibitors; thus, they could potentially reduce the tumor growth.[21,33]

According to reports, phenolic hydroxyl group in position 7 of Nar is essential for the anti-aromatase activity.[33-36]

The effects of Naringenin on apoptosis

Caspases play an essential role in programmed cell death.[37] Cell proliferation could be inhibited by activating caspase-3 in MCF-7 and T47D cells.[19]

Previous studies have reported that genomic deletion of the caspase gene causes apoptotic defects and chemo-resistance in MCF-7 cells.[38, 39] Naturally, flavonoids can trigger a novel form of apoptosis in caspase-3-deficient MCF-7 cells. Furthermore, Naringenin as a kind of flavonoid has the potential to initiate apoptosis by activation of caspase in the mentioned cells.[40]

In addition, in some studies, luciferase genes are used as reporters to analyze the apoptosis level, and it has been shown that Nar significantly increases the luciferase activity in T47D-KBluc cells.[19]

Other potential mechanisms for the anti-cancer properties of Nar are interaction with cell cycle arrest, carcinogen pathway and the reversal of multidrug resistance.[41] However, there are complex feedback mechanisms in living organisms because breast cancer tumors communicate with other tissues through prostaglandins, cytokines, and estradiol.[21]

Based on the results of several studies, some foods which are the source of Nar have other elements- such as CYP3A4 which is a member of the cytochrome P450 - that increase the plasma concentration of estrogen.[21,42] So, it might be negatively affect the activity of Nar.

It is seems that food supplements containing Nar could be advised especially in patients who have a previous history of breast tumor or are high risk.[21]

Like all reviews, this study had some limitations. First, we assessed *in vitro* studies which pure Nar was generally used. Food sources of Nar differ from its purified extracts in their anticancer effects. Moreover, interactions among bioactive components in these foods are likely to affect their biological response. Moreover, Nar is in the glycosides form in the human intestine which can be deglycosylated by certain bacterial species.[43] So, a variety of certain bacterial species in the human intestine might have an impact on the favorable effects of Nar.

In conclusion, Naringenin as a kind of flavonoids is a bioactive molecule. Generally, Nar can exert anticancer effects via suppression of aromatase and caspase enzymes and oestrogen signal transduction pathways. More studies should be conducted using oral supplementation at different doses in different human populations to confirm the results.

Financial support

This study was supported by Isfahan University of Medical Sciences, Isfahan, Iran.

Conflict of interest

The authors declare that they have no conflicts of interest concerning this study.

References

1. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, *et al*. American Cancer Society guidelines for breast screening with MRI

as an adjunct to mammography. CA Cancer J Clin 2007; 57(2): 75-89.
2. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer 2013; 132(5): 1133-45.
3. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al*. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): E359-86.
4. Figueroa A, Soria E, Cantero J, Sanchez M, Goleniowski M. Cytotoxic activity of Thelesperma megapotamicum organic fractions against MCF-7 human breast cancer cell line. J Cancer Ther 2012; 3(6): 103-9.
5. Rajkapoor B, Jayakar B, Murugesh N. Antitumor activity of Indigofera aspalathoides on Ehrlich ascites carcinoma in mice. Indian J Pharmacol 2004; 36(1): 38-40.
6. Zakaria ZA, Mohamed AM, Jamil NS, Rofiee MS, Hussain MK, Sulaiman MR, *et al*. In vitro antiproliferative and antioxidant activities of the extracts of Muntingia calabura leaves. Am J Chin Med 2011; 39(1): 183-200.
7. Ayob Z, Samad A, Bohari S. Cytotoxicity activities in local Justicia gendarussa crude extracts against human cancer cell lines. Jurnal Teknologi 2013; 64(2): 45-52.
8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009; 151(4): W65-94.
9. Nelson HD, Fu R, Humphrey L, Smith MEB, Griffin JC, Nygren P. Comparative effectiveness of medications to reduce risk of primary breast cancer in women: Agency for Healthcare Research and Quality (US), Rockville (MD); 2009.
10. Felgines C, Texier O, Morand C, Manach C, Scalbert A, Regerat F, *et al*. Bioavailability of the flavanone naringenin and its glycosides in rats. Am J Physiol Gastrointest Liver Physiol 2000; 279(6): G1148-54.
11. Bodet C, La VD, Epifano F, Grenier D. Naringenin has anti-inflammatory properties in macrophage and ex vivo human whole-blood models. J Periodontal Res 2008; 43(4): 400-7.
12. Lee CH, Jeong TS, Choi YK, Hyun BH, Oh GT, Kim EH, *et al*. Anti-atherogenic effect of citrus flavonoids, naringin and naringenin, associated with hepatic ACAT and aortic VCAM-1 and MCP-1 in high cholesterol-fed rabbits. Biochem Biophys Res Commun 2001; 284(3): 681-8.
13. Edy M, Adam H, Anindyajati A. Natural products for cancer-targeted therapy: citrus flavonoids as potent chemo-preventive agents. Asian Pac J Cancer Prev 2012; 13(2): 427-36.
14. De Martel C, Ferlay J, Franceschi S, Vignat j, Bray F, Forman D, *et al*. Global burden of cancers attributable to infections: a review and synthetic analysis. Lancet Oncol 2012;13(6): 607-15.
15. Sankaranarayanan R, Ramadas K, Thara S, Muwonge R, Prabhakar J, Augustine P, *et al*. Clinical breast examination: preliminary results from a cluster randomized controlled trial in India. J Natl Cancer Inst 2011; 103(19): 1476-80.
16. Wang J, Yang Z, Lin L, Zhao Z, Liu Z, Liu X. Protective Effect of Naringenin Against Lead-Induced oxidative stress in rats. Biol Trace Elem Res 2012; 146 (3): 354-9.
17. Kim S, Park TI. Naringenin: a partial agonist on estrogen receptor in T47D-KBluc breast cancer cells. Int J Clin Exp Med 2013; 6(10): 890-9.
18. Filho JC, Sarria AL, Becceneri AB, Fuzer AM, Batalhao JR, da Silva CM, *et al*. Copper (II) and 2,2'-bipyridine complexation improves chemopreventive effects of naringenin against breast tumor cells. PLoS One 2014; 9(9): e107058.
19. Bulzomi P, Bolli A, Galluzzo P, Acconcia F, Ascenzi P, Marino M. The naringenin-induced proapoptotic effect in breast cancer cell lines holds out against a high bisphenol a background. IUBMB Life 2012; 64(8): 690-6.
20. Kanno S, Tomizawa A, Hiura T, Osanai Y, Shouji A, Ujibe M, *et al*. Inhibitory effects of naringenin on tumor growth in human cancer cell lines and sarcoma S-180-implanted mice. Biol Pharm Bull 2005; 28(3): 527-30.
21. Van Meeuwen JA, Korthagen N, de Jong PC, Piersma AH, van den Berg M. (Anti)estrogenic effects of phytochemicals on human primary mammary fibroblasts, MCF-7 cells and their co-culture. Toxicol Appl Pharmacol 2007; 221(3): 372-83.
22. Stapel J, Oppermann C, Richter DU, Ruth W, Briese V. Polyphenol compounds with anti-carcinogenic qualities: Effects of quercetin (flavonol), chrysin (flavon), kaempferol (flavanol), naringenin (flavanon) and hesperidin (flavanoid) on in vitro breast cancer. J Med Plant Res 2013; 7(29): 2187-96.
23. Lee SH, Ryu JK, Lee KY, Woo SM, Park JK, Yoo JW, *et al*. Enhanced anti-tumor effect of combination therapy with gemcitabine and apigenin in pancreatic cancer. Cancer Lett 2008; 259(1): 39-49.
24. Choi EJ, Kim GH. 5-Fluorouracil combined with apigenin enhances anticancer activity through induction of apoptosis in human breast cancer MDA-MB-453 cells. Oncol Rep 2009; 22(6): 1533-7.
25. Singh M, Bhatnagar P, Srivastava AK, Kumar P, Shukla Y, Gupta KC. Enhancement of cancer chemosensitization potential of cisplatin by tea

polyphenols poly(lactide-co-glycolide) nanoparticles. J Biomed Nanotechnol 2011; 7(1): 202.
26. Wright CJ. Estrogen receptor status in breast cancer. Can J Surg 1980; 23(4): 316-7.
27. Harris DM, Besselink E, Henning SM, Go VL, Heber D. Phytoestrogens induce differential estrogen receptor alpha- or Beta-mediated responses in transfected breast cancer cells. Exp Biol Med (Maywood) 2005; 230(8): 558-68.
28. Ruh MF, Zacharewski T, Connor K, Howell J, Chen I, Safe S. Naringenin: a weakly estrogenic bioflavonoid that exhibits antiestrogenic activity. Biochem Pharmacol 1995; 50(9): 1485-93.
29. Kretzschmar G, Zierau O, Wober J, Tischer S, Metz P, Vollmer G. Prenylation has a compound specific effect on the estrogenicity of naringenin and genistein. J Steroid Biochem Mol Biol 2010; 118(1-2): 1-6.
30. Nathan L, Shi W, Dinh H, Mukherjee TK, Wang X, Lusis AJ, *et al*. Testosterone inhibits early atherogenesis by conversion to estradiol: critical role of aromatase. Proc Natl Acad Sci U S A 2001; 98(6): 3589-93.
31. Zhou J, Gurates B, Yang S, Sebastian S, Bulun SE. Malignant breast epithelial cells stimulate aromatase expression via promoter II in human adipose fibroblasts: an epithelial-stromal interaction in breast tumors mediated by CCAAT/enhancer binding protein beta. Cancer Res 2001; 61(5): 2328-34.
32. Chen S. Aromatase and breast cancer. Front Biosci 1998; 3: d922-33.
33. Le Bail JC, Laroche T, Marre-Fournier F, Habrioux G. Aromatase and 17beta-hydroxysteroid dehydrogenase inhibition by flavonoids. Cancer Lett 1998; 133(1): 101-6.
34. Ibrahim AR, Abul-Hajj YJ. Aromatase inhibition by flavonoids. J Steroid Biochem Mol Biol 1990; 37(2): 257-60.
35. MäkeläS, Poutanen M, Lehtimäki J, Kostian M-L, Santti R, Vihko R. Estrogen-specific 17β-hydroxysteroid oxidoreductase type 1 (EC 1.1. 1.62) as a possible target for the action of phytoestrogens. Exp Biol Med 1995; 208(1): 51-9.
36. Sanderson JT, Hordijk J, Denison MS, Springsteel MF, Nantz MH, van den Berg M. Induction and inhibition of aromatase (CYP19) activity by natural and synthetic flavonoid compounds in H295R human adrenocortical carcinoma cells. Toxicol Sci 2004; 82(1): 70-9.
37. Deniz F, Dilek K, Hande M, Umit UM, Handan K. Ki-67 and caspase expression in breast carcinoma: does variance in locational sampling exist? Int J Clin Exp Pathol 2015; 8(9): 11305-13.
38. Devarajan E, Sahin AA, Chen JS, Krishnamurthy RR, Aggarwal N, Brun AM, *et al*. Down-regulation of caspase 3 in breast cancer: a possible mechanism for chemoresistance. Oncogene 2002; 21(57): 8843-51.
39. Janicke RU, Sprengart ML, Wati MR, Porter AG. Caspase-3 is required for DNA fragmentation and morphological changes associated with apoptosis. J Biol Chem 1998; 273(16): 9357-60.
40. Yang PM, Tseng HH, Peng CW, Chen WS, Chiu SJ. Dietary flavonoid fisetin targets caspase-3-deficient human breast cancer MCF-7 cells by induction of caspase-7-associated apoptosis and inhibition of autophagy. Int J Oncol 2012; 40(2): 469-78.
41. Ren W, Qiao Z, Wang H, Zhu L, Zhang L. Flavonoids: promising anticancer agents. Med Res Rev 2003; 23(4): 519-34.
42. Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, Banerjee S, Koenig KL, Shore RE, *et al*. A prospective study of endogenous estrogens and breast cancer in postmenopausal women. J Natl Cancer Inst 1995; 87(3): 190-7.
43. Orhan IE, Nabavi SF, Daglia M, Tenore GC, Mansouri K, Nabavi SM. Naringenin and atherosclerosis: a review of literature. Curr Pharm Biotechnol 2015; 16(3): 245-51.

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163241-49

Measuring Attitude and Practice of Physician toward Breaking Bad News to the Breast Cancer Patients: Development and Validation of a Questionnaire

Somaieh Borjalilu[a], Mojgan Karbakhsh*[b], Rasool Mirsharifi[c], Kamelia Davoodzadeh[d], Mahdi Aghili[e], Ahmad Kaviani[c, d]

[a] *Tehran University of Medical Sciences, Tehran, Iran*
[b] *Department of Community and Preventive Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[c] *Department of Surgery, Tehran University of Medical Sciences, Tehran, Iran*
[d] *Kaviani Breast Disease Institute, Tehran, Iran*
[e] *Department of Radiation Oncology, Radiation Oncology Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Received:
5 May 2016
Revised:
16 May 2016
Accepted:
27 May 2016

Keywords:
Physician,
bad news,
telling truth,
psychometric,
questionnaire development

ABSTRACT

Background: Breaking bad news to cancer patients is one of the important responsibilities in the oncology setting. The purpose of this study is develop and validate a new theoretically based tool for measurement of attitude and practice of physicians toward breaking bad news.

Methods: The psychometric properties of the scale were established by following the guidelines of Clark and Watson. In the first phase, a literature review was performed to create items; then items were assessed for content validity through individual interview (n = 12) and construct validity was assessed by using factor analysis. Reliability was evaluated by Cronbach's alpha. Research data was gathered from physicians working in breast cancer setting.

Results: A total of 12 expert reviews concluded that a large amount of items of attitude and practice questionnaires were important and essential (Content Validity Ratio > 0.73). The exploratory and confirmatory factor analyses for a sample of physicians (n = 200) indicated a 12-item of attitude scale with three factors: full disclosure, non-disclosure and individual disclosure. Cronbach's Alpha for the factors returned 0.746, 0.834 and 0.795, respectively. The exploratory and confirmatory factor analyses for a sample of physicians (n = 200) indicated a 20-item of practice scale with six factors: preparation, setting of the interaction, communicate well, use of the "cancer" word, patient's right to know and close the interview, and summarized. Cronbach's Alpha for the factors returned 0.765, 0.63, 0.65, 0.793, 0.759 and 0.7, respectively.

Conclusions: A resultant 12 items of attitude and 20 items of practice questionnaire were developed to assess how physicians are giving bad news to breast cancer patients. The reliability of the new tools needs to be evaluated for further studies. This new questionnaire will provide researchers and clinicians with a thorough and suitable instrument to measure belief and practice regarding disclosing the truth to breast cancer patients.

Address for correspondence:
Mojgan Karbakhsh, M.D.
Address: Department of Community and Preventive Medicine, School of Medicine, PoorSina St, Qods St, Enqelab Ave, Tehran University of Medical Sciences, Tehran, Iran
Tel/fax: +98 21 88962357
Email: mkarbakhsh@tums.ac.ir

Introduction

Being diagnosed with cancer is a highly distressing and in some cases devastating experience.[1,2] The majority of cancer patients will at least experience elevated levels of emotional distress. A smaller group will develop significant long-term psychological problems in reaction to

this potentially traumatic event.[3-6]

Breast cancer (BC) is also the global number one type of malignancy among women.[7] In addition, BC is known to be the leading type of cancer among Iranian women; and it remains a major health problem.[8] Depression and/or anxiety can be observed within BC patients at any stage of illness.[9,10] Being informed of the diagnosis of breast cancer is emotionally challenging.[11]

In the oncological setting, patients commonly receive news of life-threatening diagnoses.[12] Giving bad news is 'any news that negatively impacts the patient's sense of her or his future. The quality of conveying bad news to patients seems to be directly related to patients percived stress and anxiety, their adjustment to the bad news, coping and satisfaction with treatment and health outcome.[13]

There is a comprehensive model proposed by the World Health Organization (WHO) in its behavioral science learning model on communicating bad news.[14] Within this structure, Donovan describes a non-disclosure, a full-disclosure, and an individualized disclosure model. According to Donovan, these three disclosure models are related to global professional attitudes regarding the doctor–patient relationship, management, decision-making style and overall doctor–patient communication.

The traditional 'non-disclosure model' assumes that knowledge of the diagnosis causes distress and anguish, the doctor-patient relationship is depicted as a paternalistic one, in which the doctor makes the best choices for the patient.[15] The full-disclosure model suggests giving full information to each patient and stresses the ethical right of each individual on knowing the truth. This model makes the patient responsible for decision making. There are several number of comprehensive studies claiming that breast cancer patients who are involved in decision-making strategies were significantly more hopeful, and had an overall better medical condition than patients who adopt the previous passive role.[16]

The individualized disclosure model recognizes that each patient should receive the amount of information suitable for themselves. Previous research has shown that when it comes to bad news, there is a difference between what patients want to know.[17, 18] Several factors cause these differences, such as primary tumor site, socio-demographic characteristics, and coping with life-threatening illness.[14]

In order to convey such bad news, various approaches have been suggested, including SPIKES, ABCDE, BREAKS and 3-step communication.[19] The most widely used guideline, the SPIKES protocol,[1] suggests a six-step protocol for bad news delivering, especially applicable to cancer patients.[2] It is used as a guide for this sensitive practice and for practicing communication skills in this context.[20,21]

The acronym SPIKES refers to six steps recommended for breaking bad news: (i) Setting up the interview, (ii) assessing the patient's Perception, (iii) obtaining the patient's Invitation, (iv) giving Knowledge and information to the patient, (v) addressing the patient's Emotions with empathic responses and (vi) Strategy and Summary. Another guideline is ABCDE which includes five stages for breaking bad news: A-Advance preparation, B-Build a therapeutic environment/relationship, C-Communicate well, D-Deal with patient and family reactions, E-Encourage and validate emotions.[22]

Physician competence in conveying bad news influences patient adjustment to illness, anxiety, depression, hope and decision making.[23] Poor delivery of bad news stems from being too "frank", discussing bad news at an inappropriate place and time, and conveying a sense of no hope.[24] In a survey of 100 women with breast cancer, adjustment to illness 6 months after diagnosis was correlated with how they felt the bad news had been given.[25] Among models of communication of bad news, women with breast cancer prefer the patient-centered model. This model is characterized by dosing and timing of the communication of information according to patients' needs and encouraging them to share their feelings and concerns.[26] They were more satisfied with patient-centered communication and experienced the least increase in negative emotions.[27, 28] So, attitude and practice of the clinician especially in oncology settings for telling the truth to the patient is important. Harvey *et al.* had shown that most radiologists in breast imaging have little teaching for the giving breaking bad news.[29]

Understanding barriers for communicating bad news and general communication, are initial steps in learning this important task. Therefore, before any action, it is necessary to know what attitudes and practices exist toward this situation. So there needs to be useful tools for their proper measurement. Several questionnaire-based studies have examined physicians' attitudes toward bad news in different cultural and professional settings.[29-31] De valck developed the Attitudes towards Breaking Bad News Questionnaire to measure attitudes regarding disclosure of bad news.[14] The questionnaire has a low number of items and increasing them will surely increase its reliability. Although several protocols exist regarding breaking bad news, there have not been many attempts to adopt current guidelines into useful tools for measurement of practice. Consequently, the purpose of this study was to develop and examine the psychometric properties of the attitude and practice of physician toward breaking bad news questionnaire.

Methods

Following the guidelines of scale development by Clark and Watson, the attitude and practice of

physician toward breaking bad news questionnaire was developed and validated with the following five-step procedure: (1) the conceptualization of main construct, (2) review of literature, (3) creation of the initial item pool, (4) initial data collection (testing the item pool), and (5) psychometric evaluation.[32]

Clark and Watson began by conceptualizing the target construct.[32] The development of the attitudes regarding disclosure of bad news questionnaire was based on a World Health Organization (WHO) guideline in its behavioral science learning model on communicating bad news.[14] Within this framework, Donovan identify a non-disclosure, a full-disclosure, and an individualized disclosure model. The practice for the telling truth questionnaire was based on SPIKES model of breaking bad news and five steps of ABCDE.[33, 34] An initial literature review was conducted in order to identify previous research that had been conducted on physicians' attitude and practice for breaking bad news.[17, 18, 35-37] These scales were content analyzed to identify factors that had been previously included in measures of attitudes and practice for breaking bad news. The initial pool of 11 items for attitude section and 16 items for practice section was then created by a research team with a breast cancer surgeon, a community medicine specialist and a psychologist.

The questionnaire is composed of three main parts: the first part includes demographic information e.g. physicians' age, gender, practice environment and the estimated number of breast cancer patients that were provided with bad news in clinical settings. The second part is about physicians' attitudes towards disclosure of bad news. This scale comprises 11 items on which participants indicated their disagreement or agreement with item statements on a Likert type rating scale ranging from 1 (disagree strongly) to 5 (agree strongly). The final part is physician's practice toward breaking bad news. This scale comprises 16 items, each with a 5-point rating scale ranging from 1, never, to 5, always.

Assessment of the psychometric properties

The assessment of the validity of scale was performed by content validity and construct validity.

Content Validity: Content validity was evaluated through qualitative and quantitative methods. Qualitative review criteria given by McKenzie and Quantitative Review Content Validity Ratio Method by Lawshe were used.[38,39]

The panel of experts was the primary and fundamental step in establishing the content validity. In this step, 12 experts were consulted of whom 1 was a hematologist-oncologist, 4 were surgeons, 1 was a radiologist, 2 were medical and radio-therapeutic oncologists, 2 were pathologists, 1 was an oncology nurse, and 1 specialist in palliative medicine. The experts were academics/professionals with relevant experiences between 2 and 25 years (Mean±SD = 8.3±16.1) in research or work on breast cancer. They had on average informed over 10 patients of breast cancer in the last three months. The experts were invited via face to face contact, a covering letter was provided and the purpose of the study was explained to all the participants. Their consent for participation in the validation phase along with their demographics and experience details were obtained.

After taking consent from the experts, they were provided with a copy of the questionnaire and an inventory of questions to be answered by the experts. The experts were requested to provide their feedback on the overall questionnaire including directions, content area, and items of the questionnaire, need for revision of items, deletion of items and any additional suggestions. They assessed the necessity of the items using a three-point rating scale: (a) not necessary, (b) useful, but not essential, and (c) essential. The reviews given by all the expert members were collected by hand and appropriate changes were made after a thorough among discussion authors. The changes were again discussed with the experts, and consensus was achieved.

Construct validity: Construct validity refers to the degree to which the items on an instrument relate to the relevant theoretical construct.[40] Factor analysis is a statistical method commonly used during instrument development to cluster items into common factors and summarize the items into a small number of factors.[41]

To be included in the current study, Iranian physicians had to be board certified in surgery, radiotherapy, radiology, medical and radio-therapeutic oncology and nursing (faculty member, clinical fellows, specialists, residents) in Tehran medical centers that most of the breast cancer patients were referred. They were included in the study from December 2015 until March 2016. The samples were selected using a convenient sampling method. All the selected subjects consented to participate in the study. The recommended sample size of 5–7 physicians per item was found when conducting factor analysis as long as there were at least 200 physicians in the sample.[42] Physicians filled in the questionnaires anonymously to ensure that investigators were not aware of their name when the data were analyzed.

Reliability: Once the validity procedures were completed, the final version of the questionnaire was examined to assess its reliability. Estimators of reliability which were used in this study were internal consistency and Cronbach's alpha.

Ethical approval

The study was approved by the Research Ethical Committee of Tehran University of Medical

Sciences. All participants provided informed consent, and all rights of the participants were protected.

Statistical Methods

After receiving each expert's ratings, the content validity ratio (CVR) was calculated by applying the formula developed by Lawshe and then, construct validity was assessed.[39] Exploratory factor (EFA) was conducted within each domain with maximum likelihood extraction and oblimin rotation to accommodate possible correlation between factors. The most parsimonious factor solution was selected according to the following criteria: a good conceptual fit, high percentage of variance explained, high factor loading scores with minimal cross loading and stability of factors across different solutions. Items were considered to load on a factor if the factor loading was ≥ 0.30.[43] Confirmatory Factor Analyses (CFA) using maximum likelihood estimation was performed to evaluate model fit and confirm the structure in the data. We evaluated the fit of these models using various fit indices including the goodness-of-fit index (GFI), the adjusted goodness-of-fit index (AGFI), the comparative fit index (CFI), and the root mean square error of approximation (RMSEA). Specifically, these indexes have been considered as indicators of good fit when GFI, AGFI and the CFI values are greater than or equal to 0.90. RMSEA, values of 0.08 or less reflected adequate fit, and values of 0.06 or less represented excellent fit.[44] Data management and statistical analysis were performed using SPSS version 21.0 (SPSS Inc., Chicago, Illinois) and Amos™ version 18.0.

Results

There were 80 males (40.9%) and 120 females (59.1%) physicians, with a mean age of 37.87 years (range 21–60). Twenty-three percent (n=46) of the physicians were faculty member, 25% (n=50) residents, 10% (n=20) clinical fellows and 42% (n=84) were clinicians. Twenty-three percent (n=45) of the physicians were surgeons, 16% (n=31) hemato-oncologists, 15% (n=30) radiologists, 19% (n=38) radiation oncologists, 20% (n=42) nurses and 7 % (n=14) were midwives. The average work experience in oncology setting was 3.88±6.09 years. overall, fifty-nine percent (n=117) had informed less than 5 patients of breast cancer, 19% (n=36) between 5-10 and 21% (n=47) over 10 patients, in the last three months

Content Validity

According to the Lawshe table, an acceptable CVR value for 12 experts is 0.56 in this study [39], No item had a CVR less than 0.73. The mean CVR for the Attitude of Physician about Breaking Bad News scale was 0.9, indicating a satisfactory content validity (see Table 1) and the mean CVR for the Practice of Physician about Breaking Bad News scale was 0.83 indicating a good content validatity (see Table 2).

Five experts argued that the important challenge in communicating about telling truth to breast cancer patients was family's requests about withholding information from patients, and patients having their diagnosis withheld from them by concerned family members. Therefore, we added two questions and changed two questions to cover this dilemma. The P9 "At first, I inform the patient about the diagnosis, then share with the family, in the event of patient's will and desire" and P14 "I disclose bad news in presence of patient's family for their support" were added.

Four experts argued that the use of "cancer" word avoidance applied to all individuals involved in the disclosure of cancer as well as the physical environment and culminated in the concealment of cancer. The use of the word "cancer" as well as related terminology was avoided during almost all communication, even when patients were informed of their diagnosis. Physicians tended not to use the language indicative of cancer in their daily communication with patients or family members. Therefore, we added one question in attitude: A12" Saying the word "cancer" leads to panic in patients" and P12: "I informed patients about diagnosis and treatment without use of word "cancer" and P13 "I avoid using the word "cancer" as a diagnosis when telling truth to patients". The revised Attitude and Practice of Physicians toward Breaking Bad News Questionnaire comprises 12 items for the attitude scale and 20 items for practice scale.

Construct validity of the scale

Attitude of Physician about Breaking Bad News scale: EFA using the Principal Axis Factoring extraction method with Promax (oblique) rotation on the twelve items of the scale was performed in sample (n = 200) to examine its factorial structure and construct validity. The appropriateness for conducting the EFA was confirmed by the Kaiser–Meyer–Olkin measure of sampling adequacy (KMO = .787) and Bartlett's test of sphericity ($\chi 2$ = 571/833, p < .0001) results. As expected, the analyses resulted in a 3 factor solution with an eigenvalue over 1 and factor loadings of 0.30 or above, explaining 54.25% of the variance.

After performing factor analysis, the subscales were renamed, as shown in Table 1. The final version of the questionnaire thus consisted of 12 items divided into the following subscales: Full-disclosure (5 items: A11, A10, A7, A3, A1), Non-disclosure (5 items: A8, A9, A5, A12, A4), and Individualized disclosure (2 items: A6, A2). All of the 12 item subscales proved to be internally consistent (Full-

disclosure α = 0.746, Non-disclosure α = 0.834, and Individualized disclosure α = 0.795). Table 1 presents the twelve-selected items and their factor loadings. Results confirmed the intended 3-factor structure of the attitude questionnaire. The 12-item scale with a correlated 3-factor structure resulted in an acceptable model fit (RMSEA = 0.01, CFI = 0.729, AGFI = 0.76 and CFI= 0.834). There was a reasonable overall fit between the model and the observed data.

Table 1. Factor loadings of the items of the Attitude about Breaking Bad News (n = 200)

Items	Number of items	Non-disclosure	Full-disclosure	Individualized disclosure	CVR
Informing patients only makes them worry and feel anxious.	a8	0.806			1
News of breast cancer diagnosis takes away the patient's hope.	a9	0.793			0.86
Disclosure is damaging to the Patients' Quality of Life.	a5	0.787			1
Mentioning the word "cancer" leads to panic in patients.	a12	0.737			1
If the family asks for information to be withheld from patients, the patient should not be told about the diagnosis of cancer.	a4	0.720			0.73
Disclosure of the diagnosis of breast cancer to patients is necessary.	a11		0.751		1
The decision for selecting the type of treatment is made easier when informed them.	a10		0.701		0.86
Confusion and ambiguity for the patient and family are avoided by informing them.	a7		0.640		0.73
Disclosure of bad news ,enables patients to further cooperate during treatment.	a3		0.592		1
Most of patients want to know the truth about their illness.	a1		0.525		1
Disclosure of bad news should be done according to psycho-emotional status of individual patients.	a6			-0.767	1
If the patient doesn't like to know what the definitive diagnosis is, their request should be respected.	a2			0.631	0.73
Eigenvalue		3.367	2.113	1.03	
Amount of variance explained by the factor (%)		28.062	17.612	8.58	
Total amount of variance explained by the factor (%)		28.062	45.674	54.254	

Physicians Practice about Breaking Bad News scale: An EFA was carried out to explore the factor structure of the data. The analyses resulted in a 6 factor solution with an eigenvalue over 1 and factor loadings of 0.30 or above, explaining 60.85% of the variance.

After performing factor analysis, the subscales were renamed. As can be seen in Table 2, the final version of the questionnaire consisted of 20 items divided into the following subscales: Preparation (4 items: P15, P10, P11, P4), Setting of the interaction (3 items: P1, P2, P5), Communicate well (4 items: P7, P8, P3, P14), Use the "cancer" word (2 items: P13, P12), Patient's right to know (2 items: P9, P6) and Close the interview and summarize (5 items: P18, P19, P17, P20, P16). All of 20 items proved to be internally consistent (Preparation: α = 0.765, Setting of the interaction: α = 0.63, Communicate well: α = 0.65, Use the "cancer" word: α = 0.793, Patient's right to know: α = 0.759 and close the interview and summarize: α = 0.7). Table 2 presents the twelve-selected items and their factor loadings. Results of CFA confirmed the intended 6-factor structure of the practice questionnaire. The 20-item scale with a correlated 3-factor structure resulted in an acceptable model fit (RMSEA = 0.05, CFI = 0.859, AGFI = 0.813 and CFI= 0.744). There was an acceptable overall fit between the model and the observed data.

Discussion

The object of this study was to develop a new scale of attitude and practice of breaking bad news and validate it. Based on Donovan's disclosure model and SPIKES protocol and ABCDE the attitude and practice of breaking bad news was developed.[14] To achieve this goal, two steps were taken. Firstly, a psychometric scale containing 12 items for attitude scale and 20 items for practice scale was developed by experts in the field. Then content validity was achieved through inclusion of stakeholders, such as physicians and residents. Including items related to use of the word "cancer" for the process of giving bad news were suggested. Studies have shown that using the word "cancer" can result in cognitive disruption for the patients and emotional distress.[29,37,45,46] So one of the challenges of clinicians in telling truth to cancer patients is whether to use or not use the word "cancer". Therefore, it's necessary to measure attitude and clinical practice in this situation. Another comment was attention to the involvement of family members in this process. Studies have shown that families' request for non-disclosure was the first and "biggest" barrier to truthful communication, which challenged their ability to talk honestly to patients at the outset.[47] Hence, cultural influences sometimes override professional consideration. Sometimes the information is shared with the relatives without patient's permission.[48-50] Considering this as neglecting patients' rights, we added items to the questionnaire. .

Secondly, the newly developed tool was used for psychometric examination. The result of EFA

Table 2. Factor loadings of the items of the physicians' practice about breaking bad news (n = 200)

Items	Number of items	Preparation	Close the interview and summarize	Communicate well	Use of the "cancer" word	Setting of the interaction	Patient's right to know	CVR
I offer support and empathy to the patient by body language and eye contact.	P15	0.815						0.86
I prepare patient for bad news by setting up an introduction.	P10	0.744						1
I inform patients about diagnosis, treatment and possible side effects in separate steps.	P11	0.729						0.78
I wear medical gowns when breaking bad news.	P4	0.718						0.73
After I introduce methods of treatment of breast cancer, I leave patients free to choose from them.	P18		0.795					0.86
I reassure the patient that I will do my utmost best for their health.	P19		0.717					1
After breaking bad news, I schedule another meeting with the patient.	P17		0.671					0.73
I introduce patients to psychosocial support team after disclosure of breast cancer.	P20		0.626					0.73
I remind her that everything is in the hands of god.	P16		0.403					0.86
If patients are silent or crying after hearing the truth, I allow them to express their emotions.	P7			-0.619				0.73
I avoid talking on the phone when breaking bad news.	P8			-0.615				0.86
I use medical jargon to hide the truth about the disease.	P3			0.609				0.73
I disclose bad news in the presence of patient's family to use their support.	P14			.539				1
I avoid using the word "cancer" as a diagnosis to patients.	P13				0.779			1
I inform patients about diagnosis and treatment plans, without using the word "cancer".	P12				0.775			1
For giving bad news, I prepare a quiet, private place.	P1					0.809		1
I choose a proper time to break the bad news to spend more time with the patient.	P2					0.785		0.86
I sit down next to the patient when telling truth.	P5					0.574		0.73
Firstly, I inform patient about diagnosis then, share with family, if the patient is willing.	P9						0.801	1
I talk to patients directly and without reservation about disease.	P6						0.673	1
Eigenvalue		4.158	2.397	1.783	1.38	1.258	1.193	
Amount of variance explained by the factor (%)		20.789	11.985	8.914	26.908	6.289	5.966	
Total amount of variance explained by the factor (%)		20.789	32.774	41.688	48.596	54.885	60.851	

demonstrated a three-factor solution for attitude scale using the twelve items and was later confirmed by the CFA results that provided fit and the proposed three-factor solution as model optimally fit the data. According to Donovan's disclosure model, three distinguished models (non-disclosure, full-disclosure, and individual disclosure) are used regarding doctor-patient communication.[14] Within this field, different prototypes of disclosure style are according to the amount of patient autonomy and physician authority.[51] The Cronbach alpha coefficient shown there has good internal consistency between items of subscale.

The result of EFA demonstrated six-factor solution for practice scale using the twenty items and was later confirmed by the CFA result that provided fit and confirmed six-factor solution. Based on SPIKES and ABCDE the scale of physician practice for giving bad news, the first component is *preparation***.** This factor shows the physician's preparedness for communication with the patient. Studies have shown that some physicians indicated stress when telling truth to patients.[52, 53] Therefore, preparation should be taken into consideration in order to decrease stress. Physicians are recommended to mentally prepare for the interaction with the patient, review what information needs to be communicated, rehearse key steps and phrases in the interaction and plan how emotional support will be provided. These are critical to be considered before giving bad news.[54]

The second component is *setting of the interaction***.** All of the protocols for giving bad news pay attention to appropriate environment. An important factor in this section is arranging for privacy, managing time constraints and interruptions, sitting down and making a connection with the patient and ensuring patient and family that appropriate social support are present.[49,54]

The third component is *communicate well.* One of

the stages of ABCDE protocol for effective delivery of bad news is "communicate well".[34] Communication is an essential part in the management of cancer patients. The impact of this communication affects the patient's emotional adjustments, treatment compliance and overall health outcome.[55] Studies have shown that higher patient–physician relationship and physician attentiveness and empathy were associated with greater patient satisfaction, increased self-efficacy, and reduced emotional distress.[56] Effective communication between clinician and patient leads to information sharing, emotional responses, management of uncertainty, and decision making.[57]

The forth component is *use of the word "cancer".* As mentioned earlier, the word "cancer" is one of the communication challenges in cancer patients and physicians tend not to use the language indicative of cancer in their daily communication with patients or family members.[37]

The fifth component is *patient's right to know.* While most patients ask for full information about their diagnosis, it's not the case in others patients.[33] It is important to ascertain whether the patient wants to have information about their diagnosis and attention to desire for involving the family in this process.

The last component is *close the interview and summarize.* The last section of interview with patients delineates the next steps for them and the family, including additional tests or interventions.[54] Patients who have a plan for the life are less likely to feel stress and uncertainty.[33] It's so much better if physicians recommend a schedule with goal and landmark and provide psychosocial support for patients. All components are important in practice of clinician for delivering bad news to cancer patients.

This questionnaire is at an early stage of development, requiring further psychometric testing. For example, test-retest reliability and criterion validity change will enhance confidence in the measure's psychometric properties. The current study demonstrated that the physician's attitude and practice toward breaking bad news scale is a reliable and valid tool for the measurement of attitude and practice of clinicians, by distinguishing between three models of disclosure and attempted to design a practical scale based on standard protocols for breaking bad news. The newly developed Attitude and practice of Physician toward Breaking Bad News is an easy-to-utilize tool available to physicians especially in breast cancer.

Acknowledgments

The author would like to acknowledge the assistance and cooperation of Dr Seyed Hasan Emami Razavi, Dr Abbas Rabani, Dr Nahid Nafisi, Dr Azadeh Jolai, Dr Adele Yazdankhah, Dr Farhad Shahi, Dr Sanambar Sadighi, Dr Zahra Ahmadinejad, Dr Fereshteh Ensani, Dr Asieh Olfatbakhsh, Dr Toktam Beheshtian and Dr Mansour Jamali Zavarehei for the content validate of questionnaire and cooperation all of physicians for fill out questionnaires

Conflict of Interest

The study was supported by Tehran University of Medical Sciences (Virtual School and Faculty of Medicine). The authors declare that there is no conflict of interests.

References

1. Jim HS, Jacobsen PB. Posttraumatic stress and posttraumatic growth in cancer survivorship: a review. Cancer J 2008; 14(6): 414-9.
2. Koutrouli N, Anagnostopoulos F, Potamianos G. Posttraumatic stress disorder and posttraumatic growth in breast cancer patients: a systematic review. Women Health 2012; 52(5): 503-16.
3. Jarrett N, Scott I, Addington-Hall J, Amir Z, Brearley S, Hodges L, *et al.* Informing future research priorities into the psychological and social problems faced by cancer survivors: a rapid review and synthesis of the literature. Eur J Oncol Nurs 2013; 17(5): 510-20.
4. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, *et al.* Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. lancet Oncol 2011; 12(2): 160-74.
5. Stein KD,Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. Cancer 2008; 112(S11): 2577-92.
6. Kangas M, Henry JL, Bryant RA. Predictors of posttraumatic stress disorder following cancer. Health Psychol 2005; 24(6): 579-85.
7. BogaartsMP, Den Oudsten BL, Roukema JA, Van Riel JM, Beerepoot LV, De Vries J. Development of the Psychosocial Distress Questionnaire-Breast Cancer (PDQ-BC): a breast cancer-specific screening instrument for psychosocial problems. Support Care Cancer 2011; 19(10): 1485-93.
8. Jazayeri SB, Saadat S, Ramezani R, Kaviani A. Incidence of primary breast cancer in Iran: Ten-year national cancer registry data report. Cancer Epidemiol. 2015; 39(4): 519-27.
9. Baumeister H, Kriston L, Bengel J, Härter M. High agreement of self-report and physician-diagnosed somatic conditions yields limited bias in examining mental–physical comorbidity. J Clin Epidemiol 2010; 63(5): 558-65.
10. Härter M, Reuter K, Aschenbrenner A, Schretzmann B, Marschner N, Hasenburg A, *et al.* Psychiatric disorders and associated factors in cancer: results of an interview study with patients in inpatient, rehabilitation and outpatient treatment. Eur J Cancer 2001; 37(11): 1385-93.

11. Azu MC, Jean S, Piotrowski J-M, O'Hea B. Effective methods for disclosing breast cancer diagnosis. Am J Surg 2007; 194(4): 488-90.
12. Fallowfield L, Jenkins V. Communicating sad, bad, and difficult news in medicine. Lancet 2004; 363(9405): 312-9.
13. Fallowfield L, Jenkins V. Effective communication skills are the key to good cancer care. Eur J Cancer 1999; 35(11): 1592-7.
14. De Valck C, Bensing J, Bruynooghe R. Medical students' attitudes towards breaking bad news: An empirical test of the World Health Organization model. Psychooncology 2001; 10(5): 398-409.
15. Murgic L, Hébert PC, Sovic S, Pavlekovic G. Paternalism and autonomy: views of patients and providers in a transitional (post-communist) country. BMC Med Ethics 2015; 16(1): 65.
16. BookerMJ, Simmonds RL, Purdy S. Patients who call emergency ambulances for primary care problems: a qualitative study of the decision-making process. Emerg Med J 2013; 31(6): 448-52.
17. Khalil RB. Attitudes, beliefs and perceptions regarding truth disclosure of cancer-related information in the Middle East: A review. Palliat Support Care 2013; 11(1): 69-78.
18. Fumis R, DeCamargo B, Del Giglio A. Physician, patient and family attitudes regarding information on prognosis: a Brazilian survey. Ann Oncol 2012; 23(1): 205-11.
19. Uprety D, Kasireddy V. Breaking Bad News in Cancer Patients. SM J Community Med 2015; 1(1): 1005.
20. Deshields T, Tibbs T, Fan MY, Taylor M. Differences in patterns of depression after treatment for breast cancer. Psychooncology 2006; 15(5): 398-406.
21. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ 2005; 330(7493): 702.
22. Fields SA, Johnson WM. Physician-patient communication: breaking bad news. W V Med J 2012; 108(2): 32-5.
23. Back AL. Communicating bad news. West J Med 2002; 176(3): 177-80.
24. Norton SA, Talerico KA. Facilitating end-of-life decision-making: strategies for communicating and assessing. J Gerontol Nurs 2000; 26(9): 6-13.
25. Roberts CS, Cox CE, Reintgen DS, Baile WF, Gibertini M. Influence of physician communication on newly diagnosed breast patients' psychologic adjustment and decision-making. Cancer 1994; 74(S1): 336-41.
26. Ford S, Fallowfield L, Lewis S. Doctor-patient interactions in oncology. Soc Sci Med 1996; 42(11): 1511-9. .
27. Mast MS, Kindlimann A, Langewitz W. Recipients' perspective on breaking bad news: how you put it really makes a difference. Patient Educ Couns 2005; 58(3): 244-51.
28. Lobb EA, Butow PN, Kenny DT, Tattersall MH. Communicating prognosis in early breast cancer: do women understand the language used? Med J Aust 1999; 171(6): 290-4.
29. Harvey JA, Cohen MA, Brenin DR, Nicholson BT, Adams RB. Breaking bad news: a primer for radiologists in breast imaging. J Am Coll Radiol 2007; 4(11): 800-8.
30. Grassi L, Giraldi T, Messina E, Magnani K, Valle E, Cartei G. Physicians' attitudes to and problems with truth-telling to cancer patients. Support Care Cancer 2000; 8(1): 40-5.
31. Spiegel W, Zidek T, Maier M, Vutuc C, Isak K, Karlic H, *et al.* Breaking bad news to cancer patients: survey and analysis. Psychooncology 2009; 18(2): 179-86.
32. Clark LA, Watson D. Constructing validity: Basic issues in objective scale development. Psychol Assess 1995; 7(3): 309-19.
33. Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP. SPIKES-A six-step protocol for delivering bad news: application to the patient with cancer. Oncologist 2000; 5(4): 302-11.
34. Rabow MW, Mcphee SJ. Beyond breaking bad news: how to help patients who suffer. West J Med 1999; 171(4): 260-3.
35. Shaw J, Brown R, Heinrich P, Dunn S. Doctors' experience of stress during simulated bad news consultations. Patient Educ Couns 2013; 93(2): 203-8.
36. Aljubran AH. The attitude towards disclosure of bad news to cancer patients in Saudi Arabia. Ann Saudi Med 2010; 30(2): 141-4.
37. Zamanzadeh V, Rahmani A, Valizadeh L, Ferguson C, Hassankhani H, Nikanfar AR, *et al.* The taboo of cancer: the experiences of cancer disclosure by Iranian patients, their family members and physicians. Psychooncology 2013; 22(2): 396-402.
38. MacKenzie SB, Podsakoff PM, Podsakoff NP. Construct measurement and validation procedures in MIS and behavioral research: Integrating new and existing techniques. MIS Q 2011; 35(2): 293-334.
39. Lawshe CH. A quantitative approach to content validity. Pers Psychol 1975; 28(4): 563-75.
40. DeVon HA, Block ME, Moyle-Wright P, Ernst DM, Hayden SJ, Lazzara DJ, *et al.* A psychometric toolbox for testing validity andreliability. J Nurs Scholarsh 2007; 39(2): 155-64.
41. Norris M, Lecavalier L. Evaluating the use of exploratory factor analysis in developmental disability psychological research. J Autism Dev Disord 2010; 40(1): 8-20.

42. Floyd FJ, Widaman KF. Factor analysis in the development and refinement of clinical assessment instruments. Psychol Assess 1995; 7(3): 286-99.
43. Izquierdo I, Olea J, Abad FJ. Exploratory factor analysis in validation studies: uses and recommendations. Psicothema 2014; 26(3): 395-400.
44. Bentler PM, Bonett DG. Significance tests and goodness of fit in the analysis of covariance structures. Psychol Bull 1980; 88(3): 588-606.
45. Hermelink K, Voigt V, Kaste J, Neufeld F, Wuerstlein R, Bühner M, *et al*. Elucidating Pretreatment Cognitive Impairment in Breast Cancer Patients: The Impact of Cancer-Related Post-Traumatic Stress. J Natl Cancer Inst 2015; 107(7): djv099.
46. Dean M, Street RL. A 3-stage model of patient-centered communication for addressing cancer patients' emotional distress. Patient Educ Couns 2014; 94(2): 143-8.
47. Chittem M, Butow P. Responding to family requests for nondisclosure: The impact of oncologists' cultural background. J Cancer Res Ther 2015; 11(1): 174-80.
48. Al-Mohaimeed AA, Sharaf FK. Breaking bad news issues: a survey among physicians. Oman Med J 2013; 28(1): 20-5.
49. Rollins LK, Hauck FR. Delivering bad news in the context of culture: a patient-centered approach. J Clin Outcomes Manag 2015; 22(1): 21-6.
50. Tang ST, Liu T-W, Lai M-S, Liu L-N, Chen C-H, Koong S-L. Congruence of knowledge, experiences, and preferences for disclosure of diagnosis and prognosis between terminally-ill cancer patients and their family caregivers in Taiwan. Cancer Invest 2006; 24(4): 360-6.
51. Emanuel EJ, Emanuel LL. Four models of the physician-patient relationship. JAMA 1992; 267(16): 2221-6.
52. Ptacek J, Ptacek JJ, Ellison NM. "I'm Sorry To Tell You..." Physicians' Reports of Breaking Bad News. J Behav Med 2001; 24(2): 205-17.
53. Shaw J, Brown R, Dunn S. The impact of delivery style on doctors' experience of stress during simulated bad news consultations. Patient Educ Couns 2015; 98(10): 1255-9.
54. Ahmady AE, Sabounchi SS, Mirmohammad sadeghi H, Rezaei A. A Suitable model for breaking bad news: review of recommendations. J Med Res 2014; 2014: 1-15.
55. Hasan I, Rashid T. Clinical communication, cancer patients & considerations to minimize the challenges. J Cancer Ther 2016; 7(02): 107-113.
56. Zachariae R, Pedersen CG, Jensen AB, Ehrnrooth E, Rossen PB, von der Maase H. Association of perceived physician communication style with patient satisfaction, distress, cancer-related self-efficacy, and perceived control over the disease. Br J cancer 2003; 88(5): 658-65.
57. Maguire P, Pitceathly C. Key communication skills and how to acquire them. BMJ 2002; 325(7366): 697-700.

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163250-55

What Can Computed Tomography Scans of the Thorax Show after Breast Surgery?

Afsaneh Alikhassi[a], Nasrin Ahmadinejad*[a], Marzieh Lashkari[b], Hedieh Akbari[a]

[a] *Department of Radiology, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran*
[b] *Department of Radiation Oncology, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Received:
17 April 2016
Revised:
19 May 2016
Accepted:
10 June 2016

Keywords:
Scar,
seroma,
computed tomography scan,
breast conserving surgery,
modified radical mastectomy

ABSTRACT

Background: Postoperative breast abnormalities after breast conserving surgery or modified radical mastectomy are frequently overlooked and inaccurately assessed or reported using multidetector computed tomography (MDCT). These inaccurate results may have legal ramifications for the clinicians, cause patients avoidable anxiety, and lead to additional unnecessary diagnostic follow-up testing and costs.

Methods: The patients with a history of breast cancer who had undergone breast-conserving surgery or modified radical mastectomy up to 6 months prior to undergoing a thoracic MDCT scan consented and enrolled in this study. These patients underwent a thoracic MDCT scan either because of respiratory or cardiac clinical symptoms or as part of breast cancer staging.

Results: Forty women were included in this study. Different postoperative breast changes observed on thoracic MDCT scans including fibrous scar tissue, fat necrosis, seroma, abscess, hematoma, and recurrent and residual tumor were described.

Conclusions: MDCT scans offer sufficient evidence in many postoperative cases to allow a confident diagnosis. General radiologists who review thoracic MDCT scans should know how to characterize breast lesions incidentally found on MDCT scans after breast surgeries. This information would enhance the value of the radiologist's report for appropriate case management.

Introduction

It is common to miss breast abnormalities in multidetector computed tomography (MDCT) or have them inaccurately reported, especially after previous breast surgeries. It is important for general radiologists to characterize breast lesions incidentally found on MDCT scans as benign, indeterminate, or sufficiently suspicious to justify further follow-up testing.

Breast changes and pathologies after surgery can be similar to malignancies.[1] Reporting these lesions as recurrent or residual tumor can cause unnecessary stress for patients after their recent treatment, or additional expensive diagnostic follow-up testing.[2,3] It may also have legal ramifications for the responsible surgeon or oncologist. Therefore, it is important to be familiar with the appearance of postoperative changes on MDCT scans. Obtaining an accurate medical history, including the time and type of any previous biopsy or surgery, is crucial for a correct MDCT scan diagnosis. Accurate description and classification of breast lesions detected on

Address for correspondence:
Nasrin Ahmadinejad, MD
Address: Department of Radiology, Cancer Institute, Imam Khomeini Hospital, Keshavarz Blvd., Tehran, 3314114197, Iran
Tel: +98 21 61192849
Fax: +98 21 66581626
Email: n_ahmadinejad@yahoo.com

The purpose of this study was to familiarize the readers with the changes in the appearance of breast tissue after breast surgery on MDCT scans, with an emphasis on the ability of the MDCT scan to provide a correct diagnosis.

Methods

Written informed consent was taken from all enrolled patients. This study evaluated women with pathologically confirmed breast cancer who had undergone breast surgery (breast conserving surgery or modified radical mastectomy) and were still under observation by an oncologist or surgeon during their follow-up period. These women underwent a thoracic CT scan either because they showed clinical symptoms (respiratory or cardiac), or as part of breast cancer staging or to evaluate the progression of the disease.

The surgery was up to 6 months prior to undergoing a thoracic CT scan and the MDCT scans were taken using a 64 multidetector CT scanner (GE Healthcare) following the same protocol for all patients. Both unenhanced and contrast–enhanced scans were obtained, using a standard protocol, from the lung apices through the adrenal glands using the following imaging parameters: section thickness, 0.625 mm; pitch, 1.05–1.25; tube potential, 120 kV. Contrast-enhance CT was performed with the intravenous (IV) administration of 100 mL iopromide (Ultravist 300; Schering, Berlin, Germany) using a mechanical power injector at a rate of 2.0–3.0 mL/sec. The scanning was performed 50 seconds after the injection of the contrast medium. The imaging parameters were identical to those used for unenhanced CT scan. The images were obtained using a standard soft-tissue algorithm and a retrospective lung algorithm. The MDCT scans were reviewed by general radiologists. All the images were re-evaluated by the authors, and the images were reviewed only in transverse planes. Depending on the MDCT scan results, either a mammography examination with routine craniocaudal and mediolateral oblique projections, or an ultrasonography was performed for more in-depth evaluation and confirmation of the nature of the pathology visible on the MDCT scan. The mammography examination was performed using the Selenia direct digital mammography system (Hologic Inc.) and the ultrasonography examination was performed using a MyLab™ machine (Esaote, Genoa, Italy) with a linear array transducer (7.5–12 MHz; Esaote, Genoa, Italy).

Results

From November 2014 to November 2015, 40 women were enrolled in this study. Their median age was 48 years (range: 36–63 years). None of them were pregnant, or had contraindications for IV contrast, renal malfunction, or previous allergic reactions to IV contrast.

These 40 patients had a known history of breast cancer and had undergone previous breast cancer surgery: 29 underwent breast conserving surgery and 11 underwent modified radical mastectomy. In 32 patients, a thoracic MDCT scan was requested by their oncologist either as part of breast cancer staging or to evaluate the progression of the disease. The remaining 8 women underwent a scan because of respiratory or cardiac symptoms.

In 30 patients, postoperative changes with scar tissue without a detailed description or explanation of the type of the postoperative change were recorded in their thoracic MDCT scan reports by the general radiologist. However, in the remaining 10 women, an indeterminate mass, spiculated mass, cancer recurrence, or lymphadenopathy was reported. A more detailed evaluation using mammography and ultrasonography confirmed that only 2 of these 10 patients had tumor recurrence. The other 8 had a seroma, scar, hematoma, or fat necrosis.

Discussion

Mammography is currently the golden standard for breast cancer screening. Breast ultrasonography and magnetic resonance imaging (MRI) are the other preferred imaging methods for the detection and characterization of breast diseases, while MDCT scans are not considered the primary method to evaluate specific breast lesions. Sometimes breast lesions can be find in MDCT accidentally as it is done because of other reasons such as respiratory or cardiac problems. Incidental breast lesions detected on unenhanced or contrast-enhanced MDCT scans have been presented in a few previous articles where the authors evaluated the incidence, imaging MDCT scan appearance, and pathologic outcomes of the breast lesions detected on the MDCT scan.[1-8]

The advantages of MDCT are good contrast resolution, and providing cross sections and a large field of view.[9, 10] It is also helpful in dense breasts, or deep lesions near the chest wall with the possibility of chest wall involvement.[2,10,11]

A general radiologist should know how to detect and characterize breast changes observed on MDCT scans after surgery as either normal scar tissue, surgical complications (such as hematoma, fat necrosis, seroma, abscess), indeterminate, residual/recurrent tumor, or sufficiently suspicious lesions, which would justify further follow-up testing.

It can be concluded from the literature that in approaching the detected breast lesions on MDCT, it would be better to describe the shape (round, oval, irregular), margins (circumscribed, microlobulated and spiculated), Hounsfield units (characterized as air, fat, fluid or soft tissue), and pattern of enhancement (homogeneous, heterogeneous, rim enhancing, central enhancement, or enhancing internal septations).[1-12]

Residual/Recurrent tumor

Postoperative changes may mimic cancer. Previous studies suggest that irregular margins, shape and rim enhancement are the most important signs for malignancy on MDCT scans.[12, 13] Time-density curves, similar to enhancement curves on breast MRI, can also be used in MDCT scans, where the washout and plateau patterns are predictive of malignancy.[14] Studies have found that washout patterns on post contrast images have a high positive predictive value but lack high sensitivity and specificity.[13, 15] Overlapping tissues decrease on CT, with better demonstration of the border of tumors.[15] CT may also show a contralateral tumor.[11, 16, 17] Calcification is a frequent finding in the breast. Microcalcifications (smaller than 0.5 mm) are more likely to be malignant and are usually too small to be seen on a thoracic MDCT owing to the limited spatial resolution. Only larger calcifications can be seen on MDCT scans and are usually benign.[14]

In a case of potential tumor recurrence in this study, a mass with soft tissue Hounsfield unit and mild enhancement was seen in the midline of the left side with extension on the surface of the sternal body (Fig. 1).

A confirmatory ultrasound was carried out and showed a hypoechoic irregular border mass appearing to contain soft tissue (Fig. 2). A biopsy confirmed tumor recurrence. Another case of tumor recurrence demonstrated a malignant appearing lymph node (the same morphologic criteria as for the ultrasound were used) with a short axis of more than 10 mm without a fatty hilum in the right axilla. The patient had a history of previous breast conserving surgery, and malignant appearing lymph nodes were seen in the mediastinum simultaneously (Fig. 3).

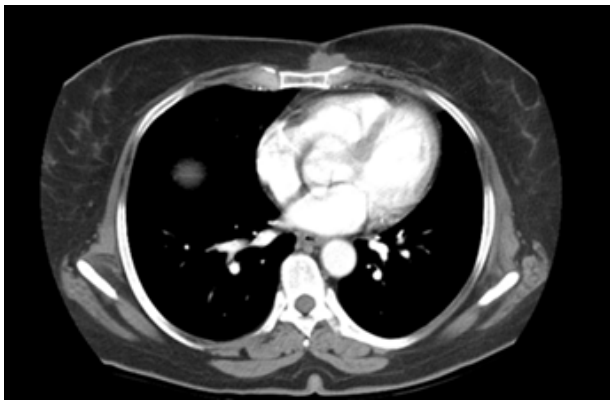


Figure 1. Axial contrast-enhanced MDCT scan showed a soft tissue mass with mild enhancement on the left side of the midline on the surface of the sternal body in a patient with previous left breast conserving breast cancer surgery.

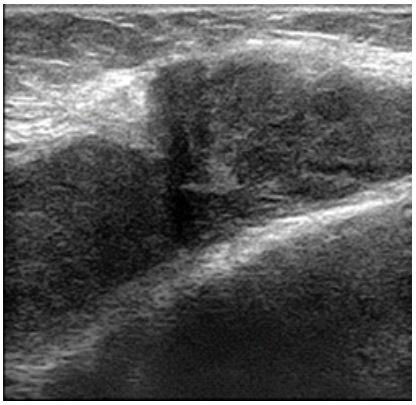


Figure 2. A confirmatory ultrasound showed a hypoechoic irregular border mass appearing to contain soft tissue, compatible with a visible mass on the MDCT scan; a biopsy confirmed the mass to be malignant, confirming the diagnosis of tumor recurrence.

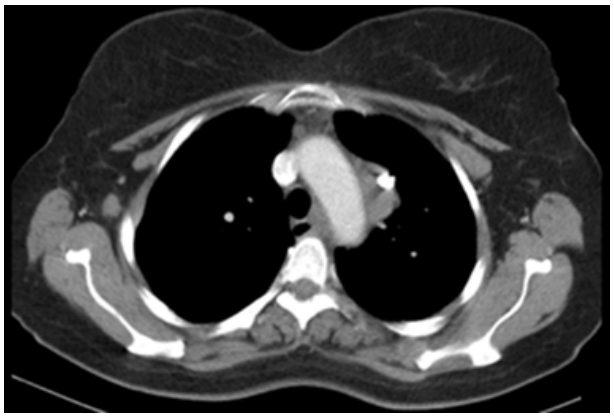


Figure 3. A 45-year-old woman with a previous history of right breast conserving cancer surgery presented with a few prominent lymph nodes in the right axilla and mediastinum, suggesting a malignancy.

Fibrous scar tissue

An accurate medical history, such as the time and type of any previous surgery, as well as signs and symptoms in the patient, such as feeling the presence of a mass and fever, are all important for a correct diagnosis. The presence of surgical clips on a MDCT scan is a good indicator of previous surgery. Normal scar tissue can show malignant features such as spiculated mass or tissue distortion but in the setting of previous surgery, these appearances are usually not a cause for concern.[18] Correlating prior surgery locations and opaque surgical markers are very important in differentiating a scar from cancer. Masses or lesions, especially when not exactly situated at the site of a prior surgery, should be regarded as suspicious. A malignancy will grow over time while any post-treatment change will remain stable or decrease over time. Figures 4 and 5 show examples of normal scar tissue.

Seroma

Seromas may be seen after surgery on MDCT scans. A seroma will appear as a well-defined oval-shaped mass at the site of a previous mass resection (Fig.6). It will not always show low attenuation fluid density. Other associated postoperative tissue such as distortion, metallic clips, or air-fluid levels will help make a diagnosis. After IV contrast, a thin peripheral enhancement can be seen.[1,19]

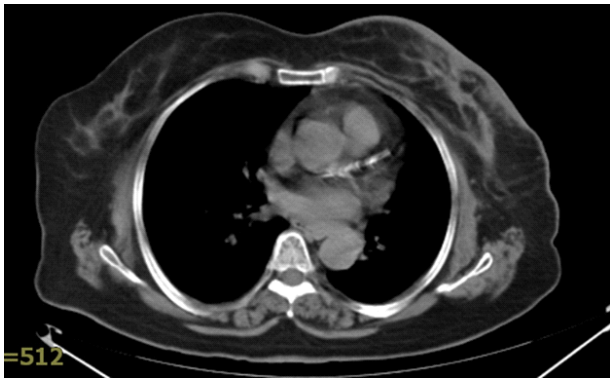


Figure 4. Thoracic MDCT scan without IV contrast. Postoperative changes, including skin thickening, tissue distortion, and fibrous scar in left breast are due to previous breast cancer conserving surgery.

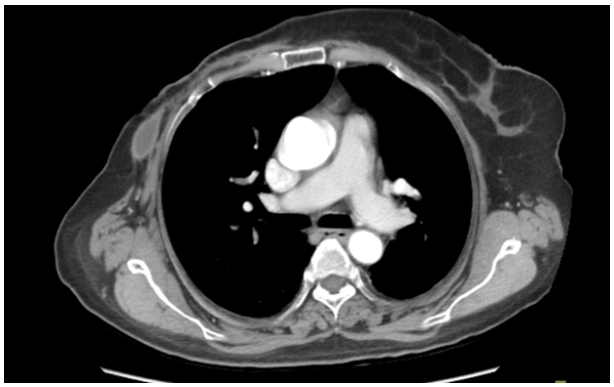


Figure 6. A patient with previous right breast mastectomy and axillary dissection presented with a mass in the lateral part of her scar tissue. A thoracic MDCT scan, performed as part of the cancer staging, showed an oval well-defined fluid density mass-shaped lesion with a thin rim of enhancement. A confirmatory ultrasonography indicated it was a seroma.

Hematoma

Breast hematomas may be seen after a biopsy or surgery. Their diagnosis needs to be correlated with whether the patient has a history of recent surgery or biopsy. A decrease in the size over time is a good diagnostic point about hematoma. When a hematoma becomes smaller, it changes to serous fluid and forms a seroma. There was no case of breast hematoma in this study, which may be a reflection of the time lapse between the previous surgery and the MDCT scan.[1,20]

Abscess

In breast surgery, abscess formation is not a common complication. Clinical history such as fever and lab tests including an elevated white blood cell count are important in proper diagnosis. An abscess can sometimes have a similar appearance to a hematoma on MDCT scans; in this context, clinical data can be essential for correct diagnosis.[1,20] None of the patients in this study showed an abscess on their MDCT scans.

Fat necrosis

Fat necrosis can manifest different imaging

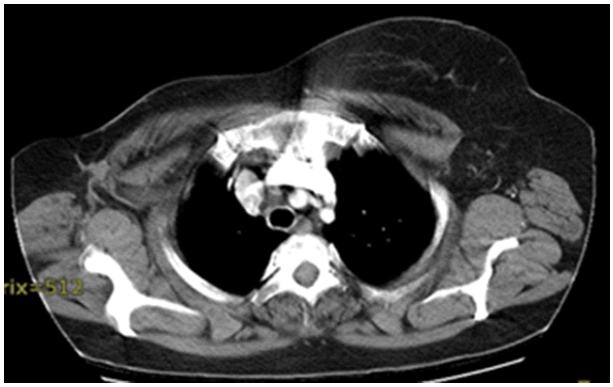


Figure 5. Thoracic MDCT scan without IV contrast. Spiculated soft tissue density in the right axilla of a patient who had axillary dissection. A confirmatory ultrasound showed scar tissue only in the axilla.

features sometimes indistinguishable from malignant lesions that warrant biopsy. Central fat with rim enhancement is its typical feature (Fig. 7). Other signs of postoperative changes accompany fat necrosis most of the time.[18, 20] Fat necrosis-related calcifications, including rim, coarse, or dystrophic calcifications, are typically benign. Fat necrosis can be associated with smaller, irregular, polymorphic, clustered calcifications but almost all calcifications visible on MDCT scans are benign and are only visible due to their size.[1]

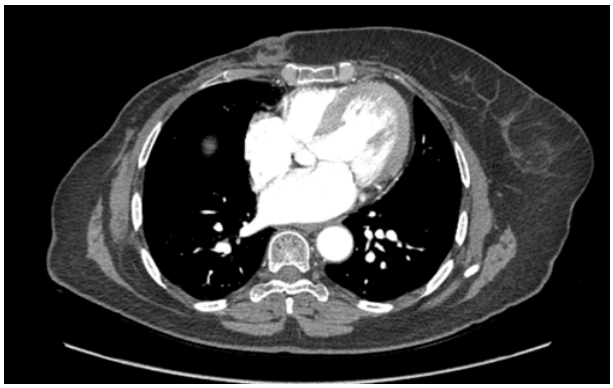


Figure 7. Thoracic MDCT scan with IV contrast in a patient with a previous right mastectomy. A complex mass containing fat components suggestive of fat necrosis in the medial part of the scar tissue can be observed.

Breast reconstruction

Breast reconstruction after a mastectomy may be performed using implants, autologous tissue, or both (Fig. 8). Occasionally, reduction mammoplasty is required for the contralateral breast in order to maintain symmetry and esthetics.

In certain circumstances, the placement of a tissue expander to expand the skin is required prior to breast prosthesis implantation. Different types of implants, which differ according to their content (saline or silicone) and number of lumens, may be used. Fibrous tissue usually develops around the implant.

Implant complications, including intracapsular or extracapsular rupture, silicone granuloma formation,

and capsular contracture, cannot be adequately evaluated on a thoracic MDCT scan. However, certain imaging signs, such as thickening of the fibrous capsule, infolding, tenting and irregularity of the prosthesis, irregular capsular contour with peri-implant calcification, and the presence of fluid collections around the implant, can be suggestive of those complications.[14] Therefore, if these imaging signs are observed on the MDCT scan, it is recommended to perform additional imaging, such as breast MRI, for better evaluation of the implant.

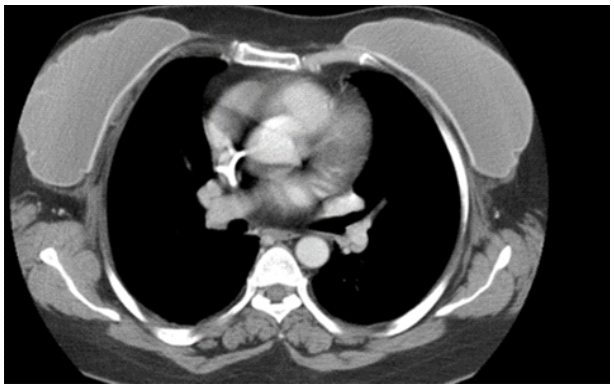


Figure 8. Thoracic MDCT scan of a 42-year-old woman with a history of bilateral mastectomy who recently underwent breast augmentation surgery using implants.

In conclusion, breast tissue should be scrutinized on MDCT scans as well as other types of images. Residual and recurrent tumors as well as benign postoperative changes including fibrotic scar, seroma, hematoma, abscess, and fat necrosis can be diagnosed correctly using MDCT, or can at least be proposed as a differential diagnosis; moreover, if needed, other appropriate imaging methods may be suggested in MDCT scan reports for confirmation. Knowing the important features of the appearance of breast tissue after surgery on MDCT scans allows the radiologist to report them well, and plays an important role in the proper management of the patient.

References

1. Harish MG, Konda SD, MacMahon H, Newstead GM. Breast lesions incidentally detected with CT: what the general radiologist needs to know. Radiographics 2007; 27 Suppl 1: S37-51.
2. Kim SM, Park JM. Computed tomography of the breast. Abnormal findings with mammographic and sonographic correlation. J Comput Assist Tomogr 2003; 27(5): 761-70.
3. Lin WC, Hsu HH, Li CS, Yu JC, Hsu GC, Yu CP, *et al*. Incidentally detected enhancing breast lesions on chest computed tomography. Korean J Radiol 2011; 12(1): 44-51.
4. Hussain A, Gordon-Dixon A, Almusawy H, Sinha P, Desai A. The incidence and outcome of incidental breast lesions detected by computed tomography. Ann R Coll Surg Engl 2010; 92(2): 124-6.
5. Moyle P, Sonoda L, Britton P, Sinnatamby R. Incidental breast lesions detected on CT: what is their significance? Br J Radiol 2010; 83(987): 233-40.
6. Porter G, Steel J, Paisley K, Watkins R, Holgate C. Incidental breast masses detected by computed tomography: are any imaging features predictive of malignancy? Clin Radiol 2009; 64(5): 529-33.
7. Shojaku H, Seto H, Iwai H, Kitazawa S, Fukushima W, Saito K. Detection of incidental breast tumors by noncontrast spiral computed tomography of the chest. Radiat Med 2008; 26(6): 362-7.
8. Yi JG, Kim SJ, Marom EM, Park JH, Jung SI, Lee MW. Chest CT of incidental breast lesions. J Thorac Imaging 2008; 23(2): 148-55.
9. Chang CH, Sibala JL, Fritz SL, Gallagher JH, Dwyer SJ, 3rd, Templeton AW. Computed tomographic evaluation of the breast. AJR Am J Roentgenol 1978; 131(3): 459-64.
10. Chang CH, Nesbit DE, Fisher DR, Fritz SL, Dwyer SJ, 3rd, Templeton AW, *et al*. Computed tomographic mammography using a conventional body scanner. AJR Am J Roentgenol 1982; 138(3): 553-8.
11. Goldberg PA, White CS, McAvoy MA, Templeton PA. CT appearance of the normal and abnormal breast with mammographic correlation. Clin Imaging 1994; 18(4): 262-72.
12. Inoue M, Sano T, Watai R, Ashikaga R, Ueda K, Watatani M, *et al*. Dynamic multidetector CT of breast tumors: diagnostic features and comparison with conventional techniques. AJR Am J Roentgenol 2003; 181(3): 679-86.
13. Sardanelli F, Calabrese M, Zandrino F, Melani E, Parodi R, Imperiale A, *et al*. Dynamic helical CT of breast tumors. J Comput Assist Tomogr 1998; 22(3): 398-407.
14. Yamamoto S, Fukuda T, Hamada S, Johkoh T, Tomiyama N, Murai S, *et al*. [Technical application of three-dimensional visualization and measurement for breast cancer using multidetector-row CT scanner]. Nihon Hoshasen Gijutsu Gakkai Zasshi 2002; 58(12): 1666-75.
15. Miyake K, Hayakawa K, Nishino M, Nakamura Y, Morimoto T, Urata Y, *et al*. Benign or malignant?: differentiating breast lesions with computed tomography attenuation values on dynamic computed tomography mammography. J Comput Assist Tomogr 2005; 29(6): 772-9.
16. Uematsu T, Sano M, Homma K, Sato N. Comparison between high-resolution helical CT and pathology in breast examination. Acta Radiol 2002; 43(4): 385-90.
17. Fujita T, Doihara H, Takabatake D, Takahashi H, Yoshitomi S, Ishibe Y, *et al*. Multidetector row

computed tomography for diagnosing intraductal extension of breast carcinoma. J Surg Oncol 2005; 91(1): 10-16.
18. Krishnamurthy R, Whitman GJ, Stelling CB, Kushwaha AC. Mammographic findings after breast conservation therapy. Radiographics 1999; 19 Spec No: S53-62; quiz S262-3.
19. Soo MS, Williford ME. Seromas in the breast: imaging findings. Crit Rev Diagn Imaging 1995; 36(5): 385-440.
20. Neal CH, Yilmaz ZN, Noroozian M, Klein KA, Sundaram B, Kazerooni EA, *et al*. Imaging of breast cancer-related changes after surgical therapy. AJR Am J Roentgenol 2014; 202(2): 262-72.

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163256-61

Evaluation of The Value of Core Needle Biopsy in The Diagnosis of a Breast Mass

Asieh Sadat Fattahi*[a], Alireza Tavassoli[a], Mahmood Reza Kalantari[b], Sajad Noorshafiee[a], Majid Rahmani[a]

[a] *Endoscopic and Minimally Invasive Surgery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

[b] *Department of Pathology, Mashhad University of Medical Sciences, Mashhad, Iran*

ARTICLE INFO

Received:
7 March 2016
Revised:
4 April 2016
Accepted:
10 June 2016

Keywords:
Breast lumps,
core needle biopsy,
sensitivity and specificity,
NHSBSP classification

ABSTRACT

Background: Core needle biopsy (CNB) with histological findings is regarded as one of the most important diagnostic measures that make preoperative assessment and planning for appropriate treatment possible. The aim of this study was to determine the sensitivity and specificity of core biopsy results in our patients with benign and malignant breast lumps, especially for borderline breast lesions, by using a classification method.

Methods: In this study, 116 patients who were referred to the Surgery Clinic of Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran with breast lump and underwent diagnostic procedures such as mammography and ultrasound were selected. Core needle biopsy (Tru-cut #14 or 16) was performed. After that, excisional biopsy was done. The benign, malignant and unspecified samples obtained by core needle biopsy were evaluated with the samples of the surgical and pathological findings. Then, false positive, false negative, sensitivity, specificity, and diagnostic accuracy of the core needle biopsy method were calculated. Also, the National Health Service Breast Screening Program (NHSBSP) classification was employed.

Results: The mean age of the participants in this study was 39±13.13 years and the mean tumor size was 2.7 cm. An average of 3.35 biopsies was taken from all patients. Most of the pathology samples taken from CNB and excisional biopsy were compatible with invasive ductal carcinoma. Of the B type classifications, B5 was the most frequent in both methods. Borderline lesions B3 and B4 had a change in their category after surgery. About 2.5% of the samples in core biopsy were inadequate. Skin bruising was the most common core biopsy complication reported. While, the most common complication of excisional biopsy was hematoma. Accuracy, sensitivity, specificity, positive and negative predictive values of the core needle biopsy procedure compared with excisional biopsy was 95.5%, 92.6%, 100%, 100%, and 91.8%, respectively.

Conclusions: Core needle biopsy has a high sensitivity and specificity with few side effects. Borderline classifications need more evaluation to rule out cancers.

Address for correspondence:
Asieh Sadat Fattahi, MD
Address: Endoscopic and Minimally Invasive Surgery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
Tel/Fax: +98 51 38402972
Email: Fattahima@mums.ac.ir

Introduction

Breast cancer is the most common cancer worldwide.[1, 2] Also, breast cancer is the most common cancer in Iranian women[3], and considering the fact that the majority of patients are referred with breast masses, selecting appropriate diagnostic and treatment method is very important.[1, 2] Today, biopsy

especially core needle biopsy (CNB) which can be used instead of open biopsy and breast surgery, has a special place in researches, particularly because it can be performed without hospitalization and therefore is not costly. In contrast, excisional biopsy, which requires surgery and an operating room and hospitalization, can increase the cost of treatment. Moreover, several studies have shown the possibility of using preoperative patient evaluations on core biopsy samples to create comprehensive treatment strategy.[4]

In core samples, genetic evaluation and assessment of hormone receptors and tumor markers can be done in addition to routine pathologic evaluation and if necessary, the clinician can discuss new treatment methods such as neo-adjuvant (pre-operative chemotherapy), sentinel lymph node biopsy (SLN), and immediate breast reconstruction after mastectomy.[3, 4] CNB can provide tissue specimens from the mass using various techniques with or without image guiding for non-palpable or palpable breast masses. This procedure can be performed either manually or with a biopsy gun.

Even if the mass is fixed on palpation, it could still be moved by the needle causing sample error. This can happen when the procedure is done manually. The use of ultrasound, even when we are dealing with palpable lesions, can be helpful for correct lesion insertion by the needle to obtain sufficient samples. A number of samples need to be collected from different parts of the lesion to ensure a sufficient amount of samples. If future follow up such as surgical resection is necessary, four to six lesions are desirable to place a marker on the lesion location.

Open biopsy is still a common method of the evaluation of a breast mass by some surgeons in our region with no national guidelines available in our country; these surgeon are not familiar with the procedure and do not use it in some cities so if our study shows good results, needle biopsy can be more popular as an available alternative method to open surgery. Also, acceptable results of our study can help to improve teamwork and interdisciplinary collaboration. In order to determine the borderline case sand diagnostic values of our core biopsies, we used the National Health Service Breast Screening Program classification (NHSBSP) (by dividing the results into five categories), for better management of borderline reports.[5] The aim of our study was to find the accuracy of our core biopsy method and to determine how the use of the NHSBSP classification method could help in the interpretation of biopsy results and evaluation of the patients for selecting a proper treatment method.

Methods

Patients referred to the Breast and Surgery Clinics of Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran with a complaint of breast mass and underwent diagnostic mammography and ultrasound procedures from May 2012 to June 2014 were selected to participate in this study.

Study inclusion and exclusion criteria

Patients included in this study had breast masses and underwent CNB biopsy. Furthermore, the benign cases had to undergo surgical biopsy (because of large-sized fibroadenomas, recurring cysts, being high risk for cancer, or the patient's desire to remove the lump).

Patients were excluded if they did not have the possibility for proper follow up and, those with benign masses or were not willing to have mass excision. After obtaining informed consent from the patients, their demographics and previous medical history (including biopsy, history of cancer, and cancer risk factors) were recorded.

Then, two surgeons who were familiar with the procedure did CNB by a 16 or 14-gauge Tru-Cut needle (TSK semiautomatic or automate needle biopsy). The procedure includes 3 to 4 mm incision and then the core needle is inserted and biopsies are taken. After that, the patients underwent an excisional biopsy or lumpectomy or mastectomy according to pathologic results. Borderline or unspecified results of the CNB sample were also evaluated by excisional surgery. Then, false-positive and false-negative rates were determined.

False negative was described when the results showed a benign lesion in core sample and a malignant lesion was reported in the final pathology. False positive was defined as the malignant report of the CNB sample but non-malignant results in the final pathology. The diagnostic value (predictive value) and, sensitivity and specificity of the core biopsy were also determined.

The complications of CNB such as infection, bleeding, hematoma, and pain were evaluated. Also, classification based on NHSBSP in all of the five result groups were determined as below[5]:

B1: Normal breast tissue like lipoma or hamartoma;

B2: Benign lesion like fibroadenoma, fibrocyctic, duct ectasia, and fat necrosis;

B3: Lesion of uncertain malignant potential like atypical ductal hyperplasia, papillary lesion, lobular neoplasia, and radial scar;

B4: Suspicious lesion like high grade atypical;

B5: Malignant lesion like *in situ* or invasive ductal or lobular carcinoma

The diagnostic value was determined in each group, especially in borderline cases.

Statistical analysis

With a study power of 90%, statistical significance set at 5% and assuming a sensitivity of 71% for carcinoma *in situ* according to Cipolla *et al*., the required sample size was at least 108 participants.[6] First, the population was classified based on demographic characteristics including age, tumor

size and type of tumor, left or right breast, the number of core biopsies, the percentage of inadequate samples, core biopsies and final pathology, tumor grade in core biopsy samples and pathological findings, and blind biopsy complications. Then, the association between complications and the number of biopsies were described in terms of frequency and p-value. Also, the false positive and false negative of this method were evaluated. Next, the relationship between false positive cases with the number of biopsies and tumor size was examined. Finally, the accuracy, sensitivity, and specificity of the CNB were determined.

Results

In this study, 116 patients with a mean age of 39±13.13 years ranging from 17 to 80 years were enrolled. About 56.9% of the patients had a mass on the right side and 43.1% on left side. The mean mass size was 2.77±1.52 cm, varying from 0.8 cm to 8 cm. The mass diameter mostly were categorized as T1 (0 to 2 cm). The number of biopsies taken from the patients varied from 1 to 7 with a mean of 3.35±1.24. In 3 cases (2.5%), core biopsy specimens were inadequate and their data were excluded from the final analysis.

Pathologic evaluation of 113 CNB samples showed that invasive ductal carcinoma was the most frequent with 59 cases (52.2%). According to the results of the excisional biopsy, invasive ductal carcinoma was the most frequent with 65 cases (57.5%). Other results in core samples were fibroadenoma (20.6%), fibrocyctic change (6.8%), mastitis (4.3%), invasive lobular carcinoma (2.5%), *in situ* carcinoma (0.8%), and granulomatousmastitis (2.5%). We had 3 inadequate specimens and 10 patients (8.6%) with other pathologies like papillary lesion, radial scar, ductal lesion with atypia, ductal ectasia, *etc*. Using the NHSBSP classification, it was found that 4(3.6%) patients were in the B3 and 2(1.8%) in the B4 group. After surgical excision, 5 of these challenging results showed malignancy. The frequencies of samples in each NHSBSP category are presented in table 1.

Of the 113 patients who underwent CNB, 31 cases of bruising, 3 of bleeding, 7 case of hematoma, one case of infection, and 7 cases of pain were reported. All complications were cured without hospitalization. The relationship between the number of biopsy samples taken and complications was studied. The number of biopsies was 4.43±1.13 in patients who had hematoma and 3.28±1.225 in other patients, which showed a significant difference (P = 0.019). Other complications had no significant relationship with the number of biopsies.

The mass status data obtained from the two series of CNB and surgical samples showed that among the 113 samples in 108 cases (95.5%), the condition in the two series was quite consistent. The 5 discordant cases (4.42%) were false negative cases in samples taken via CNB.The sensitivity, specificity, accuracy, and positive and negative predictive values of this technique to determine the status of breast masses were 92.6%, 100%, 95.5%, 100%, and 91.8%, respectively.

Table 1. Results of pathologic findings through core needle and excisional biopsy based on NHSBSP classification

NHSBSP categories	CNB N (%)	Excisional biopsy N (%)
B1	1 (0.8%)	0 (0%)
B2	43 (38.1%)	44 (39%)
B3	4 (3.6%)	1 (0.8%)
B4	2 (1.8%)	0 (0%)
B5	63 (55.7%)	68 (60.2%)
Total	113 (100%)	113 (100%)

Abbreviation: NHSBSP: National Health Service Breast Screening Program; CNB: core needle biopsy

Discussion

In recent years, the use of core needle biopsy for histopathological characterization of suspicious breast lesions has increased, which has reduced the number of surgical biopsies or intraoperative evaluation of the lumps.[7] The false negative cases of breast biopsy are very low; however, if the results are not concordant with the clinical picture or radiologic evaluations, rebiopsy is necessary.[8] The disadvantages of this technique include the need for inserting multiple needles, patient discomfort, moderate costs, and the lack of a complete set of features of the lesion.

Our aim was to determine the accuracy of needle biopsy and the rate of complications in our patients with breast mass and also to enhance decision making strategies in treatment by using a classification method. In 116 of our patients, a right mass was more prevalent and the mean size was 2.7 cm, but most of the patients had a tumor size between 0-2 cm that reduced errors in results because of the heterogenecity of larger tumors. In large size masses, core biopsy may not be reliable enough because it cannot provide adequate samples of the entire tumor; there may be malignancy in some parts of the mass where we do not have any samples for evaluation.

Several studies have reported a strong correlation between the results of CNB and surgical biopsies. In addition, it is helpful in some cases such as patients with ductal carcinoma in situ and lobular or atypical

hyperplasia.[9,10]

Cipolla *et al*. evaluated 195 patients with suspicious debris and reported that the correlation between core biopsy and final biopsy was 94.9% in infiltrative carcinoma and 71% in carcinoma in situ. The predictive value was 98.9% with a sensitivity of 96.1% and a specificity of 93.3%.[6]

In a study by Andrew *et al*., the CNB results were classified into five groups based on the NHSBSP. In a study of 3054 patients with B5 (malignant) and B4 (suspicious) tumor, the diagnostic value of core needle biopsy was 100% with no false positive cases; the negative predictive value in B2 (benign) was 97.3 % with a false negative of 3.5%.[6]. This classification of CNB results has been used by different pathologists.[11]

According to our results, the B4 lesion was reported malignant in the final surgery and half of B3 lesions were malignant, as well. So, it seems that surgical excision or rebiopsy in these categories is required.

Li and colleagues studied 177 patients and reported a sensitivity of 94.4%, false negative of 5.1%, specificity of 100%, false positive of 0%, positive predictive value of 100%, and negative predictive value of 85.4%.[12] Flegg *et al*. evaluated borderline breast lesions, ductal hyperplasia or non-atypical lobular, papillary lesions, carcinoma *in situ*. Comparison of the results of needle biopsy and surgical removal indicated 20% benign pathology, 55% borderline lesions, 17% non-invasive malignancy, and 7% invasive malignancy. The results suggested that further investigation of these lesions was required.[13]

In a systematic review study of various biopsy techniques, Bruening and colleagues discussed the best method of biopsy. In general, CNB has advantages over fine needle aspiration (FNA), including a lower number of suspected cases and determining cancer hormone receptors, while thin-needle biopsy (FNA) does not show invasion estimates. Papillary lesions in situ, fibroblasts, and less malignant cases of the epithelium can also be detected by CNB. Our CNB results also showed a good detection rate without false positive, but we did not compare the results with FNA in our patients.[14]

Ultrasound and core biopsy can be reliable diagnostic methods for benign lesions such as fibroadenoma.[15] Comparison of our results showed a good correlation between core and surgical biopsy. We only had 3 inadequate specimens, 110 patients (97.3%) had concordant core and surgical biopsy results with a sensitivity of 95% and a specificity of 100 % that was similar to other studies. CNB can provide the possibility of planning for sentinel lymph node biopsy before surgery in the early stages of cancer and pre-operative chemotherapy in advanced stages by detecting the cancer. The tumor response to chemotherapy agents is more reviewable than surgical biopsy cases.[16, 17] Moreover, breast biopsy core samples can be used for conducting genetics studies.[18]

According to Bilous, although biopsy gives a definitive answer in many cases or at least provides information that can be used to plan the treatment, there are still unresolved issues regarding the results, especially in potentially malignant lesions in which surgical removal is advised. However, more research is recommended in this regard.[19]

In a study done in Turkey in 2007, 201 patients who were supposed to have breast cancer and underwent CNB followed by surgical biopsy (lumpectomy or mastectomy) were evaluated. Then, by adjusting for factors such as size, number of biopsies, and the location of biopsy, concordant results were 82% regarding the tumor type and 68% regarding the breast grade between the two methods of CNB and surgical biopsy. According to the results of this study, CNB was recommended as a beneficial method for treatment planning. To increase the accuracy of the results, they suggested performing the procedure under the ultrasound guide.[20]

In a study in 2009 in South Korea, 104 CNB breast cancer samples were examined. The conformity of the two methods of CNB and surgical biopsy in determining the tumor type and grade was reported to be 100% and 81%, respectively. Therefore, the CNB method was found to be of use for predicting the tumor grade before surgery.[21]

In 2011, a study was conducted on 209 patients with breast cancer in the United States. The accuracy of CNB was compared with surgical biopsy and the result for tumor diagnosis was 93%. Grade determination was 86%. The samples were taken under the ultrasound guide or via stereotaxy, and four to six biopsies were available for each tumor. The results showed that CNB was not a reliable method for determining the breast tumor grade in all cases.[22]

Jangjoo *et al.* studied 30 patients with primary breast cancer who underwent CNB followed by definitive surgery. He found that CNB was a reliable method in determining the tumor pathology, grading, and also the estrogen and progesterone receptor status. Prognostic factors of breast cancer including the estrogen receptor, progesterone receptor, HER-2, P53 were concordant in the two methods (97%, 90%, 63%, and 77% respectively).[23]

Karimian assessed the value of CNB as a first approach in the management of palpable breast masses. In this study, 112 patients with palpable breast masses participated and, adequate samples were prepared in 103 cases (91.9%). In 78 (69.6%) cases in whom malignancy was reported, the results were consistent with samples obtained from surgical biopsy. In 34 (30.4%) patients, CNB with benign samples was reported and after three years of follow-up, 25 (73%) of these patients underwent surgical

biopsy and in one case (3%) malignant tumors were confirmed.[24] We did not include follow up patients in our study because of some ethical considerations as patients with benign masses may not be willing to undergo excision. It may be our limitation so further studies with more patients are needed to evaluate the follow up of patients. Also, 2.5% of the samples in core biopsy were inadequate which were excluded. In our study, the diagnostic accuracy, sensitivity, specificity, false positive, false negative, and positive and negative predictive values of CNB as compared with surgery were 97.3%, 94%, 100%, 2.7% 0%, 96%, and 100%, respectively. Moreover, the relationship between the number of biopsies, the size of the mass, and false positive was not significant. We also had a low rate of complications, and the number of biopsies was significant in association with the rate of hematoma (p=0.019). This study recommends CNB as an appropriate first step in the evaluation of breast masses.[24]

In conclusion, core needle biopsy has a good predictive value and has few complications for evaluating a breast mass. Considering the fact that core needle biopsy does not need any anesthesia and hospitalization, it is a suitable method to diagnose benign or malignant breast lumps. The use of the NHSBSP classification for the evaluation of the core results can help with making better decisions in borderline reports.

Acknowledgement

This work was supported by the Deputy for Research of Mashhad University of Medical Sciences, Mashhad, Iran, and was performed in the Endoscopic and Minimally Invasive Surgery Research Center. We would like to thank Ms. Sima Beigoli and Ms Hajebi for their kind assistance in preparing and revising the paper.

References

1. Mettlin C. Global breast cancer mortality statistics. CA Cancer J Clin 1999; 49(3): 138-44.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65(1): 5-29.
3. Mousavi SM, Montazeri A, Mohagheghi MA, Jarrahi AM, Harirchi I, Najafi M, *et al*. Breast cancer in Iran: an epidemiological review. Breast J 2007; 13(4): 383-91.
4. Xing L, He Q, Wang YY, Li HY, Ren GS. Advances in the surgical treatment of breast cancer. Chin Clin Oncol 2016; 5(3): 34.
5. Andreu FJ, Saez A, Sentis M, Rey M, Fernandez S, Dinares C, *et al*. Breast core biopsy reporting categories--An internal validation in a series of 3054 consecutive lesions. Breast 2007; 16(1): 94-101.
6. CipollaC, Fricano S, Vieni S, Amato C, Napoli L, Graceffa G, *et al*. Validity of needle core biopsy in the histological characterisation of mammary lesions. Breast 2006; 15(1): 76-80.
7. Crowe JP, Jr., Rim A, Patrick R, Rybicki L, Grundfest S, Kim J, *et al*. A prospective review of the decline of excisional breast biopsy. Am J Surg 2002; 184(4): 353-5.
8. Jacobs TW, Connolly JL, Schnitt SJ. Nonmalignant lesions in breast core needle biopsies: to excise or not to excise? Am J Surg Pathol 2002; 26(9): 1095-110.
9. Litherland J. The role of needle biopsy in the diagnosis of breast lesions. Breast 2001; 10(5): 383-7.
10. Margolin FR, Leung JW, Jacobs RP, Denny SR. Percutaneous imaging-guided core breast biopsy: 5 years' experience in a community hospital. AJR Am J Roentgenol 2001; 177(3): 559-64.
11. Zito FA, Verderio P, Simone G, Angione V, Apicella P, Bianchi S, *et al*. Reproducibility in the diagnosis of needle core biopsies of non-palpable breast lesions: an international study using virtual slides published on the world-wide web. Histopathology 2010; 56(6): 720-6.
12. Li Y, Tong XS, Mu WM, Peng WG, Su YJ, Zhao Y, *et al*. [Evaluation of the value of ultrasound-guided core needle biopsy in the diagnosis of breast lesions]. Zhonghua Zhong Liu Za Zhi 2010; 32(6): 470-1.
13. Flegg KM, Flaherty JJ, Bicknell AM, Jain S. Surgical outcomes of borderline breast lesions detected by needle biopsy in a breast screening program. World J Surg Oncol 2010; 8: 78.
14. Bruening W, Schoelles K, Treadwell J, Launders J, Fontanarosa J, Tipton K. AHRQ Comparative Effectiveness Reviews. Comparative Effectiveness of Core-Needle and Open Surgical Biopsy for the Diagnosis of Breast Lesions. Rockville (MD): Agency for Healthcare Research and Quality (US); 2009.
15. Nurko J, Mabry CD, Whitworth P, Jarowenko D, Oetting L, Potruch T, *et al*. Interim results from the FibroAdenoma Cryoablation Treatment Registry. Am J Surg 2005; 190(4): 647-51; discussion 51-2.
16. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T, *et al*. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. Lancet Oncol 2007; 8(10): 881-8.
17. Pruthi S, Brandt KR, Degnim AC, Goetz MP, Perez EA, Reynolds CA, *et al*. A multidisciplinary approach to the management of breast cancer, part 1: prevention and diagnosis. Mayo Clin Proc 2007; 82(8): 999-1012.
18. Ellis M, Davis N, Coop A, Liu M, Schumaker L,

Lee RY, et al. Development and validation of a method for using breast core needle biopsies for gene expression microarray analyses. Clin Cancer Res 2002; 8(5): 1155-66.
19. Bilous M. Breast core needle biopsy: issues and controversies. Mod Pathol 2010; 23 Suppl 2: S36-45.
20. Ozdemir A, Voyvoda NK, Gultekin S, Tuncbilek I, Dursun A, Yamac D. Can core biopsy be used instead of surgical biopsy in the diagnosis and prognostic factor analysis of breast carcinoma? Clin Breast Cancer 2007; 7(10): 791-5.
21. Park SY, Kim KS, Lee TG, Park SS, Kim SM, Han W, *et al*. The accuracy of preoperative core biopsy in determining histologic grade, hormone receptors, and human epidermal growth factor receptor 2 status in invasive breast cancer. Am J Surg 2009; 197(2): 266-9.
22. Ough M, Velasco J, Hieken TJ. A comparative analysis of core needle biopsy and final excision for breast cancer: histology and marker expression. Am J Surg 2011; 201(5): 692-4.
23. Motamedolshariati M, Memar B, Aliakbaian M, Shakeri MT, Samadi M, Jangjoo A. Accuracy of prognostic and predictive markers in core needle breast biopsies compared with excisional specimens. Breast Care (Basel) 2014; 9(2): 107-10.
24. Karimian F, Aminian A, Hashemi E, Meysamie A, Mirsharifi R, Alibakhshi A. Value of core needle biopsy as the first diagnostic procedure in the palpable breast masses. Shiraz E Med J 2008; 9(4): 188-92.

Short Communication Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163262-65

Breast One Stop Clinic – Follow up Experience at Sultan Qaboos University Hospital in the Sultanate of Oman

Adil Al Jarrah*[a], Huda S. Almoqbali[a], Ruqaya Al Shehi[a], Suad Al Aghbari[a], Syed Gauhar A. Rizvi[b], Badriya S. Al-Qassabi[c], Ritu Lakhtakia[d]

[a] *Breast Unit, Department of Surgery, Sultan Qaboos University Hospital, Muscat, Sultanate of Oman*
[b] *Department of Statistic, Sultan Qaboos University, Muscat, Sultanate of Oman*
[c] *Breast Unit, Department of Radiology, Sultan Qaboos University Hospital, Muscat, Sultanate of Oman*
[d] *Breast Unit, Department of Pathology, Sultan Qaboos University Hospital Muscat, Sultanate of Oman*

ARTICLE INFO

Received:
3 March 2016
Revised:
12 April 2016
Accepted:
19 May 2016

Keywords:
Fibroadenoma, FNAC sensitivity, breast carcinoma, breast one stop clinic

ABSTRACT

Background: The role of the breast clinics is to diagnose breast cancer and reassure patients with benign disorders. One stop clinics - same day reporting - further reduce anxiety caused by the delay in the results. The first one stop clinic was introduced in SQUH–Oman in September 2011.

Methods: This retrospective analysis of 395 consecutive cases presented to Breast One Stop Clinic at SQUH was done between September 2011 and December 2013. All patients underwent triple assessment conducted by consultants. Mammography was performed for patients above 35 years with no contraindications. Ultrasound was done for all patients with palpable lesions. The reports were assigned a score (BIRADS 0-6). Fine Needle Aspiration Cytology (FNAC) was done for all patients with palpable abnormality or nipple discharge. An immediate report was given using the standard reporting categories: acellular/inadequate, benign, atypical, suspicious, and malignant (C1-C5).

Results: Out of 395 patients, 210 were found to have palpable lesions with a mean age of 36 years (12-84 years). All patients were female. The FNAC sensitivity and specificity was 95.7% and 92.2%, respectively. Out of 210 patients, 15.3% were diagnosed with breast cancer on FNAC who were subsequently staged and discussed in the Breast Multidisciplinary Team Meeting (MDT), and 84.7% were diagnosed to have benign breast disorders who were reassured and advised to be followed up after 6 months.

Conclusions: Immediate relief and reassurance to the majority of patients with benign disease obviate the need for review appointments. A reliable diagnosis can be obtained with triple assessment which can be used to avoid unnecessary core biopsy of benign lesions, if correctly done.

Address for correspondence:
Adil Al Jarrah, MBBch, FRCS, FRCSI, MD, AFSA
Address: Sultan Qaboos University hospital, Breast Unit, Surgery Department, Alkhoud, P O Box 38 PC 112, Muscat, Oman
Tel: +96 899446622
Fax: +96 824143504
Email: adilm@squ.edu.om

Introduction

The incidence of breast cancer is increasing in Oman and worldwide. With industrialization and urban development, delayed child births and reduced fertility, westernization of the lifestyle and increasing life expectancy among women, the incidence of breast cancer is increasing in all developing countries. Although the breast cancer incidence rate has been increasing worldwide since

1950, the mortality rate has leveled off or begun to decline recently. Countries that have a downturn in mortality are generally those with the highest rates; countries with the lowest incidence rate tend to be the ones in which the mortality is increasing, mainly due to advanced stage at the time of diagnosis.[1, 2] The advanced stage at presentation of breast cancer in developing countries has been attributed to a lack of mass education and screening programs, poverty, poor access to health care facilities, lack of expertise, and poor infrastructures.[1-7]

Breast cancer patients in Oman present with advanced stages and at younger ages than their counterparts in the west; the mean age is 46.8 years and 48% of the female patients are premenopausal. Breast cancer patients in Oman present with advanced stages of the disease at younger ages than their counterparts in the west; as a result, their survival rates are lower. The overall 5-year survival of breast cancer patients in the western countries is 75%, whereas it is only 50% in eastern countries.[1] The age-standardized incidence rate is 15.6 per 100,000. In our last reported study, we found that age at diagnosis was lower in Oman than in the western world, and the majority of patients presented with advanced stages of the disease (III and IV).[1]

In this regard, we need a policy for early breast cancer detection to minimize the anxiety resulting from the breast cancer taboo. More than 80% of the patients seeking medical help for breast lump have benign disorders. However, the taboo of breast cancer and anxiety continue to exist until the patient is reassured by the treating breast specialist.[1]

With the above mentioned in mind, rather than simply expressing concern, indulging in wailing and hand wringing, it was the time to take action by setting one stop clinic at Sultan Qaboos University Hospital (SQUH) for early breast cancer diagnosis and possible treatment. Our first result was encouraging and the results were published in 2013.[8]

At Sultan Qaboos University Hospital (SQUH) which is a modern teaching institute, all patients with breast lesions undergo triple assessment, namely history and examination, imaging (breast ultrasound or mammogram), and histopathology (FNAC or core biopsy).

As a result of the increased public awareness of breast cancer results, many patients expect successful and efficient management of their symptoms. There is also an increasing professional requirement on the part of clinicians for improved health care delivery to these patients.[2]

This public and professional awareness has led to a change in the referral of patients with breast symptoms. Therefore, specialists visit more patients and the benign to malignant ratio constantly rises.[3, 4] The majority of the patients referred to a breast clinic have benign diseases.[5] Most of these patients, however, are in a state of anxiety until they have undergone triple assessment and have received eventual reassurance.[6,7]

Methods

The Breast One Stop Clinic (BOSC) is the first such clinic in the Sultanate of Oman. The data of 395 patients presenting to BOSC at SQUH, from September 2011 to December 2013, was retrospectively analyzed. The clinic is managed by a breast consultant once a week together with senior registrars, residents, a social counselor, a breast nurse, and a staff nurse. All patients were examined by a consultant breast surgeon. The clinical examination was performed using standard examination techniques in the presence of a chaperone. The clinical impression following the examination and evaluation of the symptoms was documented as normal, benign, suspicious, or malignant in the Hospital's Electronic Patient Records (EPR). The patients 35 years and above who did not have a mammogram within a year of their referral to the clinic were routinely subjected to two-view mammography unless they were pregnant or had mastitis. The mammography was performed on a LORAD Selenia full field digital mammography system. Two X-rays of each breast were taken, namely cranio-caudal (CC) and medio-lateral oblique (MLO) views. Supplemental views tailored to the specific problems were taken whenever necessary. The images were viewed by a consultant breast radiologist on a Selenia soft copy review work station. Reports were assigned a score (BIRADS 0-6) by the radiologists, and the mammograms were reviewed by the consultant breast surgeon at the clinic.[9]

Ultrasound (US) was performed by the consultant radiologist on a Philips IU 22 machine using linear 7.5 – 12.5 MHz transducers. The patients were scanned in the supine and/or contra-lateral oblique position, depending on the site of the lesion. Indications for US were the presence of a palpable abnormality in a woman below 35 years of age, a non-contributory mammogram (e.g. a dense background pattern or no obvious abnormality at the site of clinical concern), and contraindications to mammography (e.g. pregnant patients).

A written informed consent was obtained from all patients undergoing cytological or histological evaluation. Biopsy was performed as the gold standard against which the sensitivity and specificity of clinical, US/mammo/FNAC would be calculated.

The procedure was performed by the consultant surgeon, senior registrar, or supervised residents in all patients with a palpable abnormality such as a discrete lump, circumscribed area of thickening, or asymmetrical nodularity, using a UNOLOK size 21Gx38mm needle. Cytology was also performed on blood stained nipple discharges. The aspirate and smears were sent both dry and stained using "Diff-Quik" Rapid

and Papanicolou methods with 95% alcohol.

An immediate report was given using the standard reporting categories, namely acellular/ inadequate, benign, atypical, suspicious and malignant (C1-C5).[10]

Patients with BIRADS 2, 3, and 4, those with lumps bigger than 4 cm, or patients older than 25 years of age were subject to core biopsy and FNAC at the same time regardless of their imaging reports.

Core biopsy was performed in all patients with lump, as it is considered the gold standard against which the sensitivity and specificity of clinical, Ultrasound, mammogram and FNAC would be calculated.

Statistical analysis

The SPSS version 20 software package was used for all data analysis.

Results

A total of 395 patients were seen in the Breast One Stop Clinic from September 2011 to December 2013, of whom 185 (47%) patients had no palpable lumps, had nodularity, or had mastalgia who were reassured and discharged. The remaining 210 (53%) patients were found to have palpable lesions and underwent triple assessment (clinical examinations, imaging, and biopsies) on same day. The mean age of the patients was 36 years (range: 12 – 84 years). Moreover, 95% of the patients were Omanis and only 5% of the patients were expatriates. All the patients were female. Mammography was performed in 28% of the patients. Ultrasound showed a sensitivity of 85.1% and specificity of 92%, with false positive and negative of 8% and 14.9%, respectively (Table 1).

Out of 210 patients who had FNAC and core biopsy simultaneously, 84.7 % had benign breast disorders and 15.3% had malignancy. Furthermore, 29% of the benign disorders were fibroadenoma and the rest of the patients had cysts, mastitis, and other breast aberrations; all these patients were advised to be followed up after 6 months as per unit protocol. The patients diagnosed with malignancy were staged and discussed in a Multidisciplinary Team (MDT) meeting.

The sensitivity of FNAC was 95.7% and its specificity was 92.2% with false negative and false positive of 4.3% and 7.8%, respectively (Table 1).

Table 1. Comparison of the two diagnostic approaches in detecting breast cancer

	Ultrasound	Mammography
Sensitivity	85%	96%
Specificity	92%	92%
False negative	15%	4%
False positive	8%	8%

Discussion

The peculiarity of the Breast One Stop Clinic (BOSC), a "one-stop" diagnostic service, is the ability to discuss with the patient at the first outpatient visit, thus, reassuring most of patients with benign disorders and obviating the need for follow up in the outpatient clinic.

Previous studies in our institute and other centers have focused on the accuracy of triple assessment in breast lumps.[8,11-14] These results have shown a reliable diagnosis can be established, thereby avoiding unnecessary biopsy of benign lesions which can be managed conservatively.[15-18]

In this study, almost 85% of the patients were diagnosed to have benign disorders and were reassured and given a follow up appointment after 6 months. Of the remaining, 15% were diagnosed with malignancies.

Mammography remains the most important imaging investigation for breast complains and is the standard against which newer imaging modalities are compared.

Ultrasonography is operator dependent and accurate if done by a skillful operator. At SQUH, ultrasound is performed by a very senior radiologist subspecialized in women imaging; hence, the results are good and showed a sensitivity of 85% and specificity of 92%, with false positive and negative of 8% and 15%, respectively. However, radiologists generally consider breast ultrasound to have a limited role in the diagnosis of breast cancer, offering targeted evaluation of a focal area rather of the breast unlike mammography.[17] Furthermore, mammograms (when performed) are available to the radiologist at the time of performing and reporting the ultrasound scan.

FNAC of palpable breast lumps is an established diagnostic technique with high accuracy rates.[11-18] In our study, the sensitivity of FNAC was found to be 95.7%; it provided the highest overall prediction of both benign and malignant disease in our clinic. When the FNAC report was categorically malignant (i.e. C5), there were no false positive outcomes. The percentage of acellular specimens was low in our experience (9%) but nonetheless compared well with figures from other centers.[19,20]

A diagnosis was made in 98% of the patients at the first clinic consultation. The high benign to malignant ratio is a reflection of the increasing anxiety in relation to breast symptoms and need for reassurance of both patients and their general practitioners.

In conclusion, we believe that in our practice, the Breast One Stop Clinic (BOSC) diagnostic service provides a reliable and accurate means of establishing a rapid diagnosis and is a safe and efficacious process for managing the ever increasing number of patients presenting with breast symptoms.

References

1. Kumar S, Burney IA, Al-Ajmi A, Al-Moundhri MS. Changing trends of breast cancer survival in sultanate of oman. J Oncol 2011; 2011: 316243.
2. Al-Moundhri M,Al-Bahrani B,Pervez I,Ganguly SS, Nirmala V, Al-Madhani A, *et al.* The outcome of treatment of breast cancer in a developing country--Oman. Breast 2004; 13(2): 139-45.
3. Aziz Z, Iqbal J, Akram M. Predictive and prognostic factors associated with survival outcomes in patients with stage I–III breast cancer: A report from a developing country. Asia Pac J Clin Oncol 2008; 4(2): 81-90.
4. Badar F, Faruqui ZS, Ashraf A, Uddin N. Third world issues in breast cancer detection. J Pak Med Assoc 2007; 57(3): 137-40.
5. Raina V, Bhutani M, Bedi R, Sharma A, Deo SV, Shukla NK, *et al.* Clinical features and prognostic factors of early breast cancer at a major cancer center in North India. Indian J Cancer 2005; 42(1): 40-5.
6. Aziz Z, Sana S, Akram M, Saeed A. Socioeconomic status and breast cancer survival in Pakistani women. J Pak Med Assoc 2004; 54(9): 448-53.
7. Agarwal G, Ramakant P, Forgach ER, Rendon JC, Chaparro JM, Basurto CS, *et al.* Breast cancer care in developing countries. World J Surg 2009; 33(10): 2069-76.
8. Aljarrah A, AhmedKamran M, Khatib N, Aghbari S, Skuphal S, Lakhtakia R. Breast One Stop Clinic-Experience at Sultan Qaboos University Hospital in the Sultanate of Oman. Surg Clin India 2013; 1(4):
9. Eberl MM, Fox CH, Edge SB, Carter CA, Mahoney MC. BI-RADS classification for management of abnormal mammograms. J Am Board Fam Med 2006; 19(2): 161-4.
10. Medina-Franco H, Abarca-Perez L, Cortes-Gonzalez R, Soto-Germes S, Ulloa JA, Uribe N. [Fine needle aspiration biopsy of breast lesions: institutional experience]. Rev Invest Clin 2005; 57(3): 394-8.
11. Kocjan G. [Needle aspiration cytology of the breast: current perspective on the role in diagnosis and management]. Acta Med Croatica 2008; 62(4): 391-401.
12. Chandanwale SS, Gupta K, Dharwadkar AA, Pal S, Buch AC, Mishra N. Pattern of palpable breast lesions on fine needle aspiration: A retrospective analysis of 902 cases. J Midlife Health 2014; 5(4): 186-91.
13. Nguansangiam S, Jesdapatarakul S, Tangjitgamol S. Accuracy of fine needle aspiration cytology from breast masses in Thailand. Asian Pac J Cancer Prev 2009; 10(4): 623-6.
14. Kharkwal S, Sameer, Mukherjee A. Triple test in carcinoma breast. J Clin Diagn Res 2014; 8(10): NC09-NC11.
15. Kocjan G, Bourgain C, Fassina A, Hagmar B, Herbert A, Kapila K, *et al.* The role of breast FNAC in diagnosis and clinical management: a survey of current practice. Cytopathology 2008; 19(5): 271-8.
16. Berner A, Davidson B, Sigstad E, Risberg B. Fine-needle aspiration cytology vs. core biopsy in the diagnosis of breast lesions. Diagn Cytopathol 2003; 29(6): 344-8.
17. Green B, Dowley A, Turnbull LS, Smith PA, Leinster SJ, Winstanley JH. Impact of fine-needle aspiration cytology, ultrasonography and mammography on open biopsy rate in patients with benign breast disease. Br J Surg 1995; 82(11): 1509-11.
18. Wakefield SE, Powis SJ. Benign breast surgery: is there a need for outpatient follow-up? Ann R Coll Surg Engl 1995; 77(6): 457-9.
19. Dixon JM, Anderson TJ, Lamb J, Nixon SJ, Forrest AP. Fine needle aspiration cytology, in relationships to clinical examination and mammography in the diagnosis of a solid breast mass. Br J Surg 1984; 71(8): 593-6.
20. Gui GP, Allum WH, Perry NM, Wells CA, Curling OM, McLean A, *et al.* One-stop diagnosis for symptomatic breast disease. Ann R Coll Surg Engl 1995; 77(1): 24-7.

Case Report Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163266-69

Bell's Palsy As a Rare First Presentation of Breast Cancer

Mostafa Hosseini[a], Elham Vafaei[a], Rahele Moein Ara[b], Alimohamad Asghari[c], Nahid Nafissi*[a, b]

[a] *Department of Surgery, Hazrat-e Rasoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran*
[b] *Cancer center, Khatam Al-Anbia Hospital, Tehran, Iran*
[c] *Department of Otolaryngology, Hazrat-e Rasoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Received:
15 April 2016
Revised:
4 May 2016
Accepted:
10 June 2016

Keywords:
Metastasis,
breast cancer,
temporal bone,
cranial nerve palsy

ABSTRACT

Background: Otalgia and Bell's palsy are rare manifestations of metastasis and the most common presentation of an inflammatory process in the temporal bone.

Case presentation: This article explains a 34-year-old woman with breast cancer who presented with cranial nerve palsy symptoms. The 7th and 8th cranial nerves were involved in the metastatic phase and then hoarseness was added to her symptoms. Brain MRI showed a petrous lesion in the temporal bone due to metastasis, which was the first clue to cancer. Her metastatic workup showed multiple bone lesions. On chest CT scan, multiple lung lesions were noted. Also, a breast mass was discovered on her chest CT scan. On breast examination an irregular mass fixed to the pectoralis muscle was found. Pathologic evaluation of samples obtained through ultrasound-guided core needle biopsy confirmed the diagnosis of invasive ductal carcinoma.

Conclusion: Temporal bone metastases are rare and may be asymptomatic, or with mild symptoms mimicking mastoid infections. Physicians should consider metastatic cancer on the list of differential diagnoses in patients presenting with prolonged otologic symptoms or facial nerve disorders.

Introduction

Temporal bone lesions are most commonly inflammatory.[1] In patients with a history of cancer, metastases to the head and neck region are not frequent. Metastases to the temporal bone are rare and mostly originate from the breast, followed by lung, kidney, and prostate cancer and lymphoma.[2, 3] The presentation is nonspecific and stable or progressive; therefore, a high index of suspicion is necessary for prompt and accurate diagnosis.

Address for correspondence:
Nahid Nafissi, MD
Address: Hazrat-e Rasool General Hospital, Niyayesh St., Satarkhan St., Tehran, Iran
Tel: +98 21 66517341
Fax: +98 21 66517118
Email: nafissi.n@iums.ac.ir

Case presentation

We report a 34-year-old female who presented with otalgia. She was initially treated with antibiotics. After three weeks, she presented with left eye ptosis as the first presentation of facial nerve palsy and received conservative anti-inflammatory therapy.

Two weeks later, the second facial nerve palsy was detected as a change in the lateral commissure of her lips (Figure 1). Consequently, brain MRI (with and without contrast) was done to identify the cause of Bell's palsy. An expert radiologist reported mucosal thickening in the left sphenoid sinus with an enhancing mass (35*15 mm) at the body of the petrous bone with a normal CPA, and involvement of the 7th and 8th cranial nerves (Figure 2). The patient was hospitalized and prepared for open biopsy in the operating room. In this process, in less than one month, she experienced vocal hoarseness,

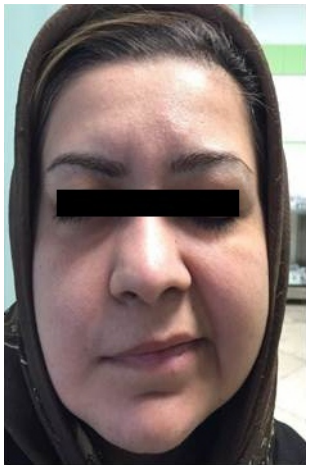


Figure 1. Left eye ptosis and facial nerve palsy

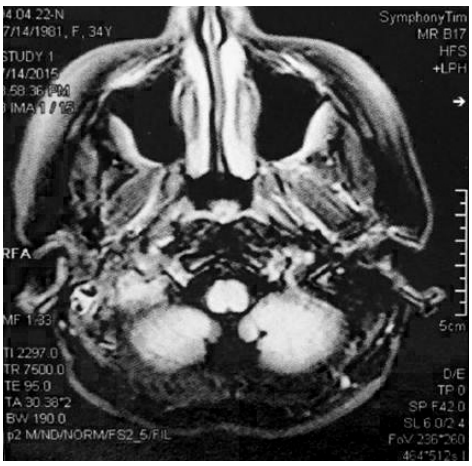


Figure 2. Mucosal thickening at right sphenoid sinus with an enhancing mass in brain MRI

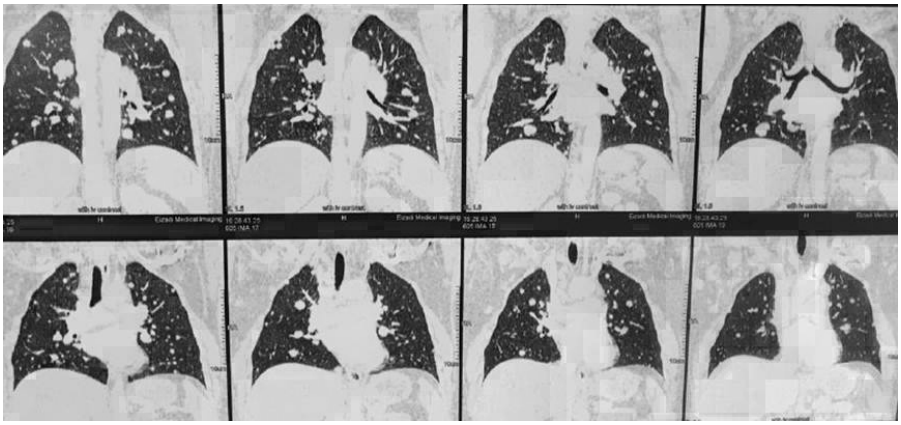


Figure 3. Multiple metastatic lesions in the lungs and a mass in right breast

proving that another cranial nerve was involved. Therefore, chest CT scan was done to rule out lung cancer or lung metastases. The CT scan showed multiple metastatic lesions in the lungs and a mass in the right breast (Figure 3). So, the team decided not to perform petrous bone biopsy and referred the case to a breast surgeon. The patient had never done breast self-examination (BSE) or undergone clinical breast exam in her life and ignored any breast problem at this time.

After a long discussion to decrease her anxiety, the breast surgeon did a physical examination and found an irregular mass of approximately 25mm and a mass fixed to the pectoralis muscle in right upper outer quadrant of the right breast and axilla; so, mammography was done to look for breast lesions which showed a spiculated mass in the upper outer quadrant (UOQ) of the right breast, near the axilla (Figure 4).

Ultrasound-guided core needle biopsy was done on the breast mass and axillary lymph node, and the pathology showed invasive ductal carcinoma NOS type, tumor grade (histologic and nuclear) II with lymphovascular invasion. The IHC showed an ER

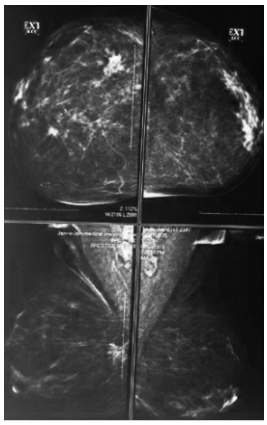


Figure 4. Speculated mass in upper outer quadrant near axilla in the right breast

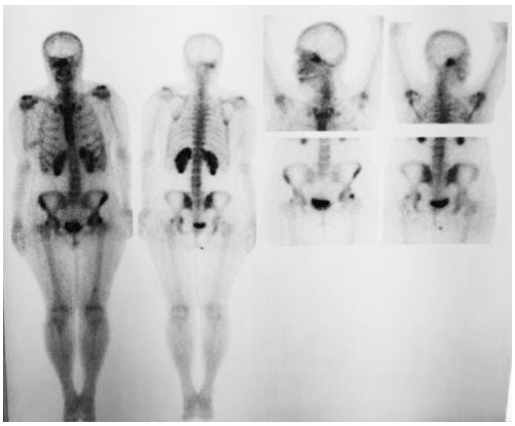


Figure 5. Bone scan of patient showing multiple metastatic involvements, in the left femur head, right femur neck, L4 spine, bilateral ischia, distal left femur and left temporal bone

and PR positive and Her2 negative tumor. The lymph node also showed tumoral involvement. Metastatic workup including whole body bone scan and abdomino-pelvic CT scan was done. The bone scan reported multiple metastatic involvements highly suggested in the left femur head, right femur neck, L4 spine, bilateral ischia, left distal femur, and right temporal bone (Figure 5). Abdomino-pelvic CT was normal. Decision making was done in a multidisciplinary team and neoadjuvant chemotherapy was initiated for her.

She received 8 sessions of AC-T chemotherapy in 5 months, in addition to 10 sessions of local temporal bone radiation therapy. Afterwards, the breast mass regressed, lung and bone metastases partially disappeared, and she looked generally better. The involvement of the cranial nerves, including ptosis and Bell's palsy, has resolved by 80%, but hoarseness and difficulty swallowing still exist after nine months. Now, she is receiving tamoxifen, zoledronic acid, and capecitabine without any signs of tumor progression.

Discussion

The incidence of breast cancer increases with age, with a vast majority of women diagnosed after the age of 40 years. Breast cancer is rare and typically aggressive in young women.[1]

Breast cancer is the most prevalent and the 5th leading cause of death among Iranian women; near 25 percent of breast cancer patients eventually die despite significant advances in diagnosis and treatment.[4] Akbari *et al.* evaluated 461 Iranian patients of breast cancer during 1994-2007 and showed that 18.4% of them were in stage I, 36.1% stage II, 27.7% stage III, and 17.7% stage IV, indicating that 54.5% of the patients were in early stages of cancer and about half of them (45.5%) were diagnosed in an advanced stage.[5]

In developing countries with no facilities for regular breast cancer screening, breast self-exam (BSE) and clinical breast examination (CBE) can still be used to down stage breast cancer. There are two surveys on knowledge and attitude in breast cancer in Iran. According to a study by Nafissi *et al.* in 2012, 59.9% of the participants were able to perform BSE but only 12.9% of the respondents practiced BSE regularly and 36.5% never did BSE. The main reasons for ignoring BSE were forgetfulness (41.6%) and lack of knowledge on the correct approach to BSE (33.4%). Also, 15.8% of the subjects feared to find a mass in their breasts, so they did not perform BSE.[6] It seems that the most common cause of delayed diagnosis of breast cancer in developing countries is that regular breast screening programs are not regularly and routinely implemented that do not offer is lack of BSEand CBE.

Metastatic disease is found in 5% of the women at the time of breast cancer diagnosis. About 30% of the women with early stage breast cancer will ultimately; develop distant metastases.[7]

The most common sites of metastases, beyond regional lymph nodes, are the bones, lung, liver, and brain.[3]

The temporal bone may be invaded by tumors originating from adjacent areas or as metastases from distant sites. About 25% of temporal metastases originate from breast cancer.[2]

Ming-Ying Lan *et al.* reported 4 routes for metastasis to the temporal bone: the first one is hematogenous dissemination of the tumors cells to the bone marrow. The second one is direct extension of the regional tumor, such as nasopharynx, hypopharynx, and parotid gland tumors. The third one is meningeal carcinomatosis (otitis interna carcinomatosa). The fourth is leptomeningeal extension from an intracranial primary tumor, like leukemic or lymphomatous infiltration.[8] The most common area of the temporal bone metastatic infiltration is the petrous apex of the mastoid.[9,10]

Temporal bone invasion may be silent or present itself with otologic symptoms like otalgia, otorrhea, tinnitus, hearing loss, vertigo, and aural mass. These conditions are most frequently the symptoms of mastoid infection; so, if there are prolonged inflammatory symptoms with no response to antibiotics and anti-inflammatory drugs, further evaluation is needed.[8]

Fascial nerve palsies are rare complications of metastatic cancer in the advanced stage of mastoid bone invasion.[9-11]

In this case, the presentation began with otalgia; then, cranial nerve palsy presented one by one as the involvement of 7th cranial nerve followed by the 8th and 9th nerves.

Imaging of the temporal bone by CT scan or MRI is important for differentiation of tumor invasion from infection. By tumor erosion, osteolytic and destructive bone lesions are seen. Moreover, sclerosis and bone formation are other presentations on imaging studies. Similar to our patient, progressive bony erosion seems to be more characteristic of a malignant disease.[8] Positron emission tomography (PET scan) should also be considered as another imaging modality for detection of all metastases like temporal bone lesions.

The treatment of metastatic temporal bone lesions is systemic chemotherapy with local radiotherapy to the affected temporal region.[2, 8, 11] A multidisciplinary team decided to do neoadjuvant chemotherapy and local radiotherapy followed by hormone therapy in this patient.

In conclusion, temporal bone metastasis is rare and may be asymptomatic, or with mild symptoms mimicking mastoid infections. Facial nerve palsy is rare as the first presentation. Otolaryngologists should consider metastatic cancer versus infection on the list of differential diagnoses in patients

presenting with prolonged otologic symptoms or facial nerve disorders. Complete physical examination, audiometry, and imaging are important for diagnosis.

References

1. Tsakiropoulou E, Fyrmpas G, Konstantinidis I, Efstratiou I, Constantinidis I. Temporal bone metastasis from breast carcinoma Otorhinolaryngol Head Neck Surg 2013; (52): 30-2.
2. Streitmann M, Sismanis A. Metastatic carcinoma of the temporal bone. Am J Otol 1996; 17(5): 780-3.
3. Wanamaker J, Kraus D, Eliachar I, Lavertu P. Manifestations of metastatic breast carcinoma to the head and neck. Head Neck 1993; 15(3): 257-62.
4. Akbari M, Akbari M, Zirakzadeh H, Nafisi N, Heidari A, HosseinizadeganShirazi F. Margin status influence on the outcome of patients treated with breast conserving surgery. Iran J Cancer Prev 2011; 4(4): 177-82.
5. Akbari M, Khayamzadeh M, Khoshnevis S, Nafisi N, Akbari A. Five and ten years survival in breast cancer patients mastectomies vs. breast conserving surgeries personal experience. Iran J Cancer Prev 2008; 1(2): 53-6.
6. Nafissi N, Saghafinia M, Motamedi M, Akbari M. A survey of breast cancer knowledge and attitude in Iranian women. J Cancer Res Ther 2012; 8(1): 46-9.
7. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist 2005; 10 Suppl 3: 20-9.
8. Lan M, Shiao A, Li W. Facial paralysis caused by metastasis of breast carcinoma to the temporal bone. J Chin Med Assoc 2004; 67(11): 587-90.
9. Carty N, Foggitt A, Hamilton C, Royle G, Taylor I. Patterns of clinical metastasis in breast cancer: an analysis of 100 patients. Eur J Surg Onc 1995; 21(6): 607-8.
10. Fukumoto M, Osaki Y, Yoshida D, Ogawa Y, Fujiwara M, Miyazaki N, *et al.* Dual-isotope SPECT diagnosis of a skull-base metastasis causing isolated unilateral hypoglossal nerve palsy. Ann Nuc Med 1998; 12(4): 213-6.
11. Jones H. Case of metastasis in the temporal bone from a carcinoma of the breast. J Laryngol Otol 1969; 83(3): 293-8.

Editorial Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163370-73

The Challenge of Obtaining and Maintaining Expertise

David Krag*[a]

[a] Department of Surgical Oncology, University of Vermont, Vermont, USA

Expertise is a special skill or knowledge. An advanced expert also knows the boundaries of that special knowledge. Knowing the boundaries of what is known and not known about a topic puts the expert in the best position to teach, provide medical care or design new questions. Experts continually struggle to maintain their expertise. However, despite substantial efforts, the goal to be on top of the full set of information in a topic and know the boundaries of that information is elusive.

Expertise is highly valued. When faced with a new diagnosis of breast cancer, patients want the person with the most expertise to treat them. Confidence in the physician is high when that person is the recognized expert and knows the boundaries of treatment options. A grant review committee readily identifies an expertly written application. The evidence of expertise of the research topic includes well-chosen citations and a well-designed plan that that steps beyond the edge of what is known. The struggle to achieve expertise is not trivial. The methods used to achieve and maintain expertise are not discussed enough. We present tools to help ameliorate this struggle as it relates to published biomedical information.

Development of the National Library of Medicine (NLM) in Bethesda Maryland is one of the most profound events in the milestones of human knowledge. This is an incomparable data base of published biomedical information that is freely and instantly available around the world via the internet. This data base of published peer reviewed biomedical information provides the foundation of expertise in biomedical sciences. The rate of new published information continuously increases. By the year 2000, the number of new articles entered into the NLM began to exceed 500,000 per year. Within a decade, the number of new articles doubled to about 1,000,000 articles per year. As of August 2016, the total number of articles at NLM was 27,489,908. This is "big data" by any standard.

"Big data" typically refers to managing and standardizing large sets of biological information. Examples include sequences of nucleotides, amino acids, and multiple types of interactomes such as binding interactions between thousands of antibodies and their targets. Tools to manage this information are essential since a single lab can routinely produce sequence information in the billions. Tools to manage this information include an expanding repertoire of powerful algorithms to analyze and compare sequence information. The tools also address more mundane tasks for example submission of sequences, data storage, and interfaces that facilitate making sense of the data. Without these latter tools, the otherwise powerful analytic algorithms would not be functional.

Achieving and maintaining expertise in biomedicine means interacting with the 27,000,000 biomedical articles at NLM which increases by 1,000,000 each year. What tools are available for the user of this "big data" and how can they help establish and maintain expertise? There are excellent search tools such as PubMed to identify sets of articles. However, software tools to help a person interact with this massive amount of data have not kept pace. Simply finding a list of articles is no longer sufficient. Multiple complex tasks are involved to interact with this data set such as identification of articles, getting the full text version, reading the documents, summarizing the key observations, articulating the content in context with a person's intellectual data base, organizing

Address for correspondence:
David Krag, MD
Address: SD Ireland Professor of Surgical Oncology, 89 Beaumont Ave, University of Vermont, College of Medicine, Given Bldg Rm E309, Burlington, VT 05405, USA
Email: david.krag@uvm.edu
Tel: +1 802 6565830
Fax:+1 802 6565833

articles for projects, and sharing information. Ultimately, this information is used for clinical decisions, teaching, and research.

I was fortunate to participate in developing a new surgical method that is now widely used. In 1993 the first article was published describing the radiotracer method for identification and surgical removal of sentinel nodes.[1] The National Cancer Institute funded our research which led to the world's largest randomized surgical trial in breast cancer.[2] Clearly, there was motivation to maintain the highest level of expertise. The number of published articles on sentinel nodes and breast cancer exploded. When that number reached 500 it became obvious that the tools available to manage this data set were inadequate. When that number reached 1000 published articles a decision had to be made to either give up tracking it all or develop new tools. For the next 10 years I was fortunate to lead a group of software engineers and bioinformaticists to develop such tools. I also became the primary experimental subject. This research project in literature management included careful examination of the multitude of mundane steps involved with managing literature. Even on initial analysis, it was clear that the time involved with mundane tasks exceeded the time of the intellectual task to read and understand the key observations of an article. The finding that the average time involved in the tedious nonintellectual tasks was greater than the intellectual task of reading an article was the first of three important and unexpected findings of this research. This indicated that major gains could be made by software that focused on the nonintellectual tasks related to managing literature.

The end result of this research is an online software system, now commercially available, at www.refbin.com. This represents the current version of the software developed over 10 years of research related to tasks associated with managing published literature. The prototype clinical topic was all articles on sentinel nodes and breast cancer which now includes more than 5,600 articles. The prototype basic science topic was all articles involved with phage display which now includes more than 7,700 articles. Both of these data bases are freely available at www.treeofmedicine.com. Working with these two data bases helped established the core principles involved with managing published literature. The following includes some of the key features of the software designed to solve critical problems in managing published literature.

Automated searches

To establish and maintain expertise the expert must read existing relevant literature and continue to read newly published literature. Automating the acquisition of these articles is not trivial. A simple list is not good enough. The software must interact with the expert to make sure that over time, only new articles are presented. The software must have a memory of all prior articles reviewed by the expert. The output of multiple automated searches will overlap and the software needs to sort this out so that the expert is not confronted with redundant articles. The articles must be presented to the user so that decisions on importing or excluding are rapid. The average time in refbin for the expert to make a decision on an article is about 5 seconds. This means that very large sets of articles can be screened. At this rate 2,880 articles can be screened in 4 hours. Once the initial screen of a newly created automated search is complete, the expert can be confident that they have pulled virtually every key article related to their topic out of the 27,000,000 at NLM. The boundaries of published information on that topic will then have been have been defined. Every 24 hours refbin repeats the search but only displays new articles to the expert. The work load then drops dramatically and the expert remains up to date on that topic.

Getting full text PDFs

This is one of the tedious and frustrating tasks that is largely addressed by the refbin software. In about 10 seconds, assuming the article is available electronically to the expert; a copy of the full text PDF is uploaded to their account and correctly affiliated with the citation.

Retrieval of single articles of interest

When reading an article, a citation in the reference list of that article is commonly of interest. In refbin, the expert copies a portion of the citation and a query to PubMed is generated. The desired article is instantly uploaded to the expert's account.

Describing key observations from an article

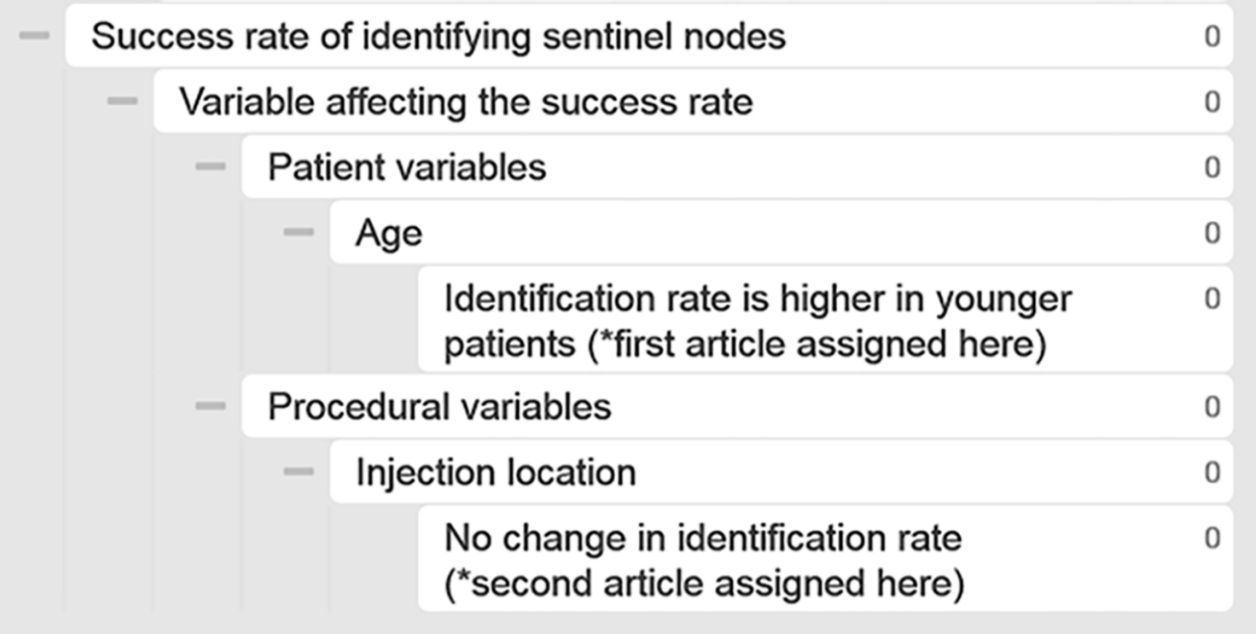
The second important finding of this research is related to the intellectual events that take place when an expert reads an article. The expert reaches a moment when an observation presented in the article becomes clear. At this moment the expert grasps the idea as an element of content. This element of content is important and the expert readily identifies the various key observations of the article. The key observation is a circumscribed unit of information. Putting a boundary around this unit of information is a uniquely human intellectual task. Computers are not yet in a position to accomplish this task. Identification and expression of these key observations are also not readily expressible through key words or by an ontological approach. The expert can extract key observations from the article because the expert already has background knowledge that allows understanding of the observation presented in the article. This means the expert has an intellectual

framework to put the new idea into context. The new observation gets incorporated into this framework making the framework just a bit bigger. Imagine visualizing the structure that represents the intellectual framework of an expert. This would allow externalization of the knowledge of the expert and provide a remarkable tool to share that information.

Translation and merging of ideas and observations

The third unanticipated outcome of this research is related to how the expert can merge multiple new ideas learned from biomedical articles. Put aside keywords for a moment. For most readers and authors key words do not have much utility. What does have utility is the language we use every day to communicate with students and our colleagues and in our own internal thinking. We use narrative statements that are not bounded by strict rules affiliated with keywords or ontology. We simply make a statement. The result is an unambiguous description of a key observation. For example, a key observation in an article is "the success rate of identifying sentinel nodes is higher in younger patients than older patients with breast cancer". There are many different ways to say the same thing with slightly different words but it will remain a clear and unambiguous statement. A next article describes "the success rate of identifying sentinel nodes in breast cancer patients is not affected by the site of injection of tracer". Refbin begins with blank data fields where each idea is typed as a complete narrative statement. The two above ideas work well in that they are both unambiguous. However, after entry of multiple narrative statements this approach becomes burdensome and less useful. The solution is to fragment and merge the narrative statements.

Narrative statement one and two are merged as follows:



From the words "Identification rate is higher in younger patients", the parent phrases, "age, patient variables, variables affecting the success rate, and success rate of identifying the SNs" are the fragments of the original narrative statement. The next narrative statement related to injection location shares the first two parent headings "Success rate of identifying sentinel nodes" and "Variables affecting the success rate".

This strategy merges and condenses the two observations. Adding observations from additional articles on the success rate of identifying SNs becomes much simpler with this framework in place.

The result of this third observation relating to articulating and merging narrative statements results in a written display of an intellectual framework of knowledge. This structure shows the thinking process of the expert. Development and merging of observations based on intact narrative statements begins free form with an unambiguous statement. It becomes obvious to the expert how to merge observations. This allows intact narrative ideas to be manipulated as units of information in ways that are very helpful to the expert. The first benefit is the generation of a visual framework of information. The second is that this allows unexpected and massive condensation of information. Basically all observations in articles that present data on the variables affecting success rate of SN surgery can be merged together in a short section. The expert is then free to see all at once the variables that collectively affect success rate. This allows easier thinking by the expert about everything that might affect the success rate of SN surgery.

How does the process of setting up this framework begin? It does not require premeditation.

Simply making the narrative statements and merging them as they present themselves during literature reading begins to create a structure. There are no limits to the number of observations that can be made for an article. The refbin software allows moving and merging statements at will. The expert lets the observations "self-declare" through narrative statements. This begins to replicate and externalize the structure of the ideas that are in the mind of the expert. We have found this framework to be dynamic and help the expert rethink ideas. Ideas merge and when visualized can be pondered further to help create new ideas.

Workflow

Multiple tasks are associated with published articles. Examples include organizing articles for preparing a grant or a manuscript. Typically this can be one of the most tedious challenges associated with grant or manuscript writing. A parent and child field-based structure in refbin, identical to the structure for entering and merging narrative statements about articles, is used for project management. For example a first level parent heading describes the project, "R01 grant application on immunology of sentinel nodes due March". Multiple child headings may include "first pass articles to read", "articles likely to use", "articles not to use", "articles published by grant review committee members", or "articles not available in the library". Articles are assigned to and moved about to additional headings as appropriate. Such entries are at the complete discretion of the expert. This important application saves considerable time and keeps articles organized during the entire process of grant or manuscript preparation.

Sharing

Sharing ideas, citations and PDFs are integral to clinical care, research and teaching. In refbin, the primary account holder allows others to share some or all of the information in their data base. Sharing is done online from anywhere which considerably facilitates joint projects. This allows clinical, teaching or research groups to combine efforts and jointly build larger data bases.

In summary, the software tools in refbin considerably reduce the time involved with frustrating mundane tasks associated with managing published literature. This liberates experts and students to focus on the intellectual aspects of reading and thinking. Refbin software supports the expert to extract key observations from articles using only common narrative descriptions without needing to learn or confine thinking to strict ontology or a simple file system. Essentially, each expert defines their own ontology. Importantly, using a field-based parent-child system allows free-form merging of ideas and observations. Remarkably this results in massive condensation of information that is built on a structure defined by the expert. Through simplification of large amounts of data, this structure opens up new opportunities to think about biomedical problems. It also allows the expert to share this structure with others in a way not otherwise possible.

Conflict of interest

The author declares ownership in Plomics which produces Refbin.

References

1. Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol 1993; 2(6): 335-9; discussion 40.
2. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, *et al.* Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010; 11(10): 927-33.

Invited Commentary Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163374-76

Is Endogenous Prolactin, Not Endocrine Prolactin, Responsible for Hyperparathyroidism in Breast Cancer Patients?

Atefeh Mohammadnejad*[a], Zhamak Khorgami[b]

[a] University of Tehran, Tehran, Iran
[b] Department of Surgery, Tehran University of Medical Sciences, Tehran, Iran

Breast cancer is the most common site-dependent cancer among females and the main cause of death due to malignancy in females aged 40-44 years. This illness is responsible for 33% of all gynecological malignancies and 20% of all females' mortality. According to the reported statistics in the USA, the probability of developing breast cancer is one in every 8 women.[1]

Hypercalcemia in patients with breast cancer is generally considered a result of osteolytic metastasis or circulating tumor derived products. In such situations, severely depressed plasma parathormone (PTH) is expected.[2,3] Hypercalcemia in malignancies is multifactorial, and results from a combination of increased bone resorption associated with decreased renal excretion of the increased extra-cellular fluid calcium.[4] One of the most frequent etiologies of hypercalcemia is hyperparathyroidism which is usually neglected in breast cancer patients, while recent studies have shown increased incidence of primary hyperparathyroidism in breast cancer patients regardless of clinical staging or anti-tumor therapy.[2]

Plasma parathormone and breast cancer

PTH-related peptide (PTHrP) has a high homology with the N-terminal portion of PTH, which is capable to act with PTH through common as well as specific receptors. In physiological circumstances, PTHrP is produced locally in many normal tissues and has both autocrine and paracrine functions. One of these circumstances is embryonic cells growth development and pregnancy period. PTHrP has an endocrine role in the bone and kidney. As a fact, PTHrP is considered the main reason for hormonal hypercalcemia in malignancies; therefore, the PTHrP plasma level is believed to be a conformational diagnostic test in 80% of breast cancer patients.[5,6]

PTHrP, as well as PTH, causes an increase in the plasma level of calcium and a decrease in the plasma level of phosphorus. In physiological conditions, increased plasma levels of calcium cause a decrement in PTH secretion while in breast cancer patients - with no vitamin D metabolism pathway or digestive disorder- the PTH plasma level is not reduced as a result of hypercalcemia, and has a higher plasma concentration in comparison with the normal population.[2,3]

Prolactin and breast cancer

Prolactin is a lactogenic hormone produced by the pituitary gland. Prolactin induces terminal differentiation in breast epithelial cells and plays a role as a growth and survivor factor.[7] Hyperprolactinemia in breast cancer leads to faster growth in cancerous cells, and is associated with a higher risk of metastasis and poor prognosis.[8, 9] These findings are more significant in cases with positive estrogen and progesterone receptors.[9-11]

Previous studies have shown plasma levels of prolactin in breast cancer patients are higher in comparison with the healthy population and also patients with other cancers.[11-13] This finding is more significant in postmenopausal women rather than premenopausal and is confirmed in animal studies.[9-14]

One study has reported a significant association between the plasma level of prolactin and PTHrP mRNA expression in the breast tissue.[4] There are some evidence about increased plasma levels of prolactin in both primary and secondary hyperparathyroidism.[15] Another study has shown the inductive role of prolactin concentration dependent secretion of PTH

Address for correspondence:
Atefeh Mohammadnejad
Address: University of Tehran, Enghelab St., Tehran, Iran
Tel/Fax: +98 21 66897723
Email: amnejad63@gmail.com

in parathyroid cells.[16]

Endocrine prolactin and endogenous prolactin in breast cancer

Considering the existing evidence on the role of prolactin in the pathogenesis and progression of breast carcinoma, various studies have not reached an agreement to blame prolactin to date. Most of the studies have evaluated endocrine prolactin secreted by the pituitary gland, but there is still less attention to endogenous prolactin produced by breast cancer cells.[17] Although prolactin and prolactin mRNA are detected in the breast tissue, their role is still not clearly defined.[18] In addition, the existence of a cycle between endogenous prolactin and prolactin receptors in basal cell carcinomas (BCCs) would make all the medication plans according to endocrine prolactin fail.

Considering this point is very important when a high percentage of breast cancer patients have hyperprolactinemia which is associated with the tumor size and the risk of recurrence and metastasis, i.e. a poorer prognosis.[19] PTH secretion due to prolactin stimulation occurs within one hour and rises during 3 hours, and seems to be effective in calcium homeostasis by this way.[16] Hypercalcaemia in such situations should suppress PTH. In breast cancer patients, not only the reasons mentioned earlier, but also PTHrP via the mentioned pathway should help to reduce the PTH plasma level. However, most of the studies in this field have reported findings contrary to what is expected. This finding, according to the discussed evidence, might suggest the stimulating effect of prolactin. Few studies have been done to clarify the relationship between PTH and PTHrP, and there is still no conclusion on any diagnostic or prognostic value of the changes of PTH or PTHrP fragments in breast cancer patients.

There is some evidence on a direct correlation between the plasma level of PTH and prolactin in primary and secondary hyperparathyroidism, and in the existence of hyperprolactinemia, plasma level of PTH is increased as well.

The plasma level of prolactin is higher in breast cancer patients in comparison with the normal population or patients with other solid tumors. Hyperprolactinemia in breast cancer patients leads to the faster growth of cancerous cells and a larger tumor size, higher risk of recurrence or metastasis, and a poor prognosis.

On the other hand, hyperparathyroidism aggregates hyperprolactinemia; recent studies have also proved the secretion of prolactin by breast cancer cells (endogenous prolactin).[20,21] This finding confirms the reason for hyperprolactinemia in breast cancer patients with previous hypophysectomy.[22] This point explains why of the according endocrine prolactin medical plans in breast cancer patients are going to be failed. In addition, we should consider the new demand of breast cancer patients for early diagnosis of hyperparathyroidism. If the increased level of prolactin is an alarme sign to treatment failure of metastasis or recurrence of breast cancer, prolactin can be defined as a new tumor marker of breast cancer.

As a summary, beside the generally accepted mechanism of hypercalcemia caused by PTHrP, we suggest PRL as an aggregating factor of hypercalcemia via stimulating the PTH production, which makes PTHrP unable to suppress PTH by elevated serum calcium levels, and elevated PTH can be a trigger for aggregation of hyperprolactinemia. As stated earlier, this vicious cycle can be considered in breast cancer patients, which can be responsible for the highest serum PRL level in breast cancer patients among solid tumors.

In order to examine our theorem, studies should be designed to evaluate the serum level of prolactin, as well as breast tissue concentration of prolactin in breast cancer patients simultaneously. In addition, the serum level of PTH should be compared with patients with benign breast disease and hyperparathyroidism to find out whether the increased serum level of PTH and prolactin is associated with breast tissue prolactin production. It is recommended to consider the difference in the serum level of prolactin and PTH in breast cancer patients in comparison with the patients with benign breast diseases and hyperparathyroidism. The authors suggests to follow up breast cancer patients, which allows them to screen and detect hyperparathyroidism in early stages.

References

1. Hartmann LC, Sellers TA, Frost MH, Lingle WL, Degnim AC, Ghosh K, *et al.* Benign breast disease and the risk of breast cancer. N Engl J Med 2005; 353(3): 229-37.
2. Fierabracci P, Pinchera A, Miccoli P, Conte PF, Vignali E, Zaccagnini M, *et al.* Increased prevalence of primary hyperparathyroidism in treated breast cancer. J Endocrinol Invest 2001; 24(5): 315-20.
3. Barutca S, Yurekli Y, Erdogan S, Kadikoylu G, Kacar F. Parathyroid adenoma-related hypercalcaemia in breast cancer: a critical diagnosis in clinical oncology. Int J Clin Pract 2003; 57(8): 729-30.
4. Mundy GR. Pathogenesis of hypercalcaemia of malignancy. Clin Endocrinol (Oxf) 1985; 23(6): 705-14.
5. Devys A, Lortholary A, Audran M. [PTHrP and breast cancer]. Bull Cancer 2001; 88(11): 1075-80.
6. Perks CM, Keith AJ, Goodhew KL, Savage PB, Winters ZE, Holly JM. Prolactin acts as a potent survival factor for human breast cancer cell lines. Br J Cancer 2004; 91(2): 305-11.
7. Nouhi Z, Chughtai N, Hartley S, Cocolakis E, Lebrun JJ, Ali S. Defining the role of prolactin as

an invasion suppressor hormone in breast cancer cells. Cancer Res 2006; 66(3): 1824-32.
8. Mujagic Z, Mujagic H, Prnjavorac B. Circulating levels of prolactin in breast cancer patients. Med Arh 2005; 59(1): 33-5.
9. Tworoger SS, Hankinson SE. Prolactin and breast cancer risk. Cancer Lett 2006; 243(2): 160-9.
10. Tworoger SS, Sluss P, Hankinson SE. Association between plasma prolactin concentrations and risk of breast cancer among predominately premenopausal women. Cancer Res 2006; 66(4): 2476-82.
11. Wang M, Wu X, Chai F, Zhang Y, Jiang J. Plasma prolactin and breast cancer risk: a meta- analysis. Sci Rep 2016; 6: 25998.
12. Mujagic Z, Mujagic H. Importance of serum prolactin determination in metastatic breast cancer patients. Croat Med J 2004; 45(2): 176-80.
13. Raymond JP, Isaac R, Merceron RE, Wahbe F. Comparison between the plasma concentrations of prolactin and parathyroid hormone in normal subjects and in patients with hyperparathyroidism or hyperprolactinemia. J Clin Endocrinol Metab 1982; 55(6): 1222-5.
14. Tikk K, Sookthai D, Fortner RT, Johnson T, Rinaldi S, Romieu I, *et al.* Circulating prolactin and in situ breast cancer risk in the European EPIC cohort: a case-control study. Breast Cancer Res 2015; 17: 49.
15. Jacobson EM, Hugo ER, Borcherding DC, Ben-Jonathan N. Prolactin in breast and prostate cancer: molecular and genetic perspectives. Discov Med 2011; 11(59): 315-24.
16. Magliola L, Forte LR. Prolactin stimulation of parathyroid hormone secretion in bovine parathyroid cells. Am J Physiol 1984; 247(5 Pt 1): E675-80.
17. Leondires MP, Hu ZZ, Dong J, Tsai-Morris CH, Dufau ML. Estradiol stimulates expression of two human prolactin receptor isoforms with alternative exons-1 in T47D breast cancer cells. J Steroid Biochem Mol Biol 2002; 82(2-3): 263-8.
18. Ando S, De Amicis F, Rago V, Carpino A, Maggiolini M, Panno ML, *et al.* Breast cancer: from estrogen to androgen receptor. Mol Cell Endocrinol 2002; 193(1-2): 121-8.
19. Gutzman JH, Miller KK, Schuler LA. Endogenous human prolactin and not exogenous human prolactin induces estrogen receptor alpha and prolactin receptor expression and increases estrogen responsiveness in breast cancer cells. J Steroid Biochem Mol Biol 2004; 88(1): 69-77.
20. Clevenger CV, Chang WP, Ngo W, Pasha TL, Montone KT, Tomaszewski JE. Expression of prolactin and prolactin receptor in human breast carcinoma. Evidence for an autocrine/paracrine loop. Am J Pathol 1995; 146(3): 695-705.
21. Shaw-Bruha CM, Pirrucello SJ, Shull JD. Expression of the prolactin gene in normal and neoplastic human breast tissues and human mammary cell lines: promoter usage and alternative mRNA splicing. Breast Cancer Res Treat 1997; 44(3): 243-53.
22. Clevenger CV, Plank TL. Prolactin as an autocrine/paracrine factor in breast tissue. J Mammary Gland Biol Neoplasia 1997; 2(1): 59-68.

Review Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163377-82

Diagnostic Value of PET/CT in Comparison with Other Conventional Imaging Modalities for the Evaluation of Breast Cancer Recurrence: A Systematic Review of the Literature

Sahel Heydarheydari[a], Abbas Haghparast*[a]

[a] *Department of Medical Physics, Faculty of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran*

ARTICLE INFO

Received:
8 January 2016
Revised:
25 February 2016
Accepted:
20 August 2016

Keywords:
PET/CT,
recurrence,
breast cancer,
diagnostic value,
imaging modalities

ABSTRACT

Background: Despite developments in surgical treatment, radiation therapy, and chemotherapy protocols, tumor recurrence and metastasis are still major problems in breast cancer management. The aim of the present report was to review and compare the performance of PET/CT with some of the conventional imaging modalities in detection of breast cancer recurrence.

Methods: A literature search was performed in PubMed, Europe PMC and ScienceDirect databases with no search restriction for the date of publication but the search was limited to papers published in English.

Results: Twenty-two studies including a total of 1378 patients with prior breast cancer and clinical suspicion of recurrence that assessed the sensitivity, specificity, and accuracy of PET/CT and other conventional imaging methods in followed up by treated breast cancer and presented the results in systematic review format. The information extracted from each article included the first author, publication year, number of patients and their characteristics, index test(s), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

Conclusions: According to the literature, PET/CT seems to be a more useful modality than current techniques to assess the patients with suspected recurrent and metastatic breast cancer. If PET/CT is not applicable, MRI and also bone scintigraphy could also be performed as alternatives.

Introduction

Breast cancer is the most frequent malignancy among women, affecting 1 in 13 women in their lifetime.[1-3] Despite developments in surgical treatment, radiation therapy, and chemotherapy protocols, tumor recurrence has remained a major problem in breast cancer management.[4] The risk of recurrence in breast cancer patients is about 7–30% in the disease course.[5] A diagnosis of breast cancer recurrence is important to define appropriate therapeutic strategies and increase the odds of treatment. Cure options have developed over the past decade and have had an impact on survival.[1, 6, 7] Positron emission tomography/computed tomography (PET/CT) is increasingly used for oncologic imaging, and the utilization of PET/CT depends not only on their diagnostic accuracy, but also on their comparative advantage over available diagnostic methods.[1,8]

PET uses a radioactive tracer to produce three-dimensional (3D) images of body processes and is increasingly used for cancer diagnosis, staging, and restaging patient with breast cancer.[9] A commonly-

Address for correspondence:
Abbas Haghparasat, PhD
Address: Department of medical physics, School of Medicine, Kermanshah University of Medical Scienses, Kermanshah, Iran
Tel.: +98 9183334998
fax: +98 83 34276477
Email: a.haghparast@kums.ac.ir

used tracer is fluorodeoxyglucose (FDG) attached to the radioactive isotope fluorine-18 that can be used to detect tumor cells, which have a higher glucose uptake than normal cells.[10, 11] Metabolic tracers such as FDG-PET overcome the limitations of anatomical imaging modalities since functional changes assessed by PET or PET/CT imaging usually precede anatomical changes assessed by MRI or CT.[12] PET/CT scan allows for simultaneous visualization of the tissue anatomy and metabolic activities; moreover, it has been recently shown to have an increasing relevance in detection and management of breast cancer recurrence.

The aim of present study was to compare the performance of PET/CT with some conventional imaging modalities in the detection of breast cancer recurrence.

Methods

Search strategy

A literature search was performed in the following databases with "PET/CT AND Breast Cancer Recurrence" as key words: PubMed, Europe PubMed Central, and ScienceDirect. No search restriction was used for the date of publication, but the search was limited to papers published in English. Articles that cited related studies were also searched to find any related publication (using PubMed, and Europe PubMed Central citation tracking tools).

Selection of Studies

Titles and abstracts obtained from the literature search were examined for inclusion. If the information provided in the title and abstract suggested that the study included patients with a history of breast cancer, conducted PET/CT scans in those patients, and evaluated test values (sensitivity, specificity, and accuracy), full paper articles were retrieved for further assessment.

Inclusion and Exclusion Criteria

Studies were included if they assessed the sensitivity, specificity, and accuracy of 18-F-FDG imaging in the follow-up of breast cancer. The included studies used PET/CT for a diagnosis of breast cancer recurrence. Recurrence could be local or distant, but the disease had to be a consequence of the originally diagnosed breast cancer. The diagnostic value was assessed in comparison with the gold standard of diagnosis, i.e. the results of pathological assessment. This review included both studies with and without comparator groups. Letters to the editor, case reports, and review articles was excluded.

Data Extraction

The information extracted from each article included the first author, publication year, number of patients and their characteristics, index test(s), sensitivity, specificity, positive predictive value, negative predictive value, and accuracy.

The patients were classified as true positive (TP) when both PET/CT scan and reference standard detected breast cancer recurrence, true negative (TN) when neither test detected recurrence, false negative (FN) when PET/CT scan failed to detect recurrence identified by the reference standard, and false positive (FP) when the PET/CT scan incorrectly suggested recurrence not detected by the reference standard.

Accuracy was defined as TN+TP / (TN + TP + FN + FP), sensitivity as TP / (TP + FN), and specificity as TN / (TN + FP).

Statistical Analysis

Twenty-two studies that assessed the sensitivity, specificity, and accuracy of PET/CT imaging in the follow-up of treated breast carcinoma and presented the results in a systematic review format were included.

SPSS version 16 was used for data analysis using descriptive statistics.

Results

Locoregional recurrence predominately affects the breast, supraclavicular nodes, skin, axillary, and the chest wall. Intrathoracic recurrence often occurs in internal mammary, mediastinal nodes, pleura, and lung parenchyma.

Brain, liver, and bone are the most frequent sites of extrathoracic recurrence. The correct identification of local and distant recurrence at the time of suggestive symptoms in the follow-up of breast cancer prompts clinical consideration for administration of different therapies. Thus, it is important and crucial to detect recurrences or metastases as soon as possible in patients with breast cancer.

This systematic review focused on evaluating the diagnostic value of PET, CT, MRI, bone scintigraphy (BS) and PET/CT, which are widely used non-invasive modalities for the detection of locally recurrent and metastatic breast cancer.

The results in Table 1 show the main characteristics of the six included studies for evaluating the diagnostic value of positron emission tomography-/computed tomography (PET/CT).

Four studies compared the diagnostic value of PET/CT with positron emission tomography (PET) (Table 2), 8 compared PET/CT with computed tomography (CT-scan) (Table 3), 2 compared PET/CT with magnetic resonance imaging (MRI) (Table 4), and 2 compared PET/CT with BS (Table 5).

Tables 1-5 show 22 studies including a total of 1378 patients with prior breast cancer and clinical suspicion of breast cancer recurrence.

Table 1. Main characteristics of the included studies for evaluating the diagnostic value of PET/CT

First author (Year)	Number of patients (Gender)	Mean age	Index test	FN (n)	TN (n)	FP (n)	TP (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Moon (1998) [13]	57 (Female)	55	PET/CT	2	22	6	27	79	93	82	92	86
Aukema (2009) [14]	56 (Female)	54	PET/CT	—	—	—	—	92	97	94	96	95
Palomar Monuz (2010) [15]	70 (Female)	—	PET/CT	4	32	5	29	86.4	87.8	85.2	88.8	87.1
Emad-Eldin (2013) [16]	34 (Female)	—	PET/CT	2	10	1	21	92.3	90.5	95	85.7	91.2
Manohar (2013) [17]	43 (Female)	—	PET/CT	—	—	—	—	96.8	100	91	100	—
Groheux (2014) [18]	15 (Male)	—	PET/CT	—	—	—	—	67	100	86	100	89

Abbreviations: PPV: Positive Predictive Value; NPV: Negative Predictive Value; PET/CT: Positron Emission Tomography/Computed Tomography

Table 2. Main characteristics of the included studies for evaluating the diagnostic value of PET/CT and PET in comparative studies

First author (Year)	Number of patients (Gender)	Mean age	Index test	FN (n)	TN (n)	FP (n)	TP (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Fueger (2005) [19]	58 (Female)	53.3	PET/CT PET	2 5	21 18	4 7	31 28	94 85	84 72	—	—	89.7 79.3
Veit-Haibach (2007) [20]	44 (Female)	—	PET/CT PET	0 2	19 17	4 6	21 19	100 89	84 76	—	—	90.9 81.8
Haug (2007) [21]	34 (Female)	—	PET/CT PET	1 3	8 7	1 1	24 23	96 88	89 78	—	—	94.1 88.2
Dirisamer (2010) [22]	52 (Female)	—	PET/CT PET	2 8	10 10	0 0	40 34	95 81	100 100	—	—	96.1 84.6

Abbreviations: PPV: Positive Predictive Value; NPV: Negative Predictive Value; PET/CT: Positron Emission Tomography/Computed Tomography; PET: Positron Emission Tomography

Table 3. Main characteristics of the included studies for evaluating the diagnostic value of PET/CT and CT in comparative studies

First author (Year)	Number of patients (Gender)	Mean age	Index test	FN (n)	TN (n)	FP (n)	TP (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Abo-Sheisha (2014) [23]	50 (Female)	50.85	PET/CT CT	1 5	14 19	1 6	34 18	97 75	93 73	97 72	93	96 74
Dirisamer (2010) [22]	52 (Female)	—	PET/CT CT	2 14	10 10	0 0	40 28	95 67	100 100	—	76 —	96.1 73
Radan (2006) [7]	37 (Female)	59.9	PET/CT CT	3 6	13 8	4 9	17 14	85 70	76 47	81 56	81 57	81 59
Haug (2007) [21]	34 (Female)	—	PET/CT CT	1 2	8 6	1 2	24 24	96 70	89 47	—	—	94.1
Piperkova (2007) [24]	48 (Female)	55.3	PET/CT CT	—	—	—	—	97.8 87.6	93.5 42	99.1 85.3	91.6 31.7	88.2 97.3
Evangelista (2011) [25]	111 (Female)	61	PET/CT CT	—	—	—	—	81 72	52 37	41 32	87 76	82.1 60
Niikura (2011) [26]	225 (Female)	53.4	PET/CT CT	1 12	162 128	7 21	55 38	97.4 85.9	91.2 67.3	—	—	47 —
Groheux (2013) [27]	117 (Female)	—	PET/CT CT	—	—	—	—	100 50	99.1 100	66.7 100	100 99.1	99.1 99.1

Abbreviations: PPV: Positive Predictive Value; NPV: Negative Predictive Value; PET/CT: Positron Emission Tomography/Computed Tomography; CT: Computed Tomography

Table 4. Main characteristics of the included studies for evaluating the diagnostic value of PET/CT compared to MRI

First author (Year)	Number of patients (Gender)	Mean age	Index test	FN (n)	TN (n)	FP (n)	TP (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Iagaru (2007) [28]	21 (Female)	52	PET/CT	—	—	—	—	75	92.3	—	—	—
			MRI	—	—	—	—	85.7	85.7	—	—	—
Schmidt (2008) [6]	33 (Female)	—	PET/CT	—	—	—	—	91	90	—	—	—
			MRI	—	—	—	—	93	86	—	—	—

Abbreviations: PPV: Positive Predictive Value; NPV: Negative Predictive Value; PET/CT: Positron Emission Tomography/Computed Tomography; MRI: Magnetic Resonance Imaging

Table 5. Main characteristics of the included studies for diagnostic value of PET/CT and BS in comparative studies

First author (Year)	Number of patients (Gender)	Mean age	Index test	FN (n)	TN (n)	FP (n)	TP (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Withofs (2011) [29]	24 (Female)	60.2	PET/CT	—	—	—	—	73.9	79.3	86.1	63.7	76
			BS	—	—	—	—	43	76.8	76.3	43.8	55
Balci (2012) [30]	158 (Female) 4 (Male)	50.6	PET/CT	—	—	—	—	83	100	100	90	100
			BS	—	—	—	—	96	100	100	98	100

Abbreviations: PPV: Positive Predictive Value; NPV: Negative Predictive Value; PET/CT: Positron Emission Tomography/Computed Tomography; BS: Bone Scintigraphy

Diagnostic Value of PET/CT for Detection of BC Recurrence

Analysis of the 22 included studies showed that the sensitivity, specificity, PPV, NPV, and accuracy of PET/CT for detection of recurrence ranged from 73.9%-100%, 52%-100%, 41%-100%, 63.7%-100%, and 60%-99.1%, respectively.

Diagnostic Value of PET for Detection of BC Recurrence

Four included studies showed that the sensitivity, specificity, and accuracy of PET for detection of recurrence ranged from 81%-89%, 72%-100%, and 79.3%-88.2%, respectively.

Diagnostic Value of CT-scan for Detection of BC Recurrence

Eight included studies showed that the sensitivity, specificity, PPV, NPV, and accuracy of CT-scan for detection of recurrence ranged from 50%-87.6%, 37%-100%, 32%-100%, 31.7%-99.1%, and 47%-99.1%, respectively.

Diagnostic Value of MRI for Detection of BC Recurrence

Based on the two included studies, the sensitivity and specificity of MRI technology for detection of recurrence ranged from 85.7%-93% and 85.7%-86%, respectively.

Diagnostic Value of PET for Detection of BC Recurrence

According to the findings of two included studies, the sensitivity, specificity, PPV, NPV, and accuracy of BS for detection of recurrence ranged from 43%-96%, 76.8%-100%, 76.3%-100%, 43.8%-98%, and 55%-100%, respectively.

Discussion

Sixteen out of 22 included studies compared PET/CT with conventional imaging modalities such as PET, CT scan, MRI, and BS. Four studies compared PET/CT with PET (marked in Table 2) and found it had a high sensitivity, specificity, and accuracy as compared with PET. The rate of the detection of recurrence and metastasis was significantly higher with PET/CT than with PET. Table 3 shows eight studies that compared PET/CT with CT scan for detection of BC recurrence and reported that the sensitivity, specificity, and accuracy of PET/CT were higher than CT scan. In six studies of combined PET/CT (marked in Table 1), the mean sensitivity and specificity for the detection of recurrence was higher than PET and CT scan, indicating a marginally increased diagnostic value or diagnostic precision. It has been reported that PET/CT is superior for the detection of BC recurrence with a mean accuracy of 89.33% versus 83.1% and 74.62% for PET and CT, respectively. Two studies compared PET/CT with MRI (marked in Table 4) and reported a high sensitivity and specificity as compared with MRI.

Table 5 shows two studies that compared PET/CT with BS for the detection of BC recurrence and bone metastases. The PET/CT sensitivity ranged from 73.9%-100% (43-96% using BS) and the PET/CT specificity ranged from 52%-100% (76.8-100% using BS). Data analysis showed a high sensitivity and a low specificity for PET/CT as compared with BS. In twenty-two included studies, PET/CT and MRI had the highest sensitivity (0.920 and 0.893, respectively), and BS and PET/CT had the highest specificity (0.884 and 0.875, respectively).

In conclusion, according to the results, PET/CT seems to be a more useful modality than the existing

techniques to assess the patients with suspected recurrent and metastatic breast cancer. However, uncertainty remains around the use of PET/CT as a substitute for current imaging technologies. If PET/CT is not applicable, MRI and also BS could also be used as alternatives.

Conflict of Interest

The authors have no potential conflict of interest concerning the content of this article.

References

1. Pennant M, Takwoingi Y, Pennant L, Davenport C, Fry-Smith A, Eisinga A, *et al.* A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence. Health Technol Assess 2010; 14(50): 1-103.
2. Pan L, Han Y, Sun X, Liu J, Gang H. FDG-PET and other imaging modalities for the evaluation of breast cancer recurrence and metastases: a meta-analysis. J Cancer Res Clin Oncol 2010; 136(7): 1007-22.
3. Warning K, Hildebrandt MG, Kristensen B, Ewertz M. Utility of 18FDG-PET/CT in breast cancer diagnostics–a systematic review. Dan Med Bull 2011; 58(7): A4289.
4. Yilmaz MH, Esen G, Ayarcan Y, Aydogan F, Özgüroglu M, Demir G, *et al.* The role of US and MR imaging in detecting local chest wall tumor recurrence after mastectomy. Diagn Interv Radiol 2007; 13(1): 13.
5. Bongers V, Perre C, de Hooge P. The use of scintimammography for detecting the recurrence of loco-regional breast cancer: histopathologically proven results. Nucl Med Commun 2004; 25(2): 145-9.
6. Schmidt GP, Baur-Melnyk A, Haug A, Heinemann V, Bauerfeind I, Reiser MF, *et al.* Comprehensive imaging of tumor recurrence in breast cancer patients using whole-body MRI at 1.5 and 3T compared to FDG–PET–CT. Eur J Radiol 2008; 65(1): 47-58.
7. Radan L, Ben-Haim S, Bar-Shalom R, Guralnik L, Israel O. The role of FDG-PET/CT in suspected recurrence of breast cancer. Cancer 2006; 107(11): 2545-51.
8. Rosen EL, Eubank WB, Mankoff DA. FDG PET, PET/CT, and Breast Cancer Imaging. Radiographics 2007; 27(suppl_1): S215-S29.
9. Cooper K, Harnan S, Meng Y, Ward S, Fitzgerald P, Papaioannou D, *et al.* Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: a systematic review and meta-analysis. Eur J Surg Oncol 2011; 37(3): 187-98.
10. Facey K, Bradbury I, Laking G, Payne E. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers: Gray Pub.; 2007.
11. Morris PG, Lynch C, Feeney JN, Patil S, Howard J, Larson SM, *et al.* Integrated positron emission tomography/computed tomography may render bone scintigraphy unnecessary to investigate suspected metastatic breast cancer. J Clin Oncol 2010; 28(19): 3154-9.
12. Sadeghi R, Gholami H, Zakavi SR, Kakhki VRD, Horenblas S. Accuracy of 18F-FDG PET/CT for diagnosing inguinal lymph node involvement in penile squamous cell carcinoma: systematic review and meta-analysis of the literature. Clin Nucl Med 2012; 37(5): 436-41.
13. Moon DH, Maddahi J, Silverman DH, Glaspy JA. Accuracy of whole-body fluorine-18-FDG PET for the detection of recurrent or metastatic breast carcinoma. J Nucl Med 1998; 39(3): 431.
14. AukemaTS, Rutgers ET, Vogel WV, Teertstra HJ, Oldenburg HS, Peeters MV, *et al.* The role of FDG PET/CT in patients with locoregional breast cancer recurrence: a comparison to conventional imaging techniques. Eur J Surg Oncol 2010; 36(4): 387-92.
15. Muñoz AP, Vicente AG, Rubio MT, Woll JP, García VP, Guardia MB, *et al.* [Diagnostic and therapeutic impact of 18F-FDG-PET/CT in patients with suspected breast cancer recurrence]. Rev Esp Med Nucl 2010; 29(3): 100-8.
16. Emad-Eldin S, Abdelaziz O, Harth M, Hussein M, Nour-Eldin N-E, Vogl TJ. The clinical utility of FDG-PET/CT in follow up and restaging of breast cancer patients. The Egyptian Journal of Radiology and Nuclear Medicine 2013; 44(4): 937-43.
17. Manohar K, Mittal BR, Bhoil A, Bhattacharya A, Singh G. Role of 18F-FDG PET/CT in identifying distant metastatic disease missed by conventional imaging in patients with locally advanced breast cancer. Nucl Med Commun 2013; 34(6): 557-61.
18. Groheux D, Hindié E, Marty M, Espié M, Rubello D, Vercellino L, *et al.* 18 F-FDG-PET/CT in staging, restaging, and treatment response assessment of male breast cancer. Eur J Radiol 2014; 83(10): 1925-33.
19. Fueger BJ, Weber WA, Quon A, Crawford TL, Allen-Auerbach M, Halpern B, *et al.* Performance of 2-deoxy-2-[F-18] fluoro-D-glucose positron emission tomography and integrated PET/CT in restaged breast cancer patients. Mol Imaging Biol 2005; 7(5): 369-76.
20. Veit-Haibach P, Antoch G, Beyer T, Stergar H, Schleucher R, Hauth E, *et al.* FDG-PET/CT in restaging of patients with recurrent breast cancer: possible impact on staging and therapy. Br J Radiol 2014; 80(955): 508-15.
21. Kessler L, McDonough R, Lee DW, Jacques L.

Comparative Effectiveness in Molecular Imaging July 21-22, 2010 Doubletree Hotel and Executive Conference Center. 2010.
22. Dirisamer A, Halpern BS, Flöry D, Wolf F, Beheshti M, Mayerhoefer ME, *et al.* Integrated contrast-enhanced diagnostic whole-body PET/CT as a first-line restaging modality in patients with suspected metastatic recurrence of breast cancer. Eur J Radiol 2010; 73(2): 294-9.
23. Abo-Sheisha DM, Badawy ME. The diagnostic value of PET/CT in recurrence and distant metastasis in breast cancer patients and impact on disease free survival. Egyptian J Radiol Nucl Med 2014; 45(4): 1317-24.
24. Piperkova E, Raphael B, Altinyay ME, Castellon I, Libes R, Sandella N, *et al.* Impact of PET/CT in comparison with same day contrast enhanced CT in breast cancer management. Clin Nucl Med 2007; 32(6): 429-34.
25. Evangelista L, Baretta Z, Vinante L, Cervino AR, Gregianin M, Ghiotto C, *et al*. Tumour markers and FDG PET/CT for prediction of disease relapse in patients with breast cancer. Eur J Nucl Med Mol Imaging 2011; 38(2): 293-301.
26. Niikura N, Costelloe CM, Madewell JE, Hayashi N, Yu T-K, Liu J, *et al.* FDG-PET/CT compared with conventional imaging in the detection of distant metastases of primary breast cancer. Oncologist 2011; 16(8): 1111-9.
27. Groheux D, Giacchetti S, Delord M, Hindié E, Vercellino L, Cuvier C, *et al.* 18F-FDG PET/CT in staging patients with locally advanced or inflammatory breast cancer: comparison to conventional staging. J Nucl Med 2013; 54(1): 5-11.
28. Iagaru A, Masamed R, Keesara S, Conti PS. Breast MRI and18F FDG PET/CT in the management of breast cancer. Ann Nucl Med 2007; 21(1): 33-8.
29. Withofs N, Grayet B, Tancredi T, Rorive A, Mella C, Giacomelli F, *et al.* 18F-fluoride PET/CT for assessing bone involvement in prostate and breast cancers. Nucl Med Commun 2011; 32(3): 168-76.
30. Balci TA, Koc ZP, Komek H. Bone Scan or 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography; Which Modality Better Shows Bone Metastases of Breast Cancer? Breast Care 2012; 7(5): 389-93

.

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163383-86

Axillary Reverse Mapping: A Potentially Safe Procedure in Oncology

Behnam Behboudi[a], Mohamadreza Neishaboury[a, b], Fezzeh Elyasinia[a], Massoome Najafi[a], Ahmad Kaviani*[a, b]

[a] *Department of Surgery, Tehran University of Medical Sciences, Tehran, Iran*
[b] *Kaviani Breast Disease Institute, Tehran, Iran*

ARTICLE INFO

Received:
16 April 2016
Revised:
10 May 2016
Accepted:
18 August 2016

Keywords:
SLNB,
oncological safety,
tumoral involvement,
axillary reverse mapping

ABSTRACT

Background: In an attempt to reduce the risk of developing lymphedema following breast cancer surgery, some researchers suggested that by identifying and preserving the lymphatic plexus which drains ipsilateral arm we can minimize the risk of lymphedema. The procedure is known as axillary reverse mapping (ARM). In the current study, we investigated the oncological safety of this technique.

Methods: A total of 60 patients who were undergoing axillary lymph node dissection were involved. The indications for axillary dissection were whether clinically node-positive axilla or positive sentinel lymph node biopsy. ARM was performed by injecting 2 ml of methylene blue subcutaneously in the upper and medial part of ipsilateral patients' arm along the intermuscular groove.

Results: ARM nodes were identified by means of methylene blue injection in 51(85%) patients (identification rate = 85%). For the subgroup of clinically positive axillary lymph nodes, identification rate was 93.1%, and the corresponding figure was 77.4% for positive SLNB group (P = 0.148). Pathological evaluation of harvested ARM nodes demonstrated metastatic involvement in 8(27.5%) and 1(3.2%) patients in clinically positive and SLNB positive groups respectively (P = 0.026).

Conclusions: Based on the findings of this study it seems that ARM could be considered as a safe procedure in patients who are a candidate for ALND when SLNB is positive. In contrast, in patients with clinically positive axillary nodes, there is a considerable risk of tumoral metastasis in ARM nodes.

Introduction

Recent studies have casted doubt on the short-term efficacy of complete axillary lymph-node dissection (ALND) in oncology patients receiving chemotherapy or axillary raditherapy.[1-4] Considering the high risk of development of lymphedema after ALND (up to 77%), sentinel lymph node biopsy (SLNB) is more commonly used to investigate the extent of axillary lymph node involvement.[5, 6] It is noteworthy that several studies aiming at assessment of the long-term side-effects of SLNB have demonstrated an increased risk of development of lymphedema by up to 13%.[7,8]

With the view of the aforementioned potential complications, efficacy and safety of modified surgical techniques for preservation of axillary lymphatic drainage have been investigated by different studies with the main objective of preventing or at least reducing risk of lymphedema. Recently, several studies have hypothesized that by

Address for correspondence:
Ahmad Kaviani, MD
Address: Kaviani Breast Disease Institute (KBDI), No 3, Tavaneer Sq., Tehran, 1434888483, Iran
Tel: +98 21 88871785
Fax: +98 21 88871698
Email: akaviani@tums.ac.ir

differentiating arm lymph nodes from the breast ones and preserving them, the risk of lymphedema may be reduced.[9-11] Accordingly, axillary reverse mapping (ARM) is introduced to distinguish and preserve arm lymph nodes.[12]

This technique is utilized by means of subdermal injection of a blue dye in upper and inner parts of patient's arm, whereby facilitating visualization of lymphatic plexus of the arm during ALND procedure. Although findings of some studies advocate this hypothesis and provide supportive evidence for potential long-term benefits of ARM,[13-19] the safety of this technique in oncology is still not well elucidated.[11] The term "cross-over" node refers to lymph nodes which receive lymphatic drainage from both the breast and the arm.[20] Therefore, it would be plausible to infer that preserving these nodes leads to an increased risk of recurrence.

The current study was designed to evaluate the metastatic involvement of lymph nodes detected in ARM procedure. The findings of this study could provide information regarding oncological safety of preserving lymph nodes draining the ipsilateral arm in breast cancer patients.

Methods

Patients and study protocol

This prospective study was designed and conducted at two referral clinics in Tehran, Iran between 2014 and 2016. Patients who were undergoing breast surgery (either mastectomy or breast conservative surgery) with ALND (level I and II nodes) were enrolled in the study. The criteria for performing ALND were as follow: 1) clinically positive lymph nodes or 2) positive SLNB. Subjects were excluded if they had previously received neoadjuvant chemotherapy, hormonal therapy or radiotherapy. Also, pregnant patients and those with known history of allergic reaction to methylene blue were not included. Written informed consent was obtained prior to the enrollment of the subjects and institutional ethical board of Tehran University of Medical Sciences reviewed and approved the study protocol.

SLNB procedure

In patients with clinically negative axillary lymph nodes, SLNB was carried out by injecting radioactive colloid in subareolar plexus. Prior to making any incision in the axillary region of the subjects, sentinel nodes were localized using a hand-held gamma probe. If the sentinel node could not be detected based on radioactivity, then methylene blue was also injected in subareolar plexus and the patient was excluded from performing ARM. If SLN was detectable by gamma probe, patients underwent ARM procedure. Subsequently, sentinel nodes were dissected and sent for frozen section analysis. Dissection of the axillary nodes was performed if the histopathological assessment of harvested nodes indicated any tumoral involvement.

Axillary reverse mapping

ARM was performed by injecting 2 ml of methylene blue subcutaneously in the upper and medial part of ipsilateral patients' arm along the intermuscular groove. Then the site of injection was gently massaged very smoothly, and patients' arms were elevated for few minutes to enhance lymphatic drainage; and, subsequently, routine prep and drape were done prior to initiation of procedure.

Axillary lymph node dissection

ALND was performed through routine axillary incision unless the patient was planned to undergo mastectomy, in which case ALND was carried out through the incision made for the surgery. The limits of ALND included axillary vein superiorly, anterior serratus muscle as medial limit and latissmus dorsi muscle as the lateral limit. Level I and II axillary nodes were dissected, and after recording of the number of blue nodes (lymph nodes draining arm lymph), and these nodes were harvested and sent for pathologic examination.

Pathology

The blue nodes were labeled as arm nodes; and, ALND harvested axillary nodes were labeled as axillary nodes before being sent for pathologic assessment in separate formalin-filled bottles. The samples then were sent to pathology department and were sectioned at 3-mm thickness along the long axis. If the largest diameter of the lymph node was < 5mm, they were bisected. One section of each node was submitted for hematoxylin and eosin staining.

Statistical analysis

Data analyses were performed using IBM SPSS version 19.0 software. Categorical data were compared between study groups by means of Chi-square or Fisher's exact tests where applicable. However, continuous variables without normal distribution among study subjects were compared using Mann-Whitney U test.

Results

A total of 60 patients were enrolled in the current study. It was observed that 29 subjects (48.3%) had clinically positive axillary lymph node involvement and 31(51.7%) had positive SLNB. The mean age of the patients was 48.23±7.57 years.

ARM nodes were identified by means of methylene blue injection in 51(85%) patients (identification rate = 85%). For the subgroup of clinically positive axillary lymph nodes, identification rate was 93.1% (27 of 29 patients) and the figure was 77.4% (24 of 31 patients) for positive SLNB group. There was no statistically significant

differences in identification rate between the two groups (P = 0.148)

The median numbers of lymph nodes detected during the procedure were 1 (IQR: 1 – 2) in the clinically positive group and 1 (IQR: 1 – 1.75) in the positive SLNB group (P = 0.734).

Pathological evaluation of harvested ARM nodes demonstrated metastatic involvement in 8(27.5%) and 1(3.2%) patients in clinically positive and SLNB positive groups respectively. Statistically significant differences were observed when the two groups were compared with respect to positive ARM nodes (P = 0.026).

No adverse effect due to injection of methylene blue (e.g. skin necrosis or inflammatory reaction) was observed among study participants.

Discussion

The aim of the present study was to determine metastatic involvement of lymph nodes identified during ARM. Our findings were consistent with previous studies on feasibility and oncological safety of ARM. We observed the detection rate of 85% for ARM nodes amongst our patients. However, this figure was different depending on the primary indication of ALND and ARM nodes were more commonly detected in the clinically positive group in comparison with those who underwent ALND following a positive SLNB (93.1% vs. 77.4%). The first group demonstrated significantly higher rates of metastatic involvement of ARM nodes (27.5% vs. 3.2%). Previously, several studies have been designed and conducted to evaluate the metastatic potential of ARM lymph nodes. Two points can be considered to be of singular importance regarding their findings: firstly, they reported different identification rates for ARM nodes (ranging from 50% to 91%), and, secondly, the rate of metastasis of the nodes is reported to be ranging from 14% to 43% by different investigators.[13-19] Therefore, it may be concluded that these findings not only cast doubt on the clinical effectiveness of ARM procedure, but also raise serious questions about its safety. The reason for metastatic involvement of ARM nodes is not clear but researchers have proposed that progression of the primary disease is responsible for tumoral metastasis to ARM nodes.[15]

In one study, Ikeda and his colleagues evaluated the oncological safety of performing ARM in a cohort of 60 patients.[21] Consistent with our findings, they reported a higher rate of tumoral involvement of ARM nodes among clinically node-positive patients in comparison with those with a positive SLNB. Moreover, they observed that clinically node-positive patients with extensive axillary metastasis (more than 4 metastatic nodes) comprised the majority of patients with positive ARM nodes. This finding further supports the hypothesis that progression of primary breast cancer may be responsible for metastasis to ARM nodes. A systematic review of eight ARM studies suggested that in order not to jeopardize the oncological safety of primary surgery, patients with the N1 disease can benefit from procedures which preserve ARM nodes. In contrast, it is demonstrated that harvesting the ARM nodes (plus reappoximating or performing lymphovenous anastomosis) would be a safe treatment option in patients with N2 or N3 disease.[22] Considering the 27.5% of tumoral involvement of ARM nodes among our clinically node-positive patients, results of this study emphasize on the mentioned proposal that this group of patients may not be an appropriate candidate for this technique.

One of the main limitations of the current study was the use of methylene blue for detecting ARM nodes. This dye was chosen due to its availability in our centre. Several reports on inflammatory skin lesions or even skin necrosis after injection of methylene blue has been reported in the literature. Some researchers used isosulfan blue for detection of ARM nodes.[17] It is worth mentioning that none of our patients experienced any adverse effect and identification rate of ARM nodes in our study was similar to those in which isosulfan blue was used for staining ARM nodes.

In conclusion, based on the findings of this study it seems that ARM could be considered as a safe procedure in patients who are a candidate for ALND when SLNB is positive. In contrast, in patients with clinically positive axillary nodes, there is a considerable risk of tumoral metastasis in ARM nodes. Further studies with larger sample size are warranted to elucidate the oncological safety of ARM in the mentioned group of patients.

References

1. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, *et al.* Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol 2013; 14(4): 297-305.
2. Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, *et al.* Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 2010; 252(3): 426-32; discussion 32-3.
3. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, *et al.* Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014; 15(12): 1303-10.
4. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher

ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med 2002; 347(8): 567-75.
5. Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. Cancer 2001; 92(6): 1368-77.
6. McLaughlin SA, Wright MJ, Morris KT, Giron GL, Sampson MR, Brockway JP, *et al.* Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. J Clin Oncol 2008; 26(32): 5213-9.
7. Schrenk P, Rieger R, Shamiyeh A, Wayand W. Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. Cancer 2000; 88(3): 608-14.
8. Del Bianco P, Zavagno G, Burelli P, Scalco G, Barutta L, Carraro P, *et al.* Morbidity comparison of sentinel lymph node biopsy versus conventional axillary lymph node dissection for breast cancer patients: results of the sentinella-GIVOM Italian randomised clinical trial. Eur J Surg Oncol 2008; 34(5): 508-13.
9. Beek MA, Gobardhan PD, Schoenmaeckers EJ, Klompenhouwer EG, Rutten HJ, Voogd AC, *et al.* Axillary reverse mapping in axillary surgery for breast cancer: an update of the current status. Breast Cancer Res Treat 2016; 158(3): 421-32.
10. Tummel E, Ochoa D, Korourian S, Betzold R, Adkins L, McCarthy M, *et al.* Does Axillary Reverse Mapping Prevent Lymphedema After Lymphadenectomy? Ann Surg 2016.
11. Ngui NK, French J, Kilby CJ, Pathmanathan N, Elder EE. Axillary reverse mapping in patients with breast cancer: Is it oncologically safe? J Surg Oncol 2016; 113(7): 726-31.
12. Gebruers N, Tjalma WA. Clinical feasibility of Axillary Reverse Mapping and its influence on breast cancer related lymphedema: a systematic review. Eur J Obstet Gynecol Reprod Biol 2016; 200: 117-22.
13. Thompson M, Korourian S, Henry-Tillman R, Adkins L, Mumford S, Westbrook KC, *et al.* Axillary reverse mapping (ARM): a new concept to identify and enhance lymphatic preservation. Ann Surg Oncol 2007; 14(6): 1890-5.
14. Nos C, Lesieur B, Clough KB, Lecuru F. Blue dye injection in the arm in order to conserve the lymphatic drainage of the arm in breast cancer patients requiring an axillary dissection. Ann Surg Oncol 2007; 14(9): 2490-6.
15. NosC, Kaufmann G, Clough KB, Collignon MA, Zerbib E, Cusumano P, *et al.* Combined axillary reverse mapping (ARM) technique for breast cancer patients requiring axillary dissection. Ann Surg Oncol 2008; 15(9): 2550-5.
16. Casabona F, Bogliolo S, Valenzano Menada M, Sala P, Villa G, Ferrero S. Feasibility of axillary reverse mapping during sentinel lymph node biopsy in breast cancer patients. Ann Surg Oncol 2009; 16(9): 2459-63.
17. Boneti C, Korourian S, Bland K, Cox K, Adkins LL, Henry-Tillman RS, *et al.* Axillary reverse mapping: mapping and preserving arm lymphatics may be important in preventing lymphedema during sentinel lymph node biopsy. J Am Coll Surg 2008; 206(5): 1038-42; discussion 42-4.
18. Noguchi M, Yokoi M, Nakano Y. Axillary reverse mapping with indocyanine fluorescence imaging in patients with breast cancer. J Surg Oncol 2010; 101(3): 217-21.
19. Bedrosian I, Babiera GV, Mittendorf EA, Kuerer HM, Pantoja L, Hunt KK, *et al.* A phase I study to assess the feasibility and oncologic safety of axillary reverse mapping in breast cancer patients. Cancer 2010; 116(11): 2543-8.
20. Pavlista D, Eliska O. Relationship between the lymphatic drainage of the breast and the upper extremity: a postmortem study. Ann Surg Oncol 2012; 19(11): 3410-5.
21. IkedaK, Ogawa Y, Komatsu H, Mori Y, Ishikawa A, Nakajima T, *et al.* Evaluation of the metastatic status of lymph nodes identified using axillary reverse mapping in breast cancer patients. World J Surg Oncol 2012; 10: 233.
22. Ahmed M, Rubio IT, Kovacs T, Klimberg VS, Douek M. Systematic review of axillary reverse mapping in breast cancer. Br J Surg 2016; 103(3): 170-8.

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163387-91

Impact of Sitting or Semi-Setting Position of Patients During Breast Surgery on Hemodynamic Indexes

Kasra Kavandian*[a], Sanaz Shabani[a], Jayran Zebardast[a]

[a] *Department of Anesthesiology and Intensive Care, Tehran University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Received:
8 July 2016
Revised:
17 July 2016
Accepted:
9 August 2016

Keywords:
Brest surgery,
sitting position,
hemodynamic changes

ABSTRACT

Background: Keeping the patient in a sitting or semi-sitting position for time-consuming oncoplastic breast surgery is a major challenge for anesthesiologists due to several considerations. This cohort study was conducted on two groups of patients undergoing breast surgery.

Methods: Study participants were categorized into two groups: one group was composed of normotensive women (group A) and the other group comprised women with controlled hypertension (group B). After the induction of anesthesia in the supine position, the position was changed to sitting and the surgery was done in the sitting position. Hemodynamic monitoring included ECG, heart rate, non-invasive blood pressure (NIBP), invasive blood pressure (IBP), cardiac output (CO), arterial O2 saturation (SPO2), end-tidal CO2 (EtCO2), and bispectral index (BIS). The amount of administrated fluid and vasopressor was recorded for each patient. Any episode of hemodynamic instability was recorded, too.

Results: Hemodynamic variation occurred in both groups, but the changes were more significant in group B and the amount of fluid and vasopressor administration was more prominent in group B. Changing the position caused no significant variation in BIS, SPO2, and EtCO2 in the two groups.

Conclusions: The sitting position can be safe for time-consuming oncoplastic breast surgery using adequate hemodynamic monitoring. Hemodynamic changes are more significant in patients with controlled hypertension, and more medical interference is needed for these patients.

Introduction

Breast surgery with conservative strategies is a preferable method for most cases with breast cancer.[1] However, in the postoperative period, some women are not satisfied with the result because of aesthetic reasons.[2, 3] The main cause is the presence of size changes in the breast and asymmetry.[1-3] In recent years, surgeons in this field pay much attention to this matter, and try to provide a better breast shape and symmetry.[2-9] Today, oncoplastic breast surgeons employ plastic surgery principles to obtain aesthetically acceptable results.[3-6] One of these principles is keeping the patient in a breast hanging position; either a sitting or a semi-sitting position, to save and reconstruct the physiologic shape of the breast.[8-17] For this time-consuming type of surgery, there are variable methods of anesthesia, and general anesthesia is one of the preferable methods.[18, 19] Keeping the patient in the sitting or semi-sitting position is an important challenge for anesthesiologists because of several considerations,[20, 21] including limited access to the airway due to surgical draping; hypotension during positioning due to blunted sympathetic reflex in the anesthetized

Address for correspondence:
Kasra Karvandian, MD
Address: Anesthesiology and Intensive care Department, Imam Khomeini Hospital, Keshavarz Blv., Tehran, Iran
Tel: +98 9121383761
Fax:+98 21 66581537
Email:karvandian@tums.ac.ir

patient;[20-22] cerebral blood insufficiency, especially when tht mean arterial blood pressure is less than 70mmHg; etc.[23, 24] This is a study on hemodynamic changes of patients with breast cancer who underwent oncoplastic breast surgery in the sitting position.

Methods

This prospective cohort study was conducted in the breast surgery operating room of Imam Khomeini General Hospital for one year from January 2015 to January 2016. In this period, all patients who were scheduled for oncoplastic breast surgery in the sitting position and met the criteria were enrolled in the study after obtaining the institutional ethics committee approval. There was no intervention in the study protocol for the patients other than close haemodynamic monitoring. Women aged 20-50 years in the early stages of breast cancer who were otherwise healthy or with controlled hypertension were divided into two groups: normotensive patients in group A and patients with controlled early stages of hypertension in group B. Exclusion criteria were a history of cervical spine pathology, rheumatologic diseases, cardiovascular diseases, diabetic mellitus, morbid obesity, peripheral neuropathies, collagen vascular diseases, and psychological problems. Before enrolling in the study and in preoperative visits, all the patients were informed about the study and written informed consent was obtained. The patients were admitted on the day of operation. They were weighed before operating room admission. All of them received 2mg midazolam in the pre-induction period. The patients with controlled hypertension took their medications as the protocol of anesthesia guidelines at the presence of a consultant cardiologist. Moreover, the induction of anesthesia was performed with proper doses of Na-thiopental and atracurium, and fentanyl was administered as an analgesic. The patients were intubated by ETT no 7. Anesthesia was maintained by isoflurane1-1.5%, and monitoring included noninvasive and invasive blood pressure control, ECG, spo2, ETco2, BIS, and cardiac output using the NCO system. After induction and before surgical draping, the ET tube was fixed and secured appropriately and the patient's head was also stabilized in a neutral position. The shoulder, arms, trunk, and legs were secured and fixed to the operating table by appropriately fitted straps and belts fastened around the legs and torso to minimize body movements in the sitting position. In the beginning of the operation before applying the sitting position, about 500ml normal saline was administered to all patients. The position was changed gently and gradually by close haemodynamic monitoring. The sitting beach-chair position was obtained with the trunk section raised to about 45º to 60º, the mid part of the table in 10º trendelberg position, and the lower part with knee flexion at about 20º. Routine anesthesia haemodynamic monitoring was recorded at 5-minute intervals and the mentioned advanced monitoring was recorded at 10-minute intervals. Intravenous fluid administration was performed according to haemodynamic monitoring and the amount of the administered fluid was recorded in the anesthetic chart. Whenever needed, the patients received incremental doses of 10 mg ephedrine as a vasopressor. Surgical interventions were done by a single expert breast surgeon in the sitting position, and an expert anesthesiologist guided the anesthesia team for all patients. Data were recorded in the charts by a resident in train in anesthesia who monitored the patient. The operation time in the sitting position was recorded in the patient chart, too.

The patients were followed up for 6 months through monthly telephone calls to ensure lack of any peripheral neuropathy due to the long time sitting position.

Results

During one year, 80 women who met the inclusion criteria were enrolled in the study. The study population was eighty patients with breast cancer divided equally into two groups.

The mean age of the participants was 29±5.15 years in group A and 42±7.25 years in group B ($P < 0.05$).

The mean operation time in the sitting position was about 112±27 minutes in group A and 102±17 minutes in group B ($P < 0.05$).

The mean interval between the induction of anesthesia and position change was about 25±4 minutes in group A and 32±5 minutes in group B.

The mean amount of fluid administration for hemodynamic support during the position change was 150±50ml in group A and 600± 120 ml in group B ($P < 0.05$).

According to invasive blood pressure monitoring, the mean systolic blood pressure in the supine and sitting position was 86±12 mmHg and 78±11 mmHg in group A and 106±15 mmHg and 81±11 mmHg in group B, respectively. The variation of the recorded mean systolic blood pressure in the sitting position is demonstrated in figure 1.

The mean cardiac output change in the sitting position was about 1.4±0.3 in group A and 2.3±0.4 in group B, which included patients with controlled hypertension ($P < 0.05$).

The mean heart rate in the supine and sitting position was 70±11 and 78±13 beat per minute in group A ($P < 0.05$) and 68±10 and 88±14 beat per minute in group B, respectively ($P < 0.05$) (Figure 2).

None of the patients in group A received ephedrine while 20 patients in group B received at least one dose of ephedrine.

Although there were significant differences in hemodynamic variables between the two groups, no clinically significant hemodynamic instability was recorded in two groups.

There was no significant change in BIS, SPO2, and EtCO2 in the sitting position between the two groups.

There were no signs or symptoms of peripheral neuropathy in the two groups in the six-month follow-up.

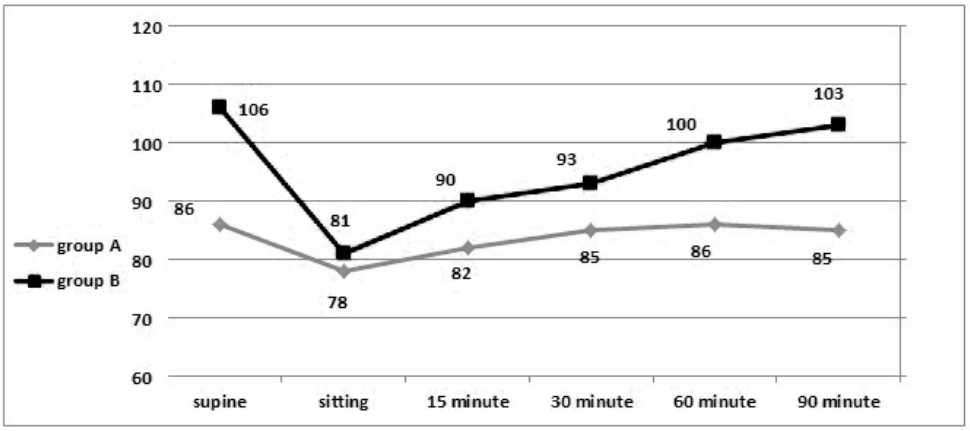


Figure 1. Systolic blood pressure variations in two groups

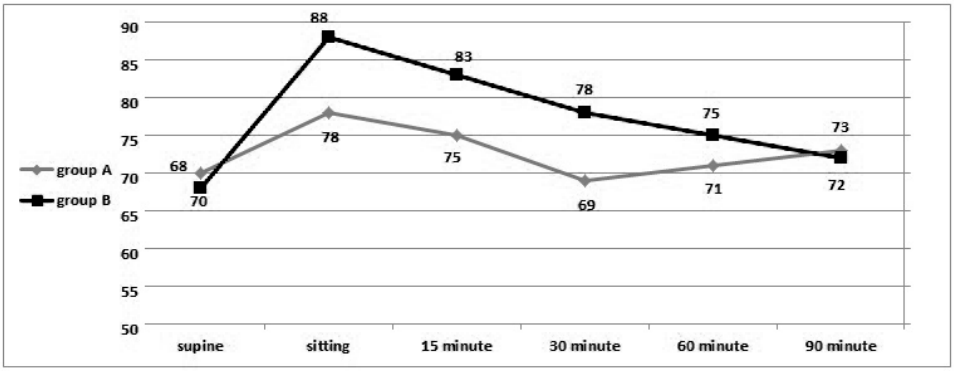


Figure 2. Heart rate variations in two groups

Discussion

Recent advances in oncoplastic breast surgery through application of a smooth surgical process have reduced breast tissue trauma, resulting in better preservation of the breast shape and improvement of the quality of life.[1-5]

In recent strategies, oncological surgery and reconstructive interventions are done in one operating session.[4-10] The major benefit of this policy is a better aesthetic outcome because reconstruction is done in the absence of the scar tissue of the previous operation.[8-12] The breast form is better evaluated and reconstructed when the breasts are hanging in the sitting position.[22] However, due to the long operation time of this surgical intervention and because of hemodynamic considerations, many centers avoid oncologic breast surgery in the sitting position.[20-22] Considering the relative risk-benefit depending on the individual cases, physical status, and surgical intervention situation is of great importance.

We studied hemodynamic variables in two groups of cohort individuals with breast cancer undergoing breast surgery in the sitting position; one group was composed of young women with no comorbidity and the other group included women with controlled hypertension. We found an acceptable safety profile in this situation with regards to proper positioning considerations.

The sitting position in an anesthetized patient may cause hypotension because sympathetic compensatory reflexes are blunted in this setting and lower extremity blood pooling may not be compensated as in non-anesthetized patients.[20, 21, 23, 24] According to figures 1 and 2 and the slope of the curves, it can be seen that the intensity of hemodynamic variation is more prominent in hypertensive patients and the compensatory mechanism is less efficient in this setting.[20-25] Gradual positioning from the supine to the sitting position and appropriate fluid or vasopressor resuscitation are important points to avoid significant or even catastrophic cardiovascular events in obtaining the sitting position.[20, 25] In the sitting position, the blood pressure to the brain is about 15 mmHg lower than the brachial artery, so it is advisable to employ invasive blood pressure monitoring and to keep the transducer at the level of ears to monitor the blood pressure of the brain.[20, 26] We did so, and this technique improved the safety profile of our patients.

We also tried to maintain the blood pressure within 25% of the baseline blood pressure as recommended by guidelines.[20, 26, 27] According to the results provided in our observational study by employing close cardiovascular monitoring, the anesthetized patient may be kept in the sitting position with fewer adverse hemodynamic events, even in long operations.

The pressure points of the body should be protected in the sitting position, especially in long operations.[27] We took this point into consideration and there was no report of peripheral neuropathy due to long time positioning in the 6-month follow up.

In conclusion, considering the better surgical outcome of oncoplastic and reconstructive breast surgery in the sitting position, we found this position safe with minimal risk. In patients with controlled hypertension, hemodynamic changes are more prominent than those with no comorbidity and the situation mandates more medical interference; by applying optimal hemodynamic monitoring and by gradually changing position, and perfect mechanical protection of the anesthetized patient`s body in this position.

Conflicts of interest

None to declare

References

1. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, *et al.* Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002; 347(16): 1227-32.
2. Clough KB, Kroll SS, Audretsch W. An approach to the repair of partial mastectomy defects. Plast Reconstr Surg 1999; 104(2): 409-20.
3. Kaviani A, Safavi A, Mohammadzadeh N, Jamei K, Ansari-Damavandi M, Salmon RJ. Oncoplastic surgery in breast conservation: a prospective evaluation of the patients, techniques, and oncologic outcomes. Am J Surg 2014; 208(5): 727-34.
4. Audretsch WP, Rezai M, Kolotas C, Zamboglou N, Schnabel T, Bojar H. Tumor-specific immediate reconstruction in breast cancer patients. Perspect Plast Surg 1998; 11(01): 71-100.
5. Munhoz AM, Aldrighi CM, Ferreira MC. Paradigms in oncoplastic breast surgery: a careful assessment of the oncological need and esthetic objective. Breast J 2007; 13(3): 326-7.
6. Munhoz AM, Montag E, Arruda E, Pellarin L, Filassi JR, Piato JR, *et al.* Assessment of immediate conservative breast surgery reconstruction: a classification system of defects revisited and an algorithm for selecting the appropriate technique. Plast Reconstr Surg 2008; 121(3): 716-27.
7. Papp C, Wechselberger G, Schoeller T. Autologous breast reconstruction after breast-conserving cancer surgery. Plast Reconstr Surg 1998; 102(6): 1932-6; discussion 7-8.
8. Kronowitz SJ, Feledy JA, Hunt KK, Kuerer HM, Youssef A, Koutz CA, *et al.* Determining the optimal approach to breast reconstruction after partial mastectomy. Plast Reconstr Surg 2006; 117(1): 1-11; discussion 2-4.
9. Clough KB, Thomas SS, Fitoussi AD, Couturaud B, Reyal F, Falcou MC. Reconstruction after conservative treatment for breast cancer: cosmetic sequelae classification revisited. Plast Reconstr Surg 2004; 114(7): 1743-53.
10. Munhoz AM, Montag E, Fels KW, Arruda EG, Sturtz GP, Aldrighi C, *et al.* Outcome analysis of breast-conservation surgery and immediate latissimus dorsi flap reconstruction in patients with T1 to T2 breast cancer. Plast Reconstr Surg 2005; 116(3): 741-52.
11. Asgeirsson KS, Rasheed T, McCulley SJ, Macmillan RD. Oncological and cosmetic outcomes of oncoplastic breast conserving surgery. Eur J Surg Oncol 2005; 31(8): 817-23.
12. Munhoz AM, Montag E, Arruda EG, Aldrighi C, Gemperli R, Aldrighi JM, *et al.* Critical analysis of reduction mammaplasty techniques in combination with conservative breast surgery for early breast cancer treatment. Plast Reconstr Surg 2006; 117(4): 1091-103; discussion 104-7.
13. Munhoz AM, Montag E, Arruda EG, Aldrighi C, Gemperli R, Aldrighi JM, *et al.* The role of the lateral thoracodorsal fasciocutaneous flap in immediate conservative breast surgery reconstruction. Plast Reconstr Surg 2006; 117(6): 1699-710.
14. Munhoz AM, Montag E, Arruda EG, Aldrighi C, Gemperli R, Aldrighi JM, *et al.* Superior-medial dermoglandular pedicle reduction mammaplasty for immediate conservative breast surgery reconstruction: technical aspects and outcome. Ann Plast Surg 2006; 57(5): 502-8.
15. Munhoz AM, Montag E, Arruda E, Aldrighi C, Filassi JR, de Barros AC, *et al.* Reliability of inferior dermoglandular pedicle reduction mammaplasty in reconstruction of partial mastectomy defects: surgical planning and outcome. Breast 2007; 16(6): 577-89.
16. Munhoz AM, Aldrighi CM, Montag E, Arruda E, Brasil JA, Filassi JR, *et al.* Outcome analysis of immediate and delayed conservative breast surgery reconstruction with mastopexy and reduction mammaplasty techniques. Ann Plast Surg 2011; 67(3): 220-5.
17. Rietjens M, Urban CA, Rey PC, Mazzarol G, Maisonneuve P, Garusi C, *et al.* Long-term oncological results of breast conservative treatment with oncoplastic surgery. Breast 2007; 16(4): 387-95.

18. Karvandian K. A comparison of total intravenous anesthesia plus intravenous paracetamol with local anesthesia plus meperidine in outpatient breast surgeries in Iranian general hospital since march 2010 up to august 2011. J Anesth Clin Res 2011; 2: 176.
19. Karvandian K, Shabani S, Zebardast J. Comparison of postoperative pain between infiltrative local anesthesia plus paracetamol and total intravenous anesthesia plus paracetamol in ambulatory breast surgery. Arch Breast Cancer 2015; 2(3): 85-90.
20. Murphy GS, Szokol JW. Blood pressure management during beach chair position shoulder surgery: what do we know? Can J Anaesth 2011; 58(11): 977-82.
21. Pohl A, Cullen DJ. Cerebral ischemia during shoulder surgery in the upright position: a case series. J Clin Anesth 2005; 17(6): 463-9.
22. Hammond DC, Hollender HA, Bouwense CL. The sit-up position in breast surgery. Plast Reconstr Surg 2001; 107(2): 572-6.
23. Larsen SL, Lyngeraa TS, Maschmann CP, Van Lieshout JJ, Pott FC. Cardiovascular consequence of reclining vs. sitting beach-chair body position for induction of anesthesia. Front Physiol 2014; 5: 187.
24. Rains DD, Rooke GA, Wahl CJ. Pathomechanisms and complications related to patient positioning and anesthesia during shoulder arthroscopy. Arthroscopy 2011; 27(4): 532-41.
25. Sawyer RJ, Richmond MN, Hickey JD, Jarrratt JA. Peripheral nerve injuries associated with anaesthesia. Anaesthesia 2000; 55(10): 980-91.
26. Domaingue CM. Anaesthesia for neurosurgery in the sitting position: a practical approach. Anaesth Intensive Care 2005; 33(3): 323-31.
27. Pin-on P, Schroeder D, Munis J. The hemodynamic management of 5177 neurosurgical and orthopedic patients who underwent surgery in the sitting or "beach chair" position without incidence of adverse neurologic events. Anesth Analg 2013; 116(6): 1317-24.

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163392-96

Relationship between Hardiness and Marital Satisfaction in Women with Breast Cancer

Farideh Nabizadeh*[a], Abed Mahdavi[b]

[a] General Medicine, Research, Education and Extension of Agriculture Organization, Tehran, Iran
[b] Department of Psychology, Faculty of Psychology and Educational Sciences, University of Payam Noor, Tehran, Iran

ARTICLE INFO

Received:
31 January 2016
Revised:
6 February 2016
Accepted:
5 August 2016

Keywords:
Hardiness,
breast cancer,
marital satisfaction

ABSTRACT

Background: When a couple confronts cancer, there is a major impact on their psychosocial life. Marital life and satisfaction are important factors in the quality of life of breast cancer patients. The aim of this research was to predict marital satisfaction based on hardiness in women with breast cancer.

Methods: A total of 100 women with breast cancer participated in this study and completed the Kobasa Personal View Survey and ENRICH (evaluation and nurturing relationship issues, communication, and happiness) Marital Satisfaction Scale. The study was conducted in Rasol Akrm Hospital, Tehran, Iran. Descriptive statistics, correlation, and linear regression were used for data analysis.

Results: The results showed a significant relationship between hardiness and marital satisfaction. Moreover, hardiness determined 13% of the variance of marital satisfaction.

Conclusions: Hardiness as an efficient coping style in breast cancer is an important factor to improve perceived marital satisfaction in breast cancer. Therefore, healthcare professionals such as psycho-oncologists can promote resiliency in breast cancer patients by improving cognitive hardiness in their patients.

Introduction

Breast cancer is one of the most common types of cancer among women worldwide and causes a high rate of morbidity annually. Breast cancer treatment methods (surgical treatment, chemotherapy, radiotherapy, and hormonal therapy) are associated with adverse effects on the patient's lifestyle and quality of life.[1,2] When a couple confronts cancer, they experience psychosocial issues such as intimacy dissatisfaction, marital distress, and fear of separation.[3,4] Studies have shown that women with breat cancer have maladjustment in the relationship with their spouse as a result of the long treatment course, risk of organ loss, and even death.[5] A woman who has lost a breast, which is related with femininity, has a distorted body image and may therefore ignore sexual intercourse with their spouse.[5-7] They are concerned about how cancer and its treatment affect their daily routine, their family, and work.[8] It has been reported that women who have undergone mastectomy experience depression, anxiety, and aggression and problems in sexual relationship which consequently affect their quality of life.[9] Finally, studies have shown that 10-40% of the breast cancer patients have a negative partnered relationship.[10]

Marital satisfaction is an individual's consent from marital relationship.[11] Marital relationship is a source of emotional and social support for both the patients and their partners during cancer, so it is crucial to protect the quality of the relationship.[12]

Address for correspondence:
Farideh Nabizadeh
Address: Research, Education and Extension of Agriculture Oraganization, Tabnak St., Tehran, Iran
Tel/Fax: +98 21 22400083
Email: nabizadehfarideh44@gmail.com

Marital dissatisfaction has a major effect on the physical health of breast cancer patients.[13] Studies show that some of the factors impacting marital satisfaction include problem-solving, dealing with conflict, stress, and crisis in a positive manner.[14,15]

Hardiness is a personality characteristic that functions as a resilience resource when facing stressful life events.[16] Kobasa believed that hardiness is one of the variables that influence mental stress.[17] It is a coping style that protects the individual against stress.[17] Hardiness is an adaptive behavior in response to stressful events. Kobasa states that cognitively hardy individuals believe that they can control life events, have a commitment to the values and goals of life, and engage in their interpersonal relationship.[18] So three specific dimensions of hardiness are control, commitment, and challenge that influence cognitive appraisal and behavior while confronting a traumatic experience.[19] Hardiness has a positive correlation with physical and mental health.[20]

Hardy people use cognitive strategies for solving problems, and usually use positive coping for this purpose. Therefore, an efficient coping style increases the people's self-esteem and psychological satisfaction.[17] Studies show that a fighting spirit is a part of the coping style of breast cancer survival.[21]

Few studies have addressed the relationship between hardiness and marital satisfaction. Avci *et al.* showed that the level of marital adjustment in breast cancer patients was about average.[5] A study among Turkish women with breast cancer who underwent mastectomy revealed that the treatment strategy did not have a major impact on the marital relationship, but had an adverse effect on the sexual relationship.[22] Hinnen *et al.* [23] showed that breast cancer itself might not be a negative factor for the relationship between couples. However, personal character and coping strategies play more important roles in maintaining marital satisfaction. Few studies have explored the role of hardiness in prediction of marital satisfaction; therefore, the aim of the present study was to describe the relationship between hardiness and marital satisfaction.

Methods

Women with breast cancer treated in Rasool Akram Hospital, Tehran, Iran participated in this study. The convenience sampling method was employed to recruit the study participants. After obtaining necessary approvals from hospital authorities, the researchers gave necessary explanations about the project and the study questionnaire to breast cancer patients and included them after obtaining their informed consent.

Hardiness scale

The Personal Views Questionnaire was used to assess hardiness. Kobasa developed this scale in 1986 which consists of 50 items including three subscales: commitment (13 items), control (14 items), and challenge (17 items). Besharat estimated alpha coefficients from 0.88 to 0.93 for commitment, 0.85 to 0.94 for control, 0.89 to 0.95 for quarrel, and 0.78 to 0.94 for hardiness, indicating its good internal correlation.[24] When repeated in an interval of two to four weeks, the correlation coefficient of all factors ranged from 0.82 to 0.90 for commitment, 0.80 to 0.88 for control,0.79 to 0.87 for quarrel, and 0.80 to 0.88 for total hardiness.[24]

ENRICH Marital Satisfaction Scale

This shortened scale which consists of 115 questions was developed by Fowres and Elson.[25]This scale is a self-report tool for estimation of the validity of marital satisfaction with marital life. The revised scale consists of 4 subscales, including marital satisfaction, communications, solving conflicts, and ideal distortion containing 35 items. The items of the questionnaire are scored from 1 to 5 (strongly agree to strongly disagree). The alpha coefficient of the sub-scales of marital satisfaction, communication, solving conflicts are 86%, 84%, 83%, 84% and the validity of reexamination for every sub-scale are 81%, 90%, 92%, 93%, respectively.

Statistical analysis

SPSS software version 18 was used to analyze the data. Descriptive statistics, correlation, and linear regression were used for data analysis.

Results

A significant association was observed between hardiness and marital satisfaction (P = 0.001). The matrix of the correlation coefficients between hardiness and marital satisfaction is demonstrated in Table 1.

Table 1. Matrix of correlation coefficients between hardiness and marital satisfactions

	Marital Satisfaction	Marital Communication	Solve conflict	Ideal distortion
Hardiness	0.521**	0.298**	0.506**	0.506**
Commitment	0.452**	0.304**	0.296**	0.457**
Control	0.574*	0.462*	0.424*	0.561*
Challenge	0.067**	0.01**	0.041**	0.085**

* $p > 0.05$
** $p < 0.001$

The result of linear regression for prediction of marital satisfaction based on hardiness components are presented in Table 2. According to the results, only 13% of the variance of marital satisfaction could be explained by commitment and challenge.

Table 2. Linear regression for prediction of marital satisfaction

Independent variable	B	T	P
Control	0.11	0.57	NS
Commitment	0.27	4.15	0.01
Challenge	0.28	3.75	0.02

Discussion

Breast cancer is one of the most prevalent diseases in the world. It is caused due to uncommon and uncontrollable reproduction of cells under the effect of different factors such as genetic, glandular, and environmental factors.[26] It is well established that the struggle to cope with breast cancer can lead to negative outcomes such as anxiety, but it can also lead to positive outcomes including the perception of benefits or positive changes in the woman's perception of herself, her relationships, and her life priorities.[27] One of the most significant parts of the cancer patients' life quality is related to sexual function.[28] Women who undergo mastectomy experience mood disorders (depression, anxiety, aggression), sexual relationship problems, and family and social problems, which may affect their life quality and sexual relationship with their spouses. Desires and tendencies, as well as the quality of the sexual life are as complex, diverse and rich as the principles of life. Sex and sexuality are important parts of marriage.[29]

Breast cancer challenges the women's hardiness.[30] Studies have shown that strong people use optimistic cognitive appraisal when dealing with difficulties, and they have positive coping styles (seeking support, accepting responsibility, and involve problem-solving task).[31] Breast cancer patient's positive coping leads to a fighting spirit in patients and makes them eager to fight for recovery from breast cancer and to overcome the disease experience.[32] On the other hand, they see the problem as an opportunity for growth.[33] One of the processes that improve the marital relationship is post-traumatic growth (PTG). PTG in women with breast cancer leads to reassessment of their values and makes them try to live each day in meaningful ways. They have a close relationship and convenient communication with their spouses, so they have perceived intimacy with their partners.[34] Several studies have shown that most patients experience positive changes after a diagnosis of cancer that leads to strengthening of interpersonal relationships and increased satisfaction with marital relationship.[16]

The results of the current study showed a significant relation between hardiness and marital satisfaction ($P < 0.001$), and hardiness determined 13% of the variance of marital satisfaction. This finding emphasizes that marital satisfaction is higher in families who have higher hardiness. Also, these results show a positive relationship between commitment and marital satisfaction in a way that marital satisfaction increases with increasing commitment. Our findings are consistent with the results of a study conducted by Kan *et al.* who discussed commitment and marital compatibility between couples.[35] Also, findings showed that challenge had a significant positive relationship with marital satisfaction. In other words, with an increase in challenge and flexibility against problems and changes due to development, marital satisfaction increased. The significant relationship between challenge and marital compatibility is determined which can be regarded as shared chapter between them. In fact, if we want to point is shared concept between them, it is better point to hardiness and compatibility, because persons who have cognitive compatibility have high flexibility.

Our study confirmed that husbands assisted their wives emotionally after cancer. Family concepts in Iran introduce a core family model, thus family members are intimate with each other. When encountering emotionally traumatic life events like breast cancer, they support each other psychologically. It may be one of the reasons which demonstrate insignificant differences between breast cancer patients and the general population.

Acknowledgement

The researcher would like to thank all the personnel of Rasool Akram Hospital and cancer patients who participated in this study.

References

1. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. The Lancet 2005; 365(9472): 1687-717.
2. Engel J, Schlesinger-Raab A, Emeny R, Holzel D, Schubert-Fritschle G. Quality of life in women with localised breast cancer or malignant melanoma 2 years after initial treatment: a comparison. Int J Behav Med 2014; 21(3): 478-86.
3. Woloski-Wruble AC, Dekeyzer Ganz F, Jiang Y, Qiang WM, Kadmon I. Israeli and Chinese partners of women with breast cancer: a cross-cultural view of marital issues. Psychooncology 2012; 21(3): 324-31.
4. Drageset S, Lindstrom TC, Giske T, Underlid K. Being in suspense: women's experiences awaiting breast cancer surgery. J Adv Nurs 2011; 67(9): 1941-51.
5. Avci IA, Okanli A, Karabulutlu E, Bilgili N. Women's marital adjustment and hopelessness

levels after mastectomy. European Journal of Oncology Nursing 2009; 13(4): 299-303.
6. Shands ME, Lewis FM, Sinsheimer J, Cochrane BB. Core concerns of couples living with early stage breast cancer. Psychooncology 2006; 15(12): 1055-64.
7. Fobair P, Stewart SL, Chang S, D'Onofrio C, Banks PJ, Bloom JR. Body image and sexual problems in young women with breast cancer. Psychooncology 2006; 15(7): 579-94.
8. Filek-Vitkay JM. Communication patterns and marital satisfaction of couples when wives are undergoing initial cycles of chemotherapy for metastatic breast cancer: a qualitative study. Dissertation Abstracts International: Section B: The Science and Engineering 2004; 65: 2623.
9. Kashani FL, Vaziri S, Akbari ME, Far ZJ, Far NS. Sexual skills, sexual satisfaction and body image in women with breast cancer. Procedia-Social and Behavioral Sciences 2014; 159: 206-13.
10. Dalton WT, 3rd, Nelson DV, Brobst JB, Lindsay JE, Friedman LC. Psychosocial variables associated with husbands' adjustment three months following wives' diagnosis of breast cancer. J Cancer Educ 2007; 22(4): 245-9.
11. Zainah A, Nasir R, Hashim RS, Yusof NM. Effects of demographic variables on marital satisfaction. Asian Social Science 2012; 8(9): 46.
12. Manne SL, Siegel S, Kashy D, Heckman CJ. Cancer-specific relationship awareness, relationship communication, and intimacy among couples coping with early-stage breast cancer. Journal of social and personal relationships 2014; 31(3): 314-34.
13. Srivastava S, McGonigal KM, Richards JM, Butler EA, Gross JJ. Optimism in close relationships: How seeing things in a positive light makes them so. J Pers Soc Psychol 2006; 91(1): 143-53.
14. Stoker SL. Factors That Influence Marital Satisfaction in Couples Raising a Child with Cerebral Palsy. 2004.
15. Israfil-Bayli F, Lowe S, Spurgeon L, Toozs-Hobson P. Managing women presenting with urinary incontinence: is hardiness significant? International urogynecology journal 2015; 26(10): 1437-40.
16. Jakšić N, Brajković L, Ivezić E, Topić R, Jakovljević M. The role of personality traits in posttraumatic stress disorder (PTSD). Psychiatria Danubina 2012; 24(3.): 256-66.
17. Kobasa SC. Stressful life events, personality, and health: an inquiry into hardiness. J Pers Soc Psychol 1979; 37(1): 1-11.
18. Beasley M, Thompson T, Davidson J. Resilience in response to life stress: the effects of coping style and cognitive hardiness. Personality and Individual differences 2003; 34(1): 77-95.
19. Crowley BJ, Hobdy J. Psychological hardiness and adjustment to life events in adulthood. Journal of adult development 2003; 10(4): 237-48.
20. Karimi S, Jaafari A, Ghamari M, Esfandiary M, Mazandarani FS, Daneshvar S, *et al*. A Comparison of Type II Diabetic Patients With Healthy People: Coping Strategies, Hardiness, and Occupational Life Quality. International journal of high risk behaviors & addiction 2016; 5(1): e24169.
21. Gonzalez P, Nuñez A, Wang-Letzkus M, Lim JW, Flores K, Nápoles AM. Coping with Breast Cancer: Reflections from Chinese-, Korean-, and Mexican-American Women. Health Psychol 2016; 35(1): 19-28.
22. Tan M, Karabulutlu E. Social support and hopelessness in Turkish patients with cancer. Cancer Nursing 2005; 28(3): 236.
23. Hinnen C, Hagedoorn M, Ranchor AV, Sanderman R. Relationship satisfaction in women: A longitudinal case-control study about the role of breast cancer, personal assertiveness, and partners' relationship-focused coping. Br J Health Psychol 2008; 13(4): 737-54.
24. Besharat MA. [Reliability, validity and factorial analysis of the Hardiness Scale]. Harakat 2008; 35: 31-46.
25. Fowers BJ, Olson DH. Enrich marital inventory: a discriminant validity and cross-validation assessment. J Marital Fam Ther 1989; 15(1): 65-79.
26. Sarafino EP, Smith TW. Health psychology: Biopsychosocial interactions: John Wiley & Sons; 2014.
27. Tedeschi RG, Tedeschi RG, Park CL, Calhoun LG. Posttraumatic growth: Positive changes in the aftermath of crisis: Routledge; 1998.
28. Gerrero MR, Weber BL. Recent advances in breast cancer biology. Curr Opin Oncol 2001; 13(6): 415-9.
29. Basson R. Women's sexual dysfunction: revised and expanded definitions. CMAJ 2005; 172(10): 1327-33.
30. Craft CA. A conceptual model of feminine hardiness. Holist Nurs Pract 1999; 13(3): 25-34.
31. Saboonchi F, Petersson L-M, Wennman-Larsen A, Alexanderson K, Brännström R, Vaez M. Changes in caseness of anxiety and depression in breast cancer patients during the first year following surgery: Patterns of transiency and severity of the distress response. Eur J Oncol Nurs 2014; 18(6): 598-604.
32. Cheng H, Sit JW, Twinn SF, Cheng KK, Thorne S. Coping with breast cancer survivorship in Chinese women: the role of fatalism or fatalistic voluntarism. Cancer Nurs 2013; 36(3): 236-44.
33. Pengilly JW, Dowd ET. Hardiness and social support as moderators of stress. J Clin Psychol 2000; 56(6): 813-20.

34. Canavarro MC, Silva S, Moreira H. Is the link between posttraumatic growth and anxious symptoms mediated by marital intimacy in breast cancer patients? Eur J Oncol Nurs 2015; 19(6): 673-9.
35. Schwartz P, Young L. Sexual satisfaction in committed relationships. Sex Res Soc Policy 2009; 6(1): 1-17.

Case Report Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.20163397-101

Contralateral Axillary Lymph Node Metastasis in Breast Cancer, an Unusual Clinical Scenario: A Case Report and Review of the Literature

A. Ali Assarian[a], Ahmad Elahi*[a]

[a] *Department of Surgery, Tehran University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Received:
9 May 2016
Revised:
26 May 2016
Accepted:
16 June 2016

Keywords:
Breast cancer, lymphatic drainage, contralateral axillary lymph node

ABSTRACT

Background: Contralateral axillary metastasis (CAM) is a rare entity in patients with breast cancer which can occur during the primary breast cancer or its follow-up. Different treatment modalities include surgery, radiotherapy, and chemotherapy, but there is no agreement on them. In our review, we found 12 series with available data, 82 patients with synchronous or metachronous contralateral axillary node involvement with no primary cancer in the contralateral breast.

Case Presentation: Our patient was a 50-year-old woman who presented with locally advanced right breast cancer with no distant metastasis. After treatment including neoadjuvant chemotherapy, MRM, and radiotherapy, her contralateral axillary lymph node was involved with metastatic carcinoma compatible with ductal carcinoma of the breast with similar IHC results. Evaluation of the contralateral breast was negative for occult lesions and metastatic workups were negative for malignancy. We assumed this presentation as a CAM and planned the treatment accordingly.

Conclusion: CAM without systemic metastasis might be considered a regional disease because in many cases the spread is lymphatic and not hematogenous. The new concept of lymphatic invasion instead of hematogenous spread has changed the intent of palliative to curative treatment. According to our study, CAM patients were mostly managed with chemotherapy (96%), ALND (45%), contralateral breast and axillary radiation (35%). The prognosis of CAM is usually poor with a high relapse rate (>60%) and a mortality rate of 15% in our review after 14-43 months follow-up, but it is better than the prognosis of the patients with systemic metastasis.

Introduction

Contralateral axillary lymph node metastasis (CAM) is an unusual clinical scenario which challenges the patient's treatment. More cases are documented as a result of the increasing use of high resolution ultrasound; therefore, clinicians who deal with breast cancer should be more aware. During the last 6 months, we had 3 documented cases at our center that were mainly detected by ultrasonography. We have the data of one patient available which we will present it in this report. We have reviewed the available data, and discussed the pathophysiology, diagnostic workup, and treatment options.

Breast cancer contralateral axillary lymph node metastasis (CAM) is rare, with an incidence of 1.9% – 6%.[1-7] This condition can be synchronous (at the same time as primary breast cancer diagnosis) or metachronous (following prior treatment of breast cancer as a recurrence).[3] Kiluk *et al.* used the term synchronous when CAM was diagnosed within one

Address for correspondence:
Ahmad Elahi, MD
Address: Department of Surgery, Imam Khomeini Hospital, Keshavarz Blvd., Tehran, Iran
Tel: +98 21 88871785
Fax: +98 21 88871698
Email: elahi84@gmail.com

year of the breast cancer diagnosis and metachronous when CAM was detected after one year.[8] Traditionally, CAM has been considered a systemic condition (stage IV) and treated as a widespread metastatic disease.[4] Some authors believe in a new concept of regional disease rather than a distant disease that may have a better outcome.[8] Jaffer *et al.* reported a case of contralateral axillary metastasis as the first evidence of recurrent breast carcinoma.[9] Kinoshita S. *et al.* reported a case of second new primary breast cancer with CAM 4.5 years after the treatment of the breast cancer with breast conserving therapy.[10] Herold CI *et al.* reported a case of new primary breast cancer with synchronously CAM in a patient 9 years after breast conserving surgery of the primary breast cancer.[11] In all of these cases, the management of such patients is controversial in terms of the curative or palliative intent.[3]

Case presentation

In February 2015, a 50-year-old woman presented with a right breast mass. There was no family history or any risk factor of breast cancer. On physical examination, she had a locally advanced breast cancer. Tissue diagnosis with core needle biopsy of the mass confirmed grade 2 invasive ductal carcinoma that was ER (estrogen receptor) positive, PR (progesterone receptor) negative, and HER-2 negative, with 15-18% ki-67. Staging did not show any evidence of distant metastasis. The patient was referred for neoadjuvant chemotherapy and after 8 courses, she underwent mastectomy and axillary lymph node dissection. After surgery, she was referred for radiotherapy. Few months after adjuvant treatment, she was referred to the surgical department with a suspicious contralateral axillary lymph node and core needle biopsy of the lymph node confirmed metastatic carcinoma compatible with ductal carcinoma of the breast that was ER positive, PR positive, and HER-2 negative (similar to the primary tumor). Evaluation of the left breast with physical examination, ultrasonography, mammography, and MRI was negative for occult lesions and again metastatic workup was negative for malignancy. We assumed this presentation as a CAM and planned the treatment accordingly.

Discussion

We reviewed the available published studies of the patients with CAM in the databases of PubMed and Science Direct. All case or series reports of CAM patients from 1995 to 2014 were included. Both synchronous and metachronous CAM were included in this study. None of the patients in the study had evidence of cancer in the contralateral breast. The data of these studies were analyzed according to age, follow-up, treatment options, and survival. Unfortunately, other data such as tumor IHC and location were not available in all reports. We found 12 studies including 82 patients with documented CAM whose information has been showed in Table 1 and 2 and the final results summarized in Table 3.

There are three possible clinical scenarios for explaining CAM: 1) Hematogenous spread, 2) Regional involvement due to occult ipsilateral breast cancer, 3) Regional metastasis to the contralateral side from the deep fascial plexus, anterior chest wall lymphatics that cross the midline.[2,7]

Barranger *et al.* reported a case of breast cancer in a 70-year-old female (with a history of bilateral mammoplasty) in whom preoperative lymphoscintigraphy above the tumor revealed one sentinel lymph node in the contralateral axilla but axillary dissection showed no node involvement.[12] Some reports have confirmed the contralateral lymphatic

Table 1. Demographic information of CAM reports

	Publication Year	Number of Patients	Median Age	Incidence	Family History (1^{st} ,2^{nd})	Tumor Position	Primary tumor	Pathology	Hormone Receptor	Her-2
Jaffer *et al.*[9]	1995	1	50							
Dauod *et al.*[17]	1998	6		4.9%		1 Outer 5 Inner & central				
Allweis *et al.*[14]	2003	1	48			Inner		IDC	Positive	Negative
Barranger *et al.*[12]	2004	1	70			Outer	Left	IDC	Positive	Negative
Huston *et al.*[4]	2007	7	49		6 (86%)	3 Outer 3 Inner 1 Central	All in Left	7 IDC		
Kinoshita *et al.*[10]	2010	1	60				Left	IDC	Positive	Positive
Morocos *et al*[15]	2011	21	51	1.9%		6 Outer 3 Inner 12 Central or diffuse		20 IDC 1 ILC	10 (48%) Positive	8 (42%) Positive
Zhou *et al.*[3]	2013	1				Outer	Left	IDC	Negative	
Kim *et al.*[7]	2013	1	52			Inner		IDC	8 (62%) Positive	2 (15%) Positive
Kiluk *et al.*[8]	2014	13	53					11 IDC 2 ILC	12 (42.8%) Positive	8 (28.5%) Negative
Dayyat *et al.*[2]	2014	1	63	0.8%		Outer	Left			
Wang *et al.*[1]	2014	28	47			2 Central 12 Inner 13 Outer		21 IDC 6 ILC 1 other		

Abbreviations: IDC: Invasive Ductal Carcinoma; ILC: Invasive lobular carcinoma

Table 2. Summary of treatment modalities in CAM reports

	Number of Patients	Median Interval (Months)	Median Follow Up (Months)	Lymph Node Surgery	Mastectomy (Contralateral)	Hormone Therapy	Chemotherapy	Radiotherapy (Contralateral)	Survival
Jaffer *et al.*[7]	1	metachronous		Yes	Yes	No	Yes	No	Good
Dauod *et al.*[18]	6	3 synch 3 meta (12 m)		5 (83%)	(no tumor) No	Yes	5(83%)	5 Axilla (83%)	2 NED 4 AWD
Allweis *et al.*[15]	1	synch		ALND(limited)	No	Yes	Yes	No	
Barranger *et al.*[14]	1	synch		No	No	2 (28%)	Yes	No	
Huston *et al.*[8]	7	6 metha 71 m 1 synchr (14%)	35 m	Node Excision 1 (14%) ALND 5(%86)	Mastectomy 1 (14%) free tumor		7 (100%) (1 NAC)	6 Breast & Axilla (85%) 1 Chest wall (15%)	2 NED 3 AWD 2 DOD
Kinoshita *et al.*[11]	1	Metha 60 m	36	Yes	No		Yes	Yes Breast	NED
Morocos *et al.*[10]	21	17 m (10 sync 11 meta)	27	4 (19%)	No	10 (84%)	21 (100%) (5NAC)	No	5 NED 12 AWD 4 DOD
Zhou *et al.*[6]	1	Synchronous	27	Yes (ALND)	Yes (no tumor)	Yes	NEC	Bilateral chest wall Not midline	Preesternal recurrnce 27 month
Kim *et al.*[16]	1	Metha 52 m	13	ALND & Supraclavicular LND	No	Yes	Yes	Yes Axilla	AWD
Kiluk *et al.*[12]	13	5 (38%) sync 8 meta	43	10 (77%)	No	5 (38%)	100%	5 Axilla (38%)	3 NED 10 AWD
Dayyat *et al.*[5]	1	Meta 48m	14	ALND	No	Yes	Yes	Yes	NED
Wang *et al.*[4]	28	All methachronous	29	6 (21%) ALND	6 (7%)		26	7 Axilla 1 Breast	3 NED 19 AWD 6 DOD

Abbreviations: NED: No evidence of disease; AWD: Alive With Disease; DOD: Dead Of Disease; BCS: Breast Conserving Surgery; NAC: Neo-Adjuvant Chemotherapy

Table 3. Results of available data in our review

	Number of Included Patients	Overall result in review
Tumor position	61	Inner: 21 (34.4%) Outer: 25 (41%) Central: 15 (24.6%)
Tumor side	7	All in left breast
Histopathology	74	IDC: 64 (86.4%) ILC: 10 (13.6%)
Hormone receptor	67	Positive: 34 (50.7%) Negative: 33 (49.3%)
Her2	66	Positive: 19 (28.7%) Negative: 47 (71.3%)
Time of axillary recurrence	82	Synchronous: 22 (26.8%) Methacronous: 60 (73.2%) (Interval 12-71 months)
ALND(contralateral)	82	Yes: 37 (45.1%) No: 45 (54.9%)
Mastectomy(contralateral)	82	Yes: 5 (6%) (No tumor found) No: 77 (94%)
Hormone therapy	82	All hormone receptor positive
Chemotherapy	82	Yes: 79 (96.3%) No: 3 (3.7%)
Radiotherpy (contralateral)	82	Breast: 5 (6%) Breast & axilla: 11 (13.5%) Axilla: 13 (15.8%) No: 53 (64.7%)
Survival	80	No evidence of disease: 18 (22.5%) Alive with disease: 50 (62.5%) Dead of disease: 12 (15%)

drainage through the deep dermal lymphatic plexus.[4,8] In a study by Gauthier *et al.*, lymphoscintigraphy of the right breast (in patient with right breast cancer), after periareolar injection, revealed lymphatic drainage from the right breast into the left contralateral axillary lymph node.[13]

Allweis *et al.* reported a case of breast cancer in a 48-year-old female that revealed 2 SLNs, one in the ipsilateral and one in the contralateral axilla, consistent with breast cancer metastasis.[14]

Involvement of the dermis in CAM was proved in a study by Kiluk *et al.* in 77% of the patients (10 from 13 patients).[8] Alternative routes of lymphatic drainage might be prompted by damage to the usual lymphatic drainage (such as irradiation or previous axillary surgery). However, alternative lymphatic drainage routes might also be present in patients without previous surgery or radiotherapy.[3,12,13]

In a review by Pentheroudakis *et al.*, CAM patients were mostly managed with axillary lymph node dissection and mastectomy (59%), primary breast irradiation (26%), or observation (15%).[15]

In a systematic review of the literature by M. Moossdorff *et al.*, 48 patients with contralateral

axillary lymph node recurrence were included and classified them into 3 categories: 1) Isolated contralateral lymph node recurrence (26 patients), 2) Ipsilateral breast tumour recurrence and synchronous contralateral lymph node recurrence, 3) Ipsilateral breast tumour recurrence and subclinical synchronous contralateral lymph node recurrence (15 patients).[6]

Morocos *et al.*, compared 21 patients with CAM with 401 breast cancer patients without CAM. They demonstrated that breast cancer patients with CAM had significantly worse histopathological features, such as a higher tumor grade (81% grade 3 carcinomas), lymphovascular invasion (81%), larger primary breast tumors (95% T3/T4 breast carcinoma), ER-receptor negativity (52%), and HER-2 overexpression (42%).[3,5]

Wang *et al.* evaluated 28 patients with pathologically confirmed metachronous CAM: 26 patients with CAM were treated with chemotherapy and hormonal therapy, and 2 refused any treatment.[1]

Hiram S *et al*. believed that ALND was indicated for patients who experienced relapse in the contralateral axilla and did not have other distant sites of the disease.[16] In a considerable part of our study, ALND was performed and acceptable results were obtained. Contralateral axillary dissection can be a good option which results in excellent axillary control.[13]

Mastectomy has been traditionally performed in patients with occult primary tumor with ipsilateral axillary metastasis. This strategy is based on the observation that approximately 50% of the patients who do not receive therapy to the breast will develop clinically evident disease in the breast. However, in CAM, surgery on the contralateral breast in which physical examination and imaging studies all are without any footprint of an occult cancer is controversial. Routine contralateral mastectomy is probably not indicated.[4]

In all series, chemotherapy was recommended in most patients and hormone therapy was advised in hormone receptor positive patients. Radiation therapy can provide additional help for local control.[7] In a study by Wang *et al.*, 7 patients underwent ALND, and no difference in median DFS was noted between patients who underwent ALND and those who did not.[1] According to Kim *et al.*, if there is no evidence of other metastatic lesions, lymph node dissection needs to be carried out, and radiation therapy can be added following proper systemic therapy.[7] In our review, a minority of CAM patients underwent breast radiotherapy (6%).

The rate of the patients that were alive without any evidence of the disease during the follow-up period is less than 30% in most studies. According to these findings, it seems that the overall survival is poorer in breast cancer patients with contralateral axillary metastases, but they have a better outcome compare to patients with distant metastasis.[8]

In conclusion, CAM without systemic metastasis might be considered a regional disease because the spread is lymphatic and not hematogenous in many cases. These patients should be discussed in breast multidisciplinary meetings to individualize the management of each patient. A significant proportion of the patients had ALND (45.1% of the patients) and systemic treatment (96.3%), suggesting a curative instead of palliative intent. Mastectomy of the contralateral breast was not performed in most reports (6% - all of them were done together with ALND) but breast radiation (with or without axillary radiation) was performed in about 19.5% of the cases.

Chemotherapy and hormone therapy are very important and effective factors in the management of CAM patients but the effectiveness of radiotherapy requires more investigations.

The prognosis of CAM is usually poor with a high relapse rate (>60%) and a mortality rate of 15% in our review after 14-43 months follow-up, but it is better than the prognosis of the patients with systemic metastasis.

We recommend thorough evaluation of the contralateral axilla during the follow-up of breast cancer to rule out contralateral axillary lymph node involvement.

References

1. Wang W, Yuan P, Wang J, Ma F, Zhang P, Li Q, *et al.* Management of contralateral axillary lymph node metastasis from breast cancer: a clinical dilemma. Tumori 2014; 100(6): 600-4.
2. Dayyat A, Sbaity E, Mula-Hussain L, Youssef B, Kaouk I, Amin Hassan A, *et al.* Treatment of Contralateral Axillary Metastases: Palliative Vs Curative Dilemma. Ann Hematol Oncol 2014; 1(2): 1-4.
3. Zhou C, Richir MC, Leenders MW, Langenhorst BL, Knol HP, Schreurs WH. Contralateral axillary lymph node metastases at the time of primary breast cancer diagnosis: curative or palliative intent? Case Rep Surg 2013; 2013: 389013.
4. Huston TL, Pressman PI, Moore A, Vahdat L, Hoda SA, Kato M, *et al.* The presentation of contralateral axillary lymph node metastases from breast carcinoma: a clinical management dilemma. Breast J 2007; 13(2): 158-64.
5. Morcos B, Jaradat I, El-Ghanem M. Characteristics of and therapeutic options for contralateral axillary lymph node metastasis in breast cancer. Eur J Surg Oncol 2011; 37(5): 418-21.
6. Moossdorff M, Vugts G, Maaskant-Braat AJ, Strobbe LJ, Voogd AC, Smidt ML, *et al.* Contralateral lymph node recurrence in breast cancer: Regional event rather than distant

metastatic disease. A systematic review of the literature. Eur J Surg Oncol 2015; 41(9): 1128-36.
7. Kim KI, Lee KH, Kim TR, Chun YS, Lee TH, Park HK. Breast Cancer with Delayed Metastasis Only to Contralateral Regional Lymph Nodes: A Case Report and Review of the Literature. Journal of Breast Disease 2013; 1(1): 35-8.
8. Kiluk JV, Prowler V, Lee MC, Khakpour N, Laronga C, Cox CE. Contralateral axillary nodal involvement from invasive breast cancer. Breast 2014; 23(3): 291-4.
9. Jaffer S, Goldfarb AB, Gold JE, Szporn A, Bleiweiss IJ. Contralateral axillary lymph node metastasis as the first evidence of locally recurrent breast carcinoma. Cancer 1995; 75(12): 2875-8.
10. Kinoshita S, Hirano A, Kobayashi S, Komine K, Kyoda S, Takeyama H, *et al.* Metachronous secondary primary occult breast cancer initially presenting with metastases to the contralateral axillary lymph nodes: report of a case. Breast Cancer 2010; 17(1): 71-4.
11. Herold CI, Gaughan EM, Lamb CC, Tung NM. Second primary ipsilateral breast cancer with contralateral axillary involvement: a case report and literature review. Clin Breast Cancer 2011; 11(6): 406-8.
12. Barranger E, Montravers F, Kerrou K, Marpeau O, Raileanu I, Antoine M, *et al.* Contralateral axillary sentinel lymph node drainage in breast cancer: a case report. J Surg Oncol 2004; 86(3): 167-9.
13. Gauthier T, Monteil J, Bourneton N, Jammet I, Tubiana N, Aubard Y. Contralateral axillary involvement in breast cancer recurrence: locoregional disease or metastasis? Eur J Gynaecol Oncol 2010; 31(6): 694-6.
14. Allweis TM, Parson B, Klein M, Sklair-Levy M, Maly B, Rivkind A, *et al.* Breast cancer draining to bilateral axillary sentinel lymph nodes. Surgery 2003; 134(3): 506-8.
15. Pentheroudakis G, Lazaridis G, Pavlidis N. Axillary nodal metastases from carcinoma of unknown primary (CUPAx): a systematic review of published evidence. Breast Cancer Res Treat 2010; 119(1): 1-11.
16. Cody HS, 3rd. Current surgical management of breast cancer. Curr Opin Obstet Gynecol 2002; 14(1): 45-52.
17. Daoud J, Meziou M, Kharrat M, Sellami D, Boudawara T, Frikha M. [Contralateral axillary lymph node metastasis of cancer of the breast]. Bull Cancer 1998; 85(8): 713-5.

Invited Commentary Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.201634102-105

Breast Cancer and Paradigm of Genomic Instability

Hossein Mozdarani*[a]

[a] *Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran*

Genome instability could be defined as an elevated tendency for the genome to acquire genetic alterations; ranging from changes to the nucleotide sequence to chromosomal gain, loss or rearrangements. Accumulating evidence indicates that cell transformation is associated with genome instability leading to an imbalance between the mechanisms of cell-cycle control and mutation rates within the genes. Genomic instability is broadly classified into microsatellite instability (MIN) associated with mutated phenotype, and chromosome instability (CIN) expressed as gross chromosomal abnormalities. The development of cancers can be mediated through DNA repair mechanisms, genetic (or epigenetic) alterations in oncogenes and tumor suppressor genes that regulate cellular processes such as cell-proliferation, differentiation, death and genome stability. Genomic instability is often associated with cancer and can be indicative of a poor prognosis for some types of cancer.[1] But, we still do not know clearly whether genomic instability is a consequence of tumor progression or an active process in tumor evolution. However, many new findings have highlighted certain DNA repair pathways and cell cycle control processes that have important consequences for genomic stability and tumor cell biology.

There are many different man-made and environmental agents that may cause genomic instability. Human is under constant exposure to toxic natural or synthethic chemical substances, air pollutions, various sources of non-ionizing radiations (microwaves, radiowaves, mobile, etc.) and natural or man-made ionizing radiation mainly used for medical (imaging and therapy) or industrial purposes. All these physico-chemical agents are mostly potent inducers of oxidative stress and reactive oxygen species (ROS). ROS are a group of highly reactive molecules implicated in the oxidative damage of biological structures; consequently give rise to various types of DNA lesions, including various types of base damage as well as DNA-DNA and DNA-protein cross links, single-strand breaks and double-strand breaks (DSBs). The formation of ROS produces not only DNA strand breakages, but also might act as a signaling event leading to the release of cytokines or epigenetic changes, or trigger DNA repair machinery. Several DNA damage processing and repair pathways constitute a guard system that protects cells against genetic instability and tumorigenesis; however, the unrepaired or misrepaired lesions may give rise to gene mutations and chromosomal aberrations (CA).[2] Although double-strand breaks are considered as serious DNA damage, they may be repaired very effectively by either one of the two different repair mechanisms namely, homologous recombinational repair (HRR) and non-homologous end joining (NHEJ).[3] HRR, an error free pathway, is able to restore the original sequence of DNA DSB leading to a lower risk of generation of deletions and insertions at the site of DSB. NHEJ, an error prone pathway, is subject to a high risk of generation of *de novo* mutations at the sites of DSBs. Thus, a direct consequence of the NHEJ repair machinery is susceptibility to mutagenesis.[4] The biological importance of genomic instability and DNA repair mechanisms in cancer development are particularly well illustrated by several heritable genetic disorders known as chromosome breakage or chromosomal instability syndromes. These chromosome breakage syndromes such as ataxia-telangiectasia and Nijmegen breakage syndrome are characterized by various defects in DNA repair, predisposition to

Address for correspondence:
Hossein Mozdarani, Ph.D
Address: Department of Medical Genetics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, 14115-111, Iran
Tel: +98 21 82883830
Fax: +98 21 88006544
Email: mozdarah@modares.ac.ir

various forms of malignancies and increased radiosensitivity. Therefore, individuals who are genetically susceptible to cancer manifest the impaired DNA damage identification and repair by exhibiting increased DNA radiosensitivity.[1,5]

Breast cancer is a common type of malignancy occurring in women in developed countries that ranks as the fifth cause of death from all cancers.[6] A worldwide increase has been estimated to around 16,500 yearly new cases of this neoplasia by 2020.[7] About 15% of breast cancer is familial and the rest (85%) is sporadic which express as different subtypes. Current approaches fail to provide a single molecular marker for breast cancer detection and prediction of treatment response and prognosis. The gene expression signatures that define specific prognostic subtypes in other breast cancer datasets, such as luminal A and B, basal, normal-like, and ERBB2+, and prognostic signatures including MammaPrint® and Oncotype DX, predicted genomic instability in breast cancer tissue samples. Gene expression profiling of breast cancer specimens have shown considerable difference in their degree of genomic instability and identified a set of 12 genes that defines the two sub groups luminal A and B.[8] There is no doubt that these approaches are expensive for screening purposes and genome instability defined as a high number of chromosomal breakpoints, is suggested as a stronge prognostic marker for early stage luminal breast carcinoma.[9]

Radiation therapy (RT) is an efficient treatment for cancer. About 50% of patients with malignant breast tumors receive RT and most patients seem tolerate it, but some suffer severe adverse effects induced by the therapy. This variability of response may be caused by several factors, such as age, life style, oxidative stress, genetic predisposition and various genes involved in the response to radiation-induced DNA damage.[10] Therefore, it is important to develop and implement new diagnostic techniques for predicting responses to cancer treatment and for identifying patients susceptible to radiation-related toxicity. The toxicity reactions of normal tissues to ionizing radiation brings limitation in efficiency of RT. Unfortunately, an appropriate protocol to prevent or treat these side effects, yet has not been developed. Therefore, inherent radiosensitivity of normal cells is supposed to be a serious problem in management of many cancers including breast cancer RT.[11] Radiosensitivity is caused by extrinsic (radiation dose), and intrinsic factors (genetic factors) which the second account for almost 80% of normal tissue responses. At present, our knowledge of molecular pathways involved in relation to adverse responses to cancer treatment agents is fairly poor. Hence, by identification of these molecular mechanisms it'll be possible to enhance the output of treatment technologies and then increase overall survival of cancer patients. Several techniques has been used to achieve this goal, for example microarray tests administration to clarify molecular mechanisms related to radiosensitivity.[11] Variation of inherent radiosensitivity between individuals has also been linked to polymorphisms in single nucleotides. Single nucleotide polymorphisms (SNPs) make up to 90% of the naturally occurring sequence variation in the human genome and SNPs in genes related to the biological response to ionizing radiation. A substantial effort has been made to discover genetic markers, primarily SNPs, associated with variation in the intrinsic radiosensitivity of individuals and adverse responses to RT.[12] Genome wide screen based studies identified microsatellite markers associated with acute adverse effects following radiotherapy in cancer patients. However, although possible associations between genetic markers and radiosensitivity has been found, strong association between a specific marker or even markers has not yet been established; probably due to inadequate knowledge of the molecular pathology of adverse reactions induced by ionizing radiation. It has also been suggested that several polymorphisms might have a possible role in radiosensitivity of normal cells in response to RT.[13] MicroRNAs, small regulatory non-coding RNA molecules, might have a role in radiosensitivity of normal tissues through pathways involved in IR responses such as changes in signaling pathway, DNA damage repair, cell differentiation, cell cycle arrest, alternation of gene expression patterns, mutations of important genes, genomic instability and initiation of carcinogenesis. MiRNAs may also have a key role in radiosensitivity. Their importance has been evaluated in several studies which show they could be potentially fine prognostic markers.[14]

It is shown a significant elevated chromosomal radiosensitivity (CRS) in some BC patients.[15, 16] CRS of lymphocytes of these patients could be a potential marker for low penetrance genes related to breast cancer development. It is estimated that almost 10% of normal individuals and over 40% of unselected BC patients exhibit increased inherent radiosensitivty.[17] A sub group of these populations are AT heterozygotes which can make a correlation between high radio sensitivity and predisposition to cancer.[18] And BC patients with known mutation in BRCA1 or BRCA2 high penetrance genes or those with positive family history have an increased CRS than healthy population.[19]

Our knowledge of mechanisms leading to higher radiosensitivity of normal tissues is fairly poor until now, but it's been estimated that 70% of this feature is a result of genome instability and defective repair of radiation induced DSB.[20] Ionizing Radiation Induced Foci (IRIF) are produced usually after IR at the site of produced DSBs. γ-H2AX is an important part of IRIF formation which act as a chromatin platform

generated on a 2-Mb size chromatin domain involving DSBs and gather related factors to DNA damage repair machine. Recent studies revealed that some γ-H2AX foci remain at the site of DSBs even after their repair has been finished.[21] The exact role of remained IRIF even after completion of repair is currently unknown but it's been suggested that they could possibly have a role in remaining chromatin alternations, late repair and mis-rejoining of DSB, apoptosis, activity of several kinases and phosphatases, and checkpoint signaling.[21] Impaired repair of DNA damage in lymphocytes of breast cancer patients was previously shown by the comet assay and G2 chromosomal aberration studies.[22, 23] It is therefore possible that genomes of individuals with cancer susceptibility as well as BC patients generate more DSBs and elevated radiosensitivity because of defective DNA repair machinery. This idea is supported by the fact that cells with elevated chromatid radiosensitivity have deficiency in DNA repair.[24] It can be suggested that radiosensitivity could be a potential predisposing condition to BC through mutations in low penetrance genes that could play a role in DNA damage repair mechanisms.

Accumulating evidence indicates that the unrepaired DSBs as the major lesion in the cellular, chromosomal, mutagenic and oncogenic effects of ionizing radiation. Radiation-induced instability endpoints have been shown to be manifested as chromosomal alterations, micronuclei, cell transformation, gene amplification, apoptosis, and sister chromatid exchange, etc. Oncogenic transformation has been demonstrated in many studies to date to be an integral stage in carcinogenesis. Gene amplification might also play an important role in oncogenic transformation. Studies on the organization of the amplified DNA in tumor cells have suggested that a single DNA DSB can trigger a cascade of events leading to amplification of a gene in the genome.[25]

In essence, detection of genetic alterations in genes associated with breast cancer, particularly those related to DSB repair, may be used for the diagnosis for breast cancer patients. Current approaches based on genomic methodologies for mutation detection are expensive and not suitable for screening individuals under risk for increased DSB events. Almost 40% of breast cancer patients exhibit elevated chromosomal radiosensitivity, hence showing adverse complications due to radiotherapy or chemotherapy. Therefore, evaluation of DSB repair or expression of unrepaired DSB as chromosomal aberrations and micronuclei might be a useful tool for assessing breast cancer risk and predicting the response and complications associated with conventional radiotherapy and even chemotherapy. These methods can also be used for screening of breast cancer predisposition. Methods for studying DSB repair deficiency in peripheral blood lymphocytes such as γ-H2AX, comet assay, G2 chromosomal aberration assay and micronucleus assay are less expensive and suitable for screening subjects at high risk for breast cancer, to reduce adverse events and to offer individualized therapies. These methods will also be relevant for preventing unnecessary radiation exposure, for screening of patients who will not benefit from radiotherapy, and for adjusting radiotherapy regimes in patients requiring RT, in order to avoid adverse side effects associated with generation of DSB in tissues ameliorating prognosis of patients.

References

1. Mozdarani H. Biological complexities in radiation carcinogenesis and cancer radiotherapy: impact of new biological paradigms. Genes (Basel) 2012; 3(1): 90-114.
2. Langie SA, Koppen G, Desaulniers D, Al-Mulla F, Al-Temaimi R, Amedei A, *et al*. Causes of genome instability: the effect of low dose chemical exposures in modern society. Carcinogenesis 2015; 36 Suppl 1: S61-88.
3. Henriquez-Hernandez LA, Carmona-Vigo R, Pinar B, Bordon E, Lloret M, Nunez MI, *et al.* Combined low initial DNA damage and high radiation-induced apoptosis confers clinical resistance to long-term toxicity in breast cancer patients treated with high-dose radiotherapy. Radiat Oncol 2011; 6: 60.
4. Borrego-Soto G, Ortiz-Lopez R, Rojas-Martinez A. Ionizing radiation-induced DNA injury and damage detection in patients with breast cancer. Genet Mol Biol 2015; 38(4): 420-32.
5. Jeggo PA, Pearl LH, Carr AM. DNA repair, genome stability and cancer: a historical perspective. Nat Rev Cancer 2016; 16(1): 35-42.
6. Youlden DR, Cramb SM, Dunn NA, Muller JM, Pyke CM, Baade PD. The descriptive epidemiology of female breast cancer: an international comparison of screening, incidence, survival and mortality. Cancer Epidemiol 2012; 36(3): 237-48.
7. Knaul FM, Nigenda G, Lozano R, Arreola-Ornelas H, Langer A, Frenk J. [Breast cancer in Mexico: an urgent priority]. Salud Publica Mex 2009; 51 Suppl 2: s335-44.
8. Habermann JK, Doering J, Hautaniemi S, Roblick UJ, Bundgen NK, Nicorici D, *et al*. The gene expression signature of genomic instability in breast cancer is an independent predictor of clinical outcome. Int J Cancer 2009; 124(7): 1552-64.
9. Vincent-Salomon A, Benhamo V, Gravier E, Rigaill G, Gruel N, Robin S, *et al*. Genomic instability: a stronger prognostic marker than proliferation for early stage luminal breast carcinomas. PLoS One 2013; 8(10): e76496.
10. Hornhardt S, Rossler U, Sauter W, Rosenberger

A, Illig T, Bickeboller H, *et al*. Genetic factors in individual radiation sensitivity. DNA Repair (Amst) 2014; 16: 54-65.
11. Batar B, Guven G, Eroz S, Bese NS, Guven M. Decreased DNA repair gene XRCC1 expression is associated with radiotherapy-induced acute side effects in breast cancer patients. Gene 2016; 582(1): 33-7.
12. Guo Z, Shu Y, Zhou H, Zhang W, Wang H. Radiogenomics helps to achieve personalized therapy by evaluating patient responses to radiation treatment. Carcinogenesis 2015; 36(3): 307-17.
13. Osti MF, Nicosia L, Agolli L, Gentile G, Falco T, Bracci S, *et al*. Potential Role of Single Nucleotide Polymorphisms of XRCC1, XRCC3, and RAD51 in Predicting Acute Toxicity in Rectal Cancer Patients Treated With Preoperative Radiochemotherapy. Am J Clin Oncol 2015:
14. Zhao L, Lu X, Cao Y. MicroRNA and signal transduction pathways in tumor radiation response. Cell Signal 2013; 25(7): 1625-34.
15. Scott D, Barber JB, Levine EL, Burrill W, Roberts SA. Radiation-induced micronucleus induction in lymphocytes identifies a high frequency of radiosensitive cases among breast cancer patients: a test for predisposition? Br J Cancer 1998; 77(4): 614-20.
16. Mozdarani H, Mansouri Z, Haeri SA. Cytogenetic radiosensitivity of g0-lymphocytes of breast and esophageal cancer patients as determined by micronucleus assay. J Radiat Res 2005; 46(1): 111-6.
17. Mozdarani H, Ziaee Mashhadi A, Alimohammadi Z. G2 chromosomal radiosensitivity and background frequency of sister chromatid exchanges of peripheral blood lymphocytes of breast cancer patients. Iranian J Radiat Res 2011; 9(3): 167-74.
18. Scott D. Chromosomal radiosensitivity and low penetrance predisposition to cancer. Cytogenet Genome Res 2004; 104(1-4): 365-70.
19. Baeyens A, Thierens H, Claes K, Poppe B, de Ridder L, Vral A. Chromosomal radiosensitivity in BRCA1 and BRCA2 mutation carriers. Int J Radiat Biol 2004; 80(10): 745-56.
20. Turesson I, Nyman J, Holmberg E, Oden A. Prognostic factors for acute and late skin reactions in radiotherapy patients. Int J Radiat Oncol Biol Phys 1996; 36(5): 1065-75.
21. Mozdarani H, Salimi M. γ-H2AX as a protein biomarker for radiation exposure response in ductal carcinoma breast tumors: Experimental evidence and literature review. Int J Radiat Res 2014; 12(1): 1-11.
22. Patel RK, Trivedi AH, Arora DC, Bhatavdekar JM, Patel DD. DNA repair proficiency in breast cancer patients and their first-degree relatives. Int J Cancer 1997; 73(1): 20-4.
23. Shahidi M, Mozdarani H, Bryant PE. Radiation sensitivity of leukocytes from healthy individuals and breast cancer patients as measured by the alkaline and neutral comet assay. Cancer Lett 2007; 257(2): 263-73.
24. Mozdarani H, Bryant PE. Induction and rejoining of chromatid breaks in X-irradiated A-T and normal human G2 fibroblasts. Int J Radiat Biol 1989; 56(5): 645-50.
25. Mondello C, Smirnova A, Giulotto E. Gene amplification, radiation sensitivity and DNA double-strand breaks. Mutat Res 2010; 704(1-3): 29-37.

Invited Commentary Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.201634106-107

The Effect of Reactive Oxygen Species Threshold on Cancer Cell Fate

Mossa Gardaneh*[a], Ava Modirzadeh Tehrani[b]

[a] National Institute of Genetic Engineering and Biotechnology, Tehran, Iran
[b] Faculty of Natural Sciences, Tabriz University, Tabriz, Iran

There has been an argument going on for the effectiveness of dietary supplements including various vitamins enriched in antioxidants in cancer treatment and prevention. Several trials have shown that vitamins are unable to suppress cancer progression and may even promote the disease.[1] Some other reports suggest that antioxidants may even accelerate cancer progression, in line with their drug resistance function.[2]

A classical model of carcinogenesis states that free radicals can act as promoters of cancer initiation, promotion and progression phases.[3] In the initiation phase where lethal mutations are absent, free radicals contribute to cell transformation and cancer initiation by generating ROS (reactive oxygen species) such as lipid peroxides that induce mutations and damage DNA.[4] An equilibrium exists between growth and death in normal cells; however, this balance is disturbed in cancer cells and free radicals act in favor of cell survival/growth by abrogating programmed death and tumor suppressing activities.

In the promotion phase that includes clonal expansion, free radicals act as second messengers to control cancer cell proliferation and differentiation. Intracellular concentrations of ROS are critical in this phase as they determine if ROS can induce apoptosis or growth.[5] In the progression phase of carcinogenesis that includes epithelial-to-mesenchymal transition and development of angiogenesis, ROS play important roles by mediating crosstalk between integrins as key players of cell proliferation, survival, and migration on the one hand and many cytokines and growth factors on the other hand.[6]

Address for correspondence:
Mossa Gardaneh, PhD
Address: Pazhoohesh Blvd Km 15, Tehran-Karaj HWY, Postcode 1497716316, Tehran, Iran.
Tel: +98 21 44580344
Fax: +98 21 44580395
Email: mossa65@nigeb.ac.ir

The multifactor and dose-dependent contribution of ROS in cancer cell fate consists of DNA modifications and other cellular processes involved in transformation. This implies that the ultimate net effect of ROS on carcinogenesis will depend on their concentration and the redox status of the tumor cell. This dose-dependent effect of ROS constitutes a platform based on which decision is made on the therapeutic utility of either antioxidants or chemotherapy-mediated induction of massive oxidative stress in cancer. Antioxidant therapy would theoretically inhibit transformation and cancer aggression at the initiation stages. Chemotherapy, on the other hand, is based on increased oxidative stress that induces apoptosis.[7]

Reports are accumulating on the mechanisms by which antioxidants actually increase the risk of cancer.[8] In lung cancer, N-acetylcystein (NAC) and vitamin E increase tumor progression by disturbing the ROS-p53 axis.[9] Likewise, NAC has been shown to induce lymph node metastasis in animal models of melanoma and enhances tumor cell migration/invasion without changing its proliferation.[10] This study found a correlation between increased melanoma cell migration and new glutathione synthesis. Antioxidants activate the small guanosinetriphosphatase (GTPase) RHOA which contributes to cell migration/invasion by mediating cytoskeletal changes,[11] and inhibition of downstream RHOA signaling abolished antioxidant-induced migration.[10]

Relevant to breast cancer cells, Davison *et al*. discovered that antioxidant enzymes facilitate cell survival upon ECM-detachment and maintain metabolic activity and anchorage-independent growth in breast cancer cells.[12] These findings imply that strategies based on elimination, instead of administration, of antioxidant activity could effectively render invasive cancer cells susceptible to death.

Based on the reports we summarized above plus

ones, a roadmap can be proposed for intracellular developments in cancer upon exposure to elevated ROS or excessive antioxidants (Figure 1). This roadmap indicates that antioxidants are able to block ROS damages in cancer cells as long as ROS molecules have not increased beyond their toxic levels. However, once their levels cross their upper threshold, antioxidants of endogenous or dietary sources cannot neutralize ROS in order to overcome ROS-mediated intracellular damages.

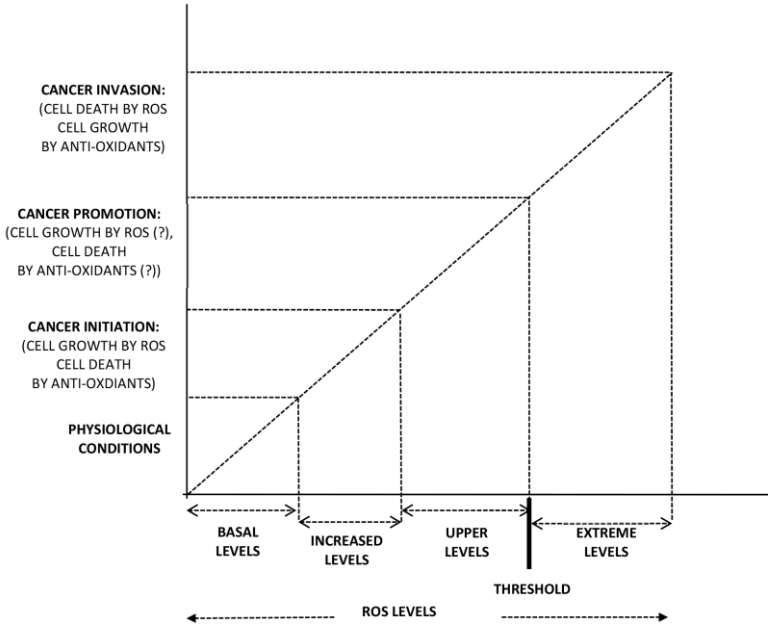


Figure 1. A roadmap for intracellular developments in cancer upon exposure to elevated ROS or excessive antioxidants.

References

1. Moyer MW. Antioxidants May Make Cancer Worse. 2015. https://www.scientificamerican.com/article/antioxidants-may-make-cancer-worse (accessed September 15 2016).
2. Antioxidants and Cancer Prevention. 2014. https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/antioxidants-fact-sheet (accessed September 16 2016).
3. Gutteridge JM, Halliwell B. Free radicals and antioxidants in the year 2000. A historical look to the future. Ann N Y Acad Sci 2000; 899: 136-47.
4. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact 2006; 160(1): 1-40.
5. Trueba GP, Sanchez GM, Giuliani A. Oxygen free radical and antioxidant defense mechanism in cancer. Front Biosci 2004; 9: 2029-44.
6. Halliwell B, Gutteridge JMC. Free radicals in biology and medicine. Fifth ed. Oxford: Oxford University Press; 2015.
7. Fang J, Seki T, Maeda H. Therapeutic strategies by modulating oxygen stress in cancer and inflammation. Adv Drug Deliv Rev 2009; 61(4): 290-302.
8. Goodman M, Bostick RM, Kucuk O, Jones DP. Clinical trials of antioxidants as cancer prevention agents: past, present, and future. Free Radic Biol Med 2011; 51(5): 1068-84.
9. Sayin VI, Ibrahim MX, Larsson E, Nilsson JA, Lindahl P, Bergo MO. Antioxidants accelerate lung cancer progression in mice. Sci Transl Med 2014; 6(221): 221ra15.
10. Le Gal K, Ibrahim MX, Wiel C, Sayin VI, Akula MK, Karlsson C, *et al.* Antioxidants can increase melanoma metastasis in mice. Sci Transl Med 2015; 7(308): 308re8.
11. Sit ST, Manser E. Rho GTPases and their role in organizing the actin cytoskeleton. J Cell Sci 2011; 124(Pt 5): 679-83.
12. Davison CA, Durbin SM, Thau MR, Zellmer VR, Chapman SE, Diener J, *et al.* Antioxidant enzymes mediate survival of breast cancer cells deprived of extracellular matrix. Cancer Res 2013; 73(12): 3704-15.

Review Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.201634108-117

Electrochemotherapy for Treatment of Cutaneous Breast Cancer Metastases: A Review

Shramana M. Banerjee[a, b], Mohammed R.S. Keshtgar*[a, b]

[a] Division of Surgery and interventional Science, University College London, London, UK
[b] Royal Free London NHS Foundation Trust, London, UK

ARTICLE INFO

Received:
10 October 2016
Revised:
16 November 2016
Accepted:
20 November 2016

Keywords:
Review,
breast cancer,
electrochemotherapy

ABSTRACT

Background: Electrochemotherapy is a relatively new technique in the treatment of skin metastases that are not amenable to conventional therapy. Its use in breast cancer is now established in many European centers.

Methods: Published literature of electrochemotherapy in terms of its scientific basis, current clinical practice of breast cancer treatment providers, as well as the future directions for the technology has been reviewed.

Results: Collective global experience of the last 10 years has demonstrated Electrochemotherapy is a safe, well-tolerated and effective treatment of cutaneous breast cancer metastases and good outcome characteristics have been identified. However, successful treatment requires appropriate patient selection.

Conclusions: Electrochemotherapy is now established as a standard of care for cutaneous metastases. Its future use may extend to gene therapy and the treatment of visceral tumors.

Introduction

Cutaneous metastases from breast cancer occur in about 2% of patients and account for only 0.7-0.9% of all metastases.[3,4] However breast cancer metastases to the skin represent 51% of all of skin metastases and often this is the only manifestation of disease progression in these patients.[4] Until recently, this rare presentation has been difficult for both the surgeon and oncologist to treat; often the surgical options are limited due to the extent of skin surface involved. Systemic chemotherapy and radiotherapy provides effective palliation. However, repeated cycles of treatment leads to chemo-resistance and radiotherapy cannot be used in previously irradiated areas.

Address for correspondence:
Mohammed R.S. Keshtgar, Professor of Surgical Oncology
Address: Royal Free London NHS Foundation Trust,
Pond street, Hampstead, London NW3 2QG.
Tel: +44 207 830 2758
Fax: +44 207 830 2194
Email: m.keshtgar@ucl.ac.uk

Patients can become increasingly symptomatic, if the skin lesions are inadequately treated. Lesions become necrotic and ulcerated and their management relies heavily on nursing resources. Electrochemotherapy (ECT), a novel treatment, which is well tolerated, repeatable and effective, provides an additional treatment option for cutaneous metastases. Electrochemotherapy (ECT) is the administration of a low dose chemotherapeutic agent that is non-permeable or poorly permeable in combination with high intensity electrical pulses of short duration to facilitate targeted drug delivery into tumour cells. Exposure of tumour cells to the pulses of electrical fields in itself can cause apoptosis by the formation of nano-pores in the cell membrane, a process known as electroporation.[5,6]

Methods

A pubmed search was conducted using keywords 'electrochemotherapy and breast cancer'. In addition publications by InSpECT was also considered. InspECT is an international collaboration formed in 2008 providing a forum and infrastructure for medical teams working with electrochemotherapy to be able to meet and discuss issues related to

its use.[7]

An international database facilitated by this organization has allowed collaborative publications. All data is monitored according to GCP procedures.[7] Publications relating to electrochemotherapy were included in this review, if they were published in English and were published from centers with experience of treatment delivery. Clinical publications were selected if they presented a retrospective study, multi-center or single prospective observation study. Case study publications were not included. Scientific publications were considered for inclusion, if they were review publications or were cited in review publications and were relevant to breast cancer.

Results

Scientific basis for electrochemotherapy

When a cell is exposed to an external electrical field for a short duration, transient thinning of the phospholipid bilayer occurs with the formation of nano-pores allowing passage of extracellular substances (Figure 1).[8] The first practical demonstration of this phenomenon was the technique of DNA transfection of bacteria by applying a current from a laboratory generator.[9] The development and production of square wave generators, that allowed precision of treatment delivery in terms of the number of pulses and their characteristics facilitated electropermeabilization of a large population of cells without lethal cytotoxicity.[10]

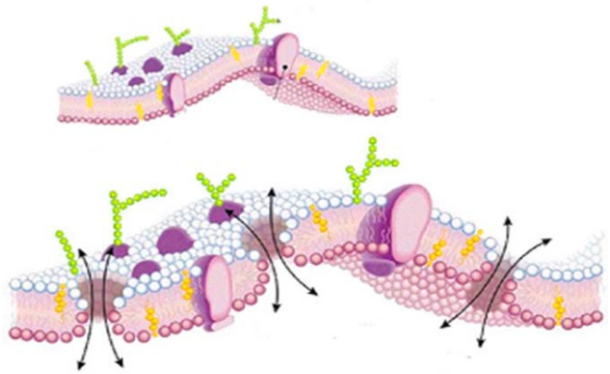


Figure 1. Mechanism of electroporation: high intensity electrical pulses applied to cells result in transient nano-pore formation (as indicated by the arrows) allows impermeable molecules molecules to enter the cell.[51]

The initial in-vitro observations by Mir *et al.* that lead to the development of this technology as a viable treatment showed that bleomycin a established cancer medication which is poorly permeable and normally absorbed by a receptor mediated endocytosis could enter tumour cells by electropermeabilization.[9-11] Low molecular concentrations of bleomycin in the intracellular environment, was highly toxic to tumour cells. Therefore, the combination of electroporation, with Bleomycin increased its potency several hundred times in vitro.[12]

There are several theories explaining mechanism of how this occurs. This includes the phase transient model, the denaturation model and the electroporation model.[13-15] The accepted understanding of the process of reversible electroporation that occurs in ECT is spontaneous, but transient pore formation occurs in the cell membrane in response the high intensity electrical fields. These nano-pores retain sufficient stability to allow relatively large molecules to become intracellular. However the presence of these pores are of extremely short duration and the cell membrane returns to it normal structure.[5,16]

An important secondary effect of the high intensity field demonstrated by in vivo studies is local vasoconstriction and hypoxia and endothelial disruption.[17-19] ECT results in a reduction in tumor blood flow that occurs in 2 phases. A short-lived episode when the electric pulses are delivered resulting in a 'vascular lock' around the tumor cells that prevents washout of the cytotoxic agent and further concentrates the cytotoxic agents in the tumor cells.[19, 20] Subsequent disruption of the endothelial cytoskeleton and intracellular junctions results in a change in the configuration of the surface of the endothelium. This leads to an impaired barrier function and interstitial edema resulting in decreased intravascular pressure and compromised blood flow. Repair of the endothelium is slow and a reduction in blood flow in feeding tumor vessels in observed causing severe hypoxia to the tumor cells evident several days after treatment with ECT.[20]

Characteristics of agents that could be effective in ECT are those that are hydrophilic, with molecular structures will not allow entry into cells by diffusion or by transport systems in the cell membrane (Figure 2).[21] Several types of chemotherapeutic agents have been tested for their suitability for ECT. These include the anthracycline group (daunorubicin, doxorubicin and adriamycin), the polypeptide anti tumour antibiotics, the actinomycines group (actinomycin D, mitomycin C), Vinca alkaloids (vinblastine, vincristine) etoposide, paclitaxel, cyclophosphamide, carboplatin, cisplatin and bleomycin.[21] However only ciplatin and bleomycin have been found to have significant potentiation of their activity. Cisplatin has its action potentiated from 10 to 80 fold by electroporation of cells , while Bleomycin, has its action potentiated between 300 and 700 in vitro (Figure 2).[12] In vivo investigations in different animal models and various tumors using ECT with either Cisplatin or bleomycin have lead to further understanding of how clinical treatment could be optimised.[21-23] The mode of drug delivery was found to effective in both intravenous injection as well as intratumoural injection; the caveat for this is intratumoral treatment requires almost immediate electroporation following drug delivery.[23] In contrast, intravenous injection route of delivery

allows a short delay before electroporation needs to commence.[23] Effective electroporation depends on the intensity of the electric field and the devices used for application to the tumor. Sub-dermal are tumours best treated with needle electrodes; superficial tumors are effectively treated with an electrode plate. In addition in vivo studies have shown that the electrical fields optimises tissue distribution.[21,24]

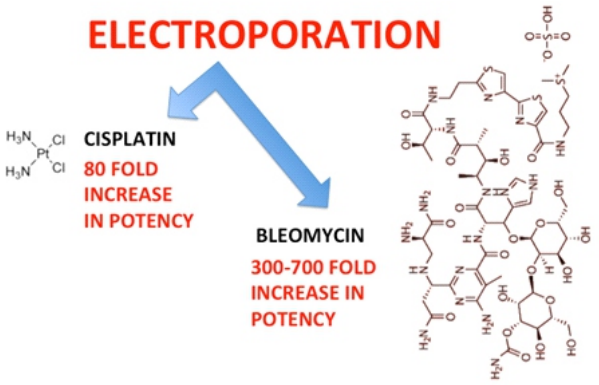


Figure 2. Chemotheraputic agents suitable for ECT: agents that are hydrophilic, impermeable at low concentrations and demonstrate increased potency after electroporation are suitable. Bleomycin and cisplatin have demonstrated the greatest potency.[52, 53]

Electrochemotherapy and breast cancer

The clinical use of ECT was pioneered in the European Union with the first cases treated in the Institute Gustave Roussy, in France and Institute of Oncology, Ljubljana, Slovenia in the 1990s.[25] Since then its use in the treatment of breast cancer skin metastases is well established throughout Europe with the largest number of published breast cancer cases treated in Denmark, Germany, Sweden, Slovenia and Italy.

In 2013, The National Institute of Clinical Excellence (NICE, UK) recommended its use in skin metastases including breast cancer.[26] Prior to this, the first center in the UK to start using ECT was James Cook University Hospital, Middlesborough, in 2010. Then, 6 other hospitals in the UK including our institution also started using the technology. ECT was used to treat patients when all other treatment modalities were unsuccessful or prohibitive. Currently, there are more than 15 centers in the UK offering this treatment. Our Institution is a designated center solely for the treatment of cutaneous metastases from breast cancer in the United Kingdom.[27]

The European Standard Operating Procedures of Electrochemotherapy (ESOPE) study in 2006 recruited 62 patients across 4 cancer centres in France, Ljubljana, Denmark and Ireland.[28] It evaluated and confirmed the efficacy and safety of ECT using bleomycin and cisplatin. This prospective non-randomised study enrolled patients with progressive cutaneous and subcutaneous metastases of any histologically proven cancer. They found an objective response rate of 85% achieved on the ECT treated nodules, regardless of tumor histology. They demonstrated ECT is not limited to non-irradiated skin, as 85 of the 171 nodules treated in the study were in previously irradiated skin. The procedure could also be performed under local anaesthetic for small areas.[28] The ESOPE study standardised the operating procedures for ECT a highly effective and safe approach for the treatment of skin metastases. Patients reported only minor and acceptable side effects. Indeed, 93% said they would be willing to accept the treatment next time, if indicated. Furthermore, it is quick and easy to perform.[11] The results of the study was particularly pertinent to treatment of breast cancer skin metastases, as, 27 patients out of 63 patients included in the study were confirmed to have cutaneous metastases form breast cancer.

Outcome of ECT treatment in breast cancer

A number of studies since then have shown ECT can induce partial or complete response of nodules to the therapy for breast cancer related cutaneous metastases.[29-37] (see Table 1). Specifically, lesions that are associated with bleeding or skin ulceration may benefit from this treatment that would otherwise be refractory to treatment. The ESOPE study demonstrated that, ECT is an effective treatment for elderly patients for whom surgery is not possible, as 16 patients (39% of all treated patients) were over 75 years old.[28] Subsequent publications by Campana *et al.* have also confirmed this finding; elderly patients showed significantly higher complete response rate above the age of 70 compared to patients below this age ($p<0.01$) as shown in table 2.[36, 38] The only justification for patient non- selection in this age group, would be, poor performance status and frailty. Elderly patients are more likely to discontinue treatment early and experience more post-treatment symptoms.[33] The largest published study consisting of 125 breast cancer patients treated with ECT, performed by Cabula *et al.* (2015), showed complete response in 58.4%, with overall response rate of 90.2%.[37] This was a multicenter retrospective study with 113 patients evaluated initially and after at 2 months, with median follow up of 5.9 months. Multivariate analysis of patients and tumors characteristics indicated small tumor size (<3cm), absence of visceral metastases, estrogen receptor positivity and KI-67 positivity were all associated with complete response.[37] Table 2 summarizes these findings. These results suggest that patient selection may be further refined and ECT would be more beneficial, if offered early at first presentation of skin metastases, although the presence of visceral metastases is not a contra-indication to treatment. ECT does not influence disease progression and at present is used as a replacement for other palliative measures. A recent meta-analysis of skin-based

treatment for cutaneous metastasis in advanced cancer by Spratt *et al.*, has demonstrated ECT has low toxicity and comparable outcome to other treatments, including radiotherapy.[39] ECT provides an alternative treatment for patients that have irradiated skin, and an option when all other therapies have failed. One of the most promising aspects of ECT is its unique ability to selectively kill tumor cells without

Table 1. Response rates of breast cancer skin lesions treated with electrochemotherapy in the published literature.

Reference	Year	No. Patients	No. Nodules	Typechemo-therapy	CR	SD/UR	PR	NR
Heller[29]	1995	1	2	IV Bleomycin	2/2 (100%)		0/2 (0%)	0/2 (0%)
Rodrigues-Cuevas[30]	2001	2	14	IT Bleomycin	8/14 (58%)		6/14 (42%)	0/14 (0%)
Rebersek[31]	2004	6	12	IT Cisplatin	4/12 (33%)		8/12 (67%)	0/12 (0%)
ESOPE[28]	2006	61*	58*	IV +IT Bleomycin, IT Cisplatin	73.7%*		11.3%*	14%
Larkin[32]	2007	15**	100	IV / IT Bleomycin	63%	3% (UR)	20%	7%*
Campana[33]	2009	11	174	IV / IT Bleomycin	43%*		50%*	7/25 (28%)
Madero and Parez[34]	2011	25			11/25 (44%)		7/25 (28%)	1/12 (~8%)
Matthiessen[35]	2012	17	1-5 per patient	IV /IT Bleomycin	1/12 (~8%)	9/12 (75%)	1/12 (~8%)	
Campana[36]	2012	35	15/20***	IV Bleomycin	19/35 (54.3%)	3/35 (8.6%)	13/35 (37.1%)	
Campana[38]	2014	55	55	IV Bleomycin	22/55 (40%)	7/55 (12.7%) (SD)	26/55 (47.3%)	
Cabula[37]	2015	125	1-5 per patient	IV /IT Bleomycin	58.4%	0.9% with disease progression + 7.1% stable disease	31.8% + 1.8% with disease progression	

This table only refers to the breast cancer patients in each study. No. nodules refers to those treated with ECT. IV: intravenous; IT: intratumoral; CR: complete response; PR: partial response; SD/UR: unknown response; NR: no response; SD: stable disease
** figures for all cancers (response rates not separated into those specifically for breast cancer) with breast cancer patient in a sub-group of 27 patients and accounting for 58 nodules in the ESOPE study, **1 patient was not treated, one was lost to follow-up, ***15 nodules and 20 plaques in the cohort*

Table 2. Characteristics that have been shown to effect outcome of ECT treatment

Tumor /treatment Characteristic	Prognostic value for outcome	Study size (n)	P value[Reference]
Size 3 cm or less	Associated with CR and LPFS	125	$p < 0.001$ LPFS $P = 0.008$[35]
Size greater than 3 cm	Risk of prolonged post operative pain	125	$P = 0.008$[35]
ER receptor positive	Associated with CR	125	$P = 0.016$[35]
Ki-67	Associated with CR	125	$P = 0.02$[35]
Absence of visceral metastases	Associated with CR	125	$P = 0.001$[35]
Breast cancer subtype: Luminal A*	Associated with CR	125	$P = 0.02$[35]
Irradiated skin	No difference for CR	61*	$P > 0.05$[26]
Current intensity > 5 Amps	Risk of post operative pain	120	$P < 0.0001$[42]
Irradiated skin	Risk of post operative pain	120	$P = 0.014$[42]
Pre-existing pain	High risk of post operative pain	120	$P < 0.0001$[42]
Age over 70	Associated with CR	55 (28)**	$P = 0.023$[42]
Patients with poor performance status at any age	May result in poor outcome for tumor response	55	$P = 0.048$[42]

** Breast cancer classification based on gene expression. Subtype luminal A is estrogen receptor (ER)–positive. Luminal A cancers are low grade, tend to grow fairly slowly, and have the best prognosis,** 28 patients in this study had breast cancer skin metastases and age over 70*

harming normal surrounding tissue as is targeted by the application directly over the lesions to be treated. It is cost-effective, having an incremental cost effectiveness ratio of €1571 with an average cost per achieved response of €1901 (compared to €2007 for radiotherapy and €2851 for combined hyperthermia, chemotherapy and radiotherapy).[40]

Patient selection and treatment considerations

Clinical treatment with ECT has been performed most frequently in patients with advanced metastatic cancer in whom the possibility of standard treatment has been exhausted.[31, 41, 42] NICE guidelines in the U.K. recommends that patients should be considered for ECT, if conventional therapies have been used and are no longer effective, or if the patient cannot have conventional treatment.[26] In our practice, patients with breast cancer skin metastases are assessed through the multi-disciplinary team with regard to their completion of conventional treatment, absence of visceral metastases or their relative stability in the presence of progressing cutaneous disease. As bleomycin is the chemotherapeutic agent of choice, relative and absolute contraindications to its use such as pulmonary fibrosis or severe chronic obstructive airways disease are also contra-indications for ECT unless cisplatin is used instead. Patients should not be taking medications, which increase the risk of life threatening haemorrhage at the time of ECT. Other important considerations to be assessed at the pre-treatment consultation include the patient's general health, mobility, general fitness and pre-existence of pain at the site of cutaneous lesions. Patients with life expectancy less than 3 months should not be considered for treatment. Table 3 summarises the indications and relative contra-indications for ECT. Pre-treatment investigations include staging CT imaging and bone scan to exclude visceral disease progression, which would be an indication for further systemic treatment. Lung function tests are necessary to obtain baseline observations prior to treatment with bleomycin. Post treatment this should be repeated, if further treatments are planned or if patients become symptomatic.

Patients at our institute are given gabapentin prior to their surgery and this is continued for a period of a month post-operatively or longer according to symptoms, to reduce the sustained discomfort that occurs from the muscle stimulation a side-effect of the electrical pulses. In our institute, patients are usually admitted on the day of treatment and discharged the following day, unless symptomatic. Patients referred from outside the catchment area or with medical conditions e.g. on warfarin therapy require admission for optimisation prior to treatment.

ECT can be delivered under both general and local anaesthetisia; however due to the type of lesions and their distribution, all patients treated so far at our institute were given general anaesthesia.[28] Due to the risk of potential risk of pulmonary fibrosis from bleomycin, patients are anaesthetised with inspired oxygen concentrations between 28-32%. If large

Table 3. Patient selection for electrochemotherapy and pre-treatment considerations.[54]

Indications for treatment	Cutaneous and subcutaneous metastases of skin and non-skin origin and melanoma in the presence or absence of disseminated disease WITH or WITHOUT: bleeding, pain and ulceration.
Treatment contra- indications	Patients should not be referred for electrochemotherapy, if they have pre-existing conditions that would become significantly worse or life threatening, if treatment was performed. This includes: 1. Symptomatic and/or rapidly progressive non-cutaneous metastasis are relatively contraindicated and treatment suitability will be decided by Multi Disciplinary Team 2. Allergic reactions to bleomycin (BLM) or cisplatin (CDDP) 3. Cumulative dose of 250 mg BLM/m2 4. Peripheral neuropathy >grade 2 5. Coagulation anomalies whose severity is such as to be life threatening or deemed unsuitable for electrochemotherapy by the MDM (Multidisciplinary team meeting) 6. Chronic renal dysfunction (creatinine> 150micromol/lit) 7.Arrhythmia/Pacemaker* 8. Epilepsy 9. Patients who are currently pregnant or lactating are not suitable for electrochemotherapy. 10. They should not have any inter-current infection at the time of electrochemotherapy.
Pre-treatment investigations/ assessments	Eligible patients should have the following investigations within 3 weeks of referral date and preferably at least 3 weeks after any chemotherapy treatment: 1. Full Blood Count, 2. Urea & Electrolytes AND Creatinine 3. Liver Function Tests & Clotting 4. Pulmonary Function Tests 5. STAGING contrast CT (thorax/abdomen/pelvis) AND whole body bone scan within 3 months of treatment date. 6.The MRSA status of the patient should be known and if positive, appropriate treatment should have been given. Eligible patients should be reviewed in a joint clinic by the oncologist and surgeon who will perform the electrochemotherapy. This should usually take place within 4 weeks prior to treatment date.

** Electrochemotherapy may be performed in areas other than directly over and around the pacemaker with cardiology supervision or external pacing. Pre-treatment cardiology opinion is essential.*

areas are to be treated, intra-operative fentanyl or morphine infusions are given. These may be continued as required post treatment. Intravenous bleomycin is given under general anaesthesia (Figures 3 to 7) and after 8 minutes, ECT is commenced. The dose of bleomycin is pre-calculated by the medical oncologist according to the Dubois formula[43] and is based on height and weight measurements; it is much lower than the standard therapeutic doses used in systemic chemotherapy. The choice of the electrodes is determined by the size and extent of the lesions, with 3 types of electrodes currently being employed; these are linear row needle electrodes, hexagonal array needle electrodes and plate electrodes. The linear row electrodes more effective with smaller less extensive lesions, while the hexagonal electrodes used typically in extensive diffuse lesions.

Prior to treatment, careful documentation of the size of each lesion to be treated and the dimensions of the field of treatment supplemented by photographs allow objective assessment of outcome. ECT is performed, by inserting the electrode needles subcutaneously into the lesions to be treated, and then firing the electrodes generated pulses (Figures 3-7). This is then also applied up to a centimetre circumferentially around the lesions. The treatment duration is limited to a maximum of 40 minutes reflecting the fall in concentration of bleomycin, which becomes sub-therapeutic after this. At the end the procedure, the wounds are dressed with gauze soaked with local anaesthetic gel. Following treatment, patients are usually observed for 24 hours and given standard surgical nursing care. Most patients are discharged with simple analgesics. Post treatment wound review usually occurs at 4-6 weeks post ECT with outcome review at 3 months. In our center, we have only treated patients with breast cancer skin metastases; the practice in other centers that also treat other types of skin lesions such as melanoma and other skin cancer metastases will invariably have differences in practice to what comprises optimal treatment. Typically in some European centers, patients are treated for small lesions without need for post-treatment admission to hospital, while treatment of extensive chest lesions may require a period of admission in hospital for post treatment analgesia. All ECT treatments require a multidisciplinary approach for determining patient selection as well as delivery of treatment. Figures 8 and 9 shows treatment outcome with ECT at our institute.

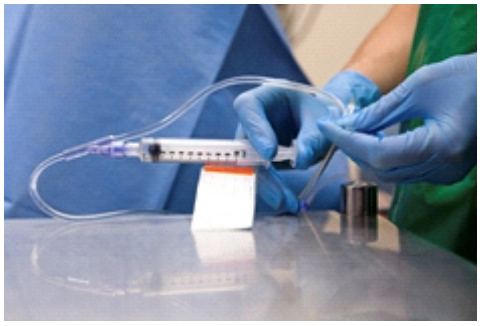


Figure 3

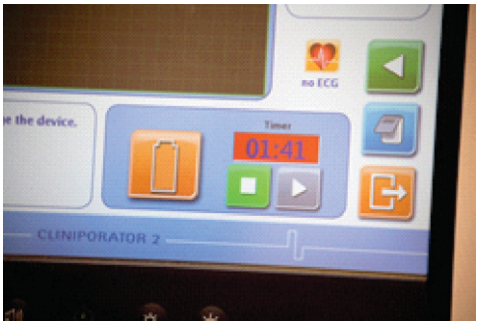


Figure 4

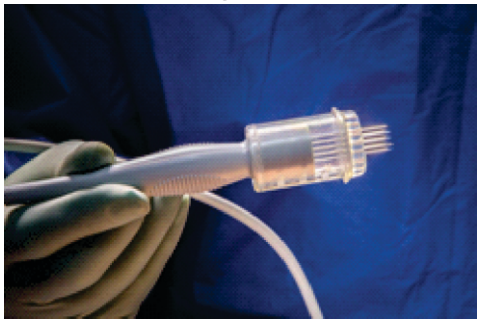


Figure 5

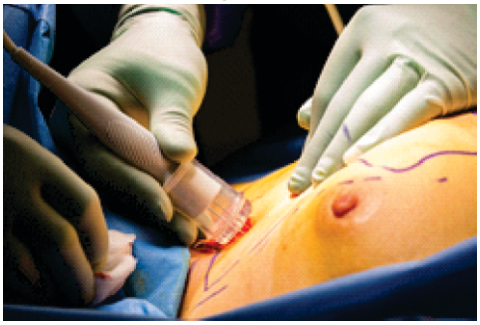


Figure 6

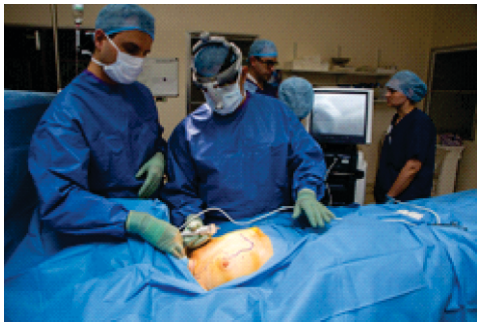


Figure 7

Figures 3 to 7. ECT treatment:[1]
3) Intra-venous bleomycin is given
4) 8 minutes elapsed before ECT treatment
5, 6 and 7) needle electrodes are inserted through the skin directly at the site of the lesions and circumferential area and the electrical impulses fired by a hand/foot pedal.

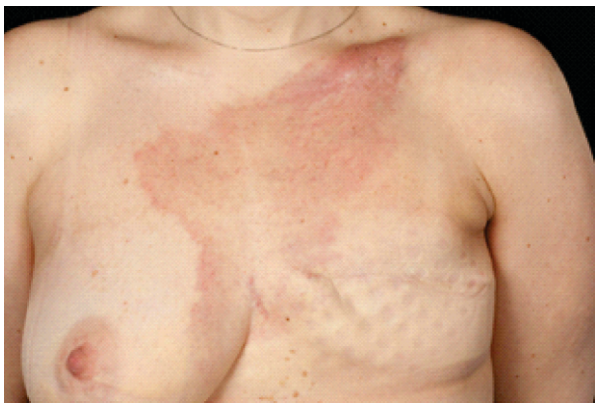


Figure 8

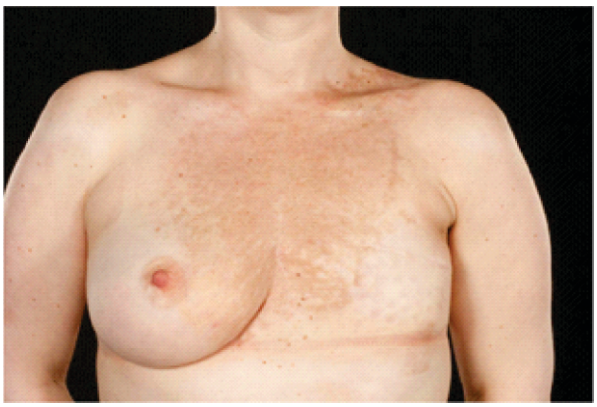


Figure 9

Figure 8 and 9. Electrochemotherapy outcome [1, 2]. Figure 8 Shows chest wall lesions in a 37 year-old patient who was diagnosed with left breast cancer (T3N2M0), which was triple receptor positive. She was initially treated mastectomy and axillary node clearance. She was given chemotherapy and chest wall radiotherapy followed by zoladex and tamoxifen. Three years later she developed liver metastases and a chest wall rash proven to be skin metastases. After second line chemotherapy, the visceral lesions were stabilized; however the chest wall lesions were persistent and extending in area. Figure 9 shows this patient 6 weeks after ECT treatment. There is minimal hyperpigmentation and there was complete response of all treated lesions. She was skin lesion-free for 6 months.

Observed adverse effects and their management

In general, patients who undergo ECT do not have significant adverse symptoms and in our experience and that of the other authors, the majority have minimal symptoms and would be willing to be re-treated.[28, 38, 44] However ECT-related side effects have been identified in breast cancer patients. Hyperpigmentation occurs in the treated areas of all patients who have ECT; but the extent and intensity is variable. Patients with tumour regression are associated with less hyperpigmentation but this finding is not universal. Only in 10% of patients adverse symptoms are severe.[37,44]

Breast cancer patients are more likely to experience post-operative pain (see Table 2).[44] Studies of treatment conducted before 2014 have included pain as a significant side effect; however after this period, the use of new electrodes which cause less fasciculation during treatment; fewer patients at our institute have had persistent pain symptoms after this. A recent review of post-operative pain showed that 74% of patients have little or no pain immediately after treatment and in the immediate follow up period.[44] In most patients pain was experienced as dull aching discomfort, typically appearing by 4-8 weeks after treatment and in most resolving by 12 weeks.[44] This is temporary in most patients, who experience pain and is adequately treated with simple analgesia. However more persistent high intensity pain can occur and may need to be treated with opiate medication. Investigations of factors, which may increase the likelihood of post-operative pain have shown that treatment of the chest wall, or irradiated skin are associated with post-operative symptoms.[44] Patients who already experience pain from their skin lesions are also more likely to be symptomatic.[44] Tumor size and the extent of treatment area are also implicated to post treatment pain; tumors greater than 3 cm and a large surface area of treatment are associated with pain.[44]

Other adverse effects include skin ulceration as a result of necrosis and regression of the tumor following treatment.[44] This may take some time to heal and need repeated debridement and specialist skin care or surgical intervention.[27,44] Excision of the lesion en bloc, and then treatment of the base and circumferential area with ECT, before primary closure, may avoid this problem. In our experience, diffuse infiltration of the skin with tumor may cause post treatment skin loss. In cases where this has occurred, the authors have combined treatment with plastic surgery; initially debridement of the necrotic tissue followed by VAC® dressings to reduce edema and encourage wound healing. Biopsy of the wound bed may be considered first to exclude tumor as this treatment facilitates angiogenesis and if tumor is present, this may stimulate further recurrence.

Bleomycin has been associated with pulmonary fibrosis when used in systemic chemotherapeutic regimens. The dose of bleomycin used in ECT is much lower than the therapeutic dose used in conventional systemic therapy, and due to its relative insolubility has no systemic effect. There has been no cases of bleomycin toxicity in the published series; however repeated treatment may increase this risk. Therefore, careful patient selection and treatment planning with assessment of pulmonary function would be of benefit.

Discussion

The promising objective response rates achieved so far suggest that in the future this therapy may be a treatment option in an earlier phase in the management of breast cancer in conjunction with chemotherapy. This is suggested by findings of

Cabula *et al.* and further refinement of patient selection using favorable characteristics to improve outcome may also be possible.[37] Prospective randomised trial to investigate these possibilities is the next step to advance the use of this treatment.

It is also likely that as the technology develops, it will be used on an even wider range of tumors including those deep within the body. Indeed, endoscopic devices have been shown to be successful against breast cancer cell lines that may be used in the future for inaccessible cancers.[45] Electrical pulses are not limited to use in conjunction with chemotherapy. Electroporation for gene therapy has been demonstrated for melanoma.[46] Direct therapy may generate a direct anti-tumor effect and delivery to alternative sites may lead to the production of cancer vaccines, reduction in tumor angiogenesis, or the induction of tumor cell apoptosis.[46] This immune therapeutic effect may be responsible for the local benefits seen in clinical treatment; however investigation of the immune effects induced by electrochemotherapy in breast cancer are restricted to pre-clinical studies.[47] The electrical pulses in themselves have also been shown to be beneficial. Nanosecond pulsed electric fields (nsPEFs) have been shown to inhibit tumor growth and can target intracellular organelles and has been studied in other cancer cell lines in vitro.[48] Irreversible electroporation (IRE) is a new ablation procedure that uses pulses to provoke permanent permeability of the cells resulting in their death without any thermal effects making it better tolerated than other ablation technologies.[49] ECT may also be used in adjunct to other forms of established treatment such as radiotherapy; although hypoxia causes radio-resistance, ECT agents have also radio-sensitizing effects that are further amplified during ECT.[50] This advantage may be utilized in the development of combined therapeutic treatment planning.

In conclusion, ECT has already been established as a standard of care for the treatment of breast cancer skin metastases and compares favourably with other skin treatments. Its potential for expansion from its current rather limited use to first line, widespread treatment is supported by recent publications.

References

1. Banerjee S, Khan S, Newby J, Keshtgar M. Electrochemotherapy for cutaneous metastases in breast cancer: Experience from a designated treatment centre. Eur J Surg Oncol 2015; 41(6): S48.
2. Matthiessen LW, Keshtgar M, Kunte C, Grischke E-M, Odili J, Muir T, *et al.* Electrochemotherapy for breast cancer - results from the INSPECT database. Ann Oncol 2016; 27(suppl 6):
3. Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. J Am Acad Dermatol 1993; 29(2 Pt 1): 228-36.
4. Benevento R, Santoriello A, Perna G, Canonico S. Electrochemotherapy of cutaneous metastastes from breast cancer in elderly patients: a preliminary report. BMC Surg 2012; 12 Suppl 1: S6.
5. Weaver JC, Chizmadzhev YA. Theory of electroporation: a review. Bioelectrochem Bioenerg 1996; 41(2): 135-60.
6. Neal RE, 2nd, Singh R, Hatcher HC, Kock ND, Torti SV, Davalos RV. Treatment of breast cancer through the application of irreversible electroporation using a novel minimally invasive single needle electrode. Breast Cancer Res Treat 2010; 123(1): 295-301.
7. Insp-ECT Purposes and history. 2016. www.insp-ect.org (accessed Octobor 6 2016).
8. Mir LM. Therapeutic perspectives of in vivo cell electropermeabilization. Bioelectrochemistry 2001; 53(1): 1-10.
9. Potter H. Electroporation in biology: methods, applications, and instrumentation. Anal Biochem 1988; 174(2): 361-73.
10. Mir LM, Banoun H, Paoletti C. Introduction of definite amounts of nonpermeant molecules into living cells after electropermeabilization: direct access to the cytosol. Exp Cell Res 1988; 175(1): 15-25.
11. Pron G, Mahrour N, Orlowski S, Tounekti O, Poddevin B, Belehradek J, Jr., *et al.* Internalisation of the bleomycin molecules responsible for bleomycin toxicity: a receptor-mediated endocytosis mechanism. Biochem Pharmacol 1999; 57(1): 45-56.
12. Gothelf A, Mir LM, Gehl J. Electrochemotherapy: results of cancer treatment using enhanced delivery of bleomycin by electroporation. Cancer Treat Rev 2003; 29(5): 371-87.
13. Sugar IP. A theory of the electric field-induced phase transition of phospholipid bilayers. Biochim Biophys Acta 1979; 556(1): 72-85.
14. Jacobs RE, Hudson B, Andersen HC. A theory of the chain melting phase transition of aqueous phospholipid dispersions. Proc Natl Acad Sci U S A 1975; 72(10): 3993-7.
15. Tsong TY. Electroporation of cell membranes. Biophys J 1991; 60(2): 297-306.
16. Neumann E, Kakorin S, Toensing K. Fundamentals of electroporative delivery of drugs and genes. Bioelectrochem Bioenerg 1999; 48(1): 3-16.
17. Sersa G, Cemazar M, Parkins CS, Chaplin DJ. Tumour blood flow changes induced by application of electric pulses. Eur J Cancer 1999; 35(4): 672-7.

18. Sersa G, Krzic M, Sentjurc M, Ivanusa T, Beravs K, Kotnik V, *et al.* Reduced blood flow and oxygenation in SA-1 tumours after electrochemotherapy with cisplatin. Br J Cancer 2002; 87(9): 1047-54.
19. Sersa G, Jarm T, Kotnik T, Coer A, Podkrajsek M, Sentjurc M, *et al.* Vascular disrupting action of electroporation and electrochemotherapy with bleomycin in murine sarcoma. Br J Cancer 2008; 98(2): 388-98.
20. Markelc B, Sersa G, Cemazar M. Differential mechanisms associated with vascular disrupting action of electrochemotherapy: intravital microscopy on the level of single normal and tumor blood vessels. PLoS One 2013; 8(3): e59557.
21. Serša G, Čemažar M, Miklavčič D, Rudolf Z. Electrochemotherapy of tumours. Radiol Oncol 2006; 40(3):
22. Jaroszeski MJ, Heller R, Gilbert R. Electrochemotherapy, electrogenetherapy, and transdermal drug delivery: electrically mediated delivery of molecules to cells: Humana Press; 2000.
23. Gehl J. Electroporation: theory and methods, perspectives for drug delivery, gene therapy and research. Acta Physiol Scand 2003; 177(4): 437-47.
24. Miklavcic D, Pucihar G, Pavlovec M, Ribaric S, Mali M, Macek-Lebar A, *et al.* The effect of high frequency electric pulses on muscle contractions and antitumor efficiency in vivo for a potential use in clinical electrochemotherapy. Bioelectrochemistry 2005; 65(2): 121-8.
25. Rudolf Z, Stabuc B, Cemazar M, Miklavcic D, Vodovnik L, Sersa G. Electrochemotherapy with bleomycin. The first clinical experience in malignant melanoma patients. Radiol Oncol 1995; 29(6): 229-35.
26. Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma. 2016. https://www.nice.org.uk/guidance/ipg446 (accessed October 8 2016).
27. Banerjee S, Newby J, Whittaker D, Johnson R, Keshtgar M. Electrochemotherapy in the treatment of skin metastases in breast cancer: Lessons learned. Eur J Surg Oncol 2014; 40(5): 624-5.
29. Marty M, Sersa G, Garbay JR, Gehl J, Collins CG, Snoj M, *et al.* Electrochemotherapy–An easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: Results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study. EJC Suppl 2006; 4(11): 3-13.
29. Heller R, Jaroszeski MJ, Glass LF, Messina JL, Rapaport DP, DeConti RC, *et al.* Phase I/II trial for the treatment of cutaneous and subcutaneous tumors using electrochemotherapy. Cancer 1996; 77(5): 964-71.
30. Rodriguez-Cuevas S, Barroso-Bravo S, Almanza-Estrada J, Cristobal-Martinez L, Gonzalez-Rodriguez E. Electrochemotherapy in primary and metastatic skin tumors: phase II trial using intralesional bleomycin. Arch Med Res 2001; 32(4): 273-6.
31. Rebersek M, Cufer T, Cemazar M, Kranjc S, Sersa G. Electrochemotherapy with cisplatin of cutaneous tumor lesions in breast cancer. Anticancer Drugs 2004; 15(6): 593-7.
32. Larkin JO, Collins CG, Aarons S, Tangney M, Whelan M, O'Reily S, *et al.* Electrochemotherapy: aspects of preclinical development and early clinical experience. Ann Surg 2007; 245(3): 469-79.
33. Campana LG, Mocellin S, Basso M, Puccetti O, De Salvo GL, Chiarion-Sileni V, *et al.* Bleomycin-based electrochemotherapy: clinical outcome from a single institution's experience with 52 patients. Ann Surg Oncol 2009; 16(1): 191-9.
34. Munoz Madero V, Ortega Perez G. Electrochemotherapy for treatment of skin and soft tissue tumours. Update and definition of its role in multimodal therapy. Clin Transl Oncol 2011; 13(1): 18-24.
35. Matthiessen LW, Johannesen HH, Hendel HW, Moss T, Kamby C, Gehl J. Electrochemotherapy for large cutaneous recurrence of breast cancer: a phase II clinical trial. Acta Oncol 2012; 51(6): 713-21.
36. Campana LG, Valpione S, Falci C, Mocellin S, Basso M, Corti L, *et al.* The activity and safety of electrochemotherapy in persistent chest wall recurrence from breast cancer after mastectomy: a phase-II study. Breast Cancer Res Treat 2012; 134(3): 1169-78.
37. Cabula C, Campana LG, Grilz G, Galuppo S, Bussone R, De Meo L, *et al.* Electrochemotherapy in the Treatment of Cutaneous Metastases from Breast Cancer: A Multicenter Cohort Analysis. Ann Surg Oncol 2015; 22 Suppl 3: S442-50.
38. Campana LG, Galuppo S, Valpione S, Brunello A, Ghiotto C, Ongaro A, *et al.* Bleomycin electrochemotherapy in elderly metastatic breast cancer patients: clinical outcome and management considerations. J Cancer Res Clin Oncol 2014; 140(9): 1557-65.
39. Spratt DE, Gordon Spratt EA, Wu S, DeRosa A, Lee NY, Lacouture ME, *et al.* Efficacy of skin-directed therapy for cutaneous metastases from advanced cancer: a meta-analysis. J Clin Oncol 2014; 32(28): 3144-55.
40. Colombo GL, Matteo SD, Mir LM. Cost-effectiveness analysis of electrochemotherapy with the Cliniporatortrade mark vs other methods for the control and treatment of cutaneous and subcutaneous tumors. Ther Clin

Risk Manag 2008; 4(2): 541-8.
41. Sersa G, Cemazar M, Rudolf Z. Electrochemotherapy: advantages and drawbacks in treatment of cancer patients. Cancer Ther 2003; 1: 133-42.
42. Jaroszeski MJ, Dang V, Pottinger C, Hickey J, Gilbert R, Heller R. Toxicity of anticancer agents mediated by electroporation in vitro. Anticancer Drugs 2000; 11(3): 201-8.
43. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition 1989; 5(5): 303-11; discussion 12-3.
44. Quaglino P, Matthiessen LW, Curatolo P, Muir T, Bertino G, Kunte C, *et al.* Predicting patients at risk for pain associated with electrochemotherapy. Acta Oncol 2015; 54(3): 298-306.
45. Recht A, Come S, Troyan S. Local-regional recurrence after mastectomy or breast-conserving therapy. In: Harris JR, Lippman ME, Osborne CK, Morrow M, eds. Diseases of the Breast. Philadelphia: Lippincott Williams & Wilkins; 2012.
46. Heller LC, Heller R. Electroporation gene therapy preclinical and clinical trials for melanoma. Curr Gene Ther 2010; 10(4): 312-7.
47. Calvet CY, Mir LM. The promising alliance of anti-cancer electrochemotherapy with immunotherapy. Cancer Metastasis Rev 2016; 35(2): 165-77.
48. Yin S , Chen X, Hu C, Zhang X, Hu Z, Yu J, *et al.* Nanosecond pulsed electric field (nsPEF) treatment for hepatocellular carcinoma: a novel locoregional ablation decreasing lung metastasis. Cancer Lett 2014; 346(2): 285-91.
49. Deipolyi AR, Golberg A, Yarmush ML, Arellano RS, Oklu R. Irreversible electroporation: evolution of a laboratory technique in interventional oncology. Diagn Interv Radiol 2014; 20(2): 147-54.
50. Kranjc S, Tevz G, Kamensek U, Vidic S, Cemazar M, Sersa G. Radiosensitizing effect of electrochemotherapy in a fractionated radiation regimen in radiosensitive murine sarcoma and radioresistant adenocarcinoma tumor model. Radiat Res 2009; 172(6): 677-85.
51. Modified image of Electroporation. Original Image from IGEA medical. http://www.igeamedical.com/oncology/electrochemotherapy-effective-treatment-cancer
52. Modified image of the structure of Cisplatin. Original Image from https://www.drugs.com/ingredient/cisplatin.html
53. Modified image of the structure of Bleomycin. Original image from http://www.selleckchem.com/products/Bleomycin-sulfate.html
54. London Cancer Electrochemotherapy Guidelines. 2016. http://londoncancer.org/wp-content/uploads/2016/07/ECT-Guidelines-1.pdf (accessed September 18 2016).

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.201634118-125

Evaluation of Saline Sonohysterography Findings in Patients with Breast Cancer Receiving Tamoxifen Adjuvant Therapy

Maryam Rahmani*[a], Leila Farmanbordar[a], Ramesh Omranipour[b], Mahrooz Malek[a], Sanaz Zand[c]

[a] *Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Department of Radiology, Tehran University of Medical Sciences, Tehran, Iran*
[b] *Division of Surgical Oncology, Department of Surgery, Tehran University of Medical Sciences, Tehran, Iran*
[c] *Kaviani Breast Diseases Institute (KBDI), Tehran, Iran*

ARTICLE INFO

Received:
17 October 2016
Revised:
7 November 2016
Accepted:
13 November 2016

Keywords:
Tamoxifen,
breast cancer,
endometrial lesions,
endometrial cancer,
saline sonohysterography

ABSTRACT

Background: Transvaginal ultrasound is one of the most common means to examine endometrial cavity lesions although its negative results are more valuable. Saline sonohysterography can reduce the number of false negative rates of endometrial lesions diagnoses in Tamoxifen consumers. The Objective of this study was to determine the diagnostic values of saline infusion sonohysterography (SIS) and hysteroscopy as gold standard in diagnosis of endometrial pathologies in patients with breast cancer receiving adjuvant therapy with Tamoxifen for at least 6 months.

Methods: This cross-sectional study was conducted on 40 patients with breast cancer who were treated with for at least 6 months and referred by the gynecologist for evaluation. Age, duration of Tamoxifen use and symptoms were recorded. Patients were examined by saline sonohysterography. Ultrasonic endometrial findings were recorded. Patients with positive findings were referred for hysteroscopy and biopsy was taken for pathologic examination. Then we compared the results.

Results: In total, 40 patients with a mean age of 46.5±7.81 years and mean duration of Tamoxifen treatment 18.4 ±13.98 months were included. There were intrauterine lesions in 22 patients and they did not undergo hysteroscopy. For others, 9 patients with endometrial polyp (21.41%), 3 patients with endometrial hyperplasia (7.14%) were found. The accuracy of SSH in diagnosing endometrial polyp, endometrial hyperplasia and submucosal fibroma were 87.5%, 92.5% ,97.5%, respectively.

Conclusions: Saline sonohysterography is a viable option for screening of the patients instead of endometrial biopsy as it has great negative predictive value. Sonohysterography is easy, non-invasive, inexpensive and has great accuracy.

Introduction

Transvaginal ultrasound is one of the most common means to examine endometrial cavity lesions although its negative results are more valuable.[1] Elderly women with breast cancer who are treated with Tamoxifen are among the patients with higher risk of endometrial neoplastic lesions.[2] Tamoxifen has anti-estrogenic effects on breast tissue; but can act as an estrogen agonist on endometrial receptors, therefore it appears that Tamoxifen consumption can increase the risk of endometrial cancers.[3] Salazar *et al.* in 1985 for the first time reported an association

Address for correspondence:
Maryam Rahmani, MD
Address: Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Medical Imaging Center, Imam Khomeini Hospital, 1419733141, Tehran, Iran
Tel: +98 21 66581579
Fax: +98 21 66581578
Email: m49rahmani@yahoo.com

between Tamoxifen consumption and development of endometrial cancer.[3,4] Still, some of the researchers believe only patients who have abnormal vaginal bleeding should be evaluated for endometrial pathologies.[5] On the other hand, others believe that all those patients should undergo careful pelvic examination and ultrasonic endometrial thickness evaluation every 6 months.[3] Some studies on the effect of Tamoxifen on endometrial thickness in breast cancer patients, have shown that by regular repeated examinations of these patients and evaluation of endometrial thickness with ultrasound, endometrial cancer can be detected in early stages.[6,7] Essentially, Tamoxifen can be the cause of endometrial thickening by initiating polyps, hyperplasia and/or neoplasia, or can reduce the thickness and cause atrophy.[3,8] It appears that the main cause of developing malignancy from endometrial hyperplasia is the duration of Tamoxifen consumption.[8]

Recent studies have shown that sonohysterography with limited intrauterine injection of sterile saline can reduce the number of false negative diagnosis of endometrial lesions in Tamoxifen consumers.[9,10] Since this technique can better distinct focal and diffuse lesions compared to other methods such as transvaginal ultrasonography. Also with SIS, in order to make a definitive diagnosis, a biopsy can be taken.[11,12] Multiple studies have shown that sonohysterography with normal saline has higher sensitivity, specificity, positive predictive value and negative predictive value than transvaginal ultrasound and it is comparable to hysteroscopy as the gold standard, therefore, we can use this technique as the first screening tool in patients with abnormal uterine bleeding prior to hysteroscopy since it's simple, minimally invasive, cost-effective.[13-16]

Since breast cancer is one of the most common cancers among Iranian women population and most of them receive adjuvant therapy with Tamoxifen for their treatment, thus they're exposed to a high risk of endometrial pathologies.[4,17,18]

We conducted this study to evaluate relation of endometrial pathologies with abnormal saline infusion sonohysterography (SIS) features and hysteroscopic findings as the gold standard in patients with breast cancer receiving adjuvant therapy with Tamoxifen for at least 6 months, thereby to investigate the diagnostic values of SIS and hysteroscopy, to estimate whether SIS can be a good alternative for hysteroscopy as a screening tool in diagnosis of endometrial pathologies.

Methods

This cross-sectional study was approved by research committee of Tehran University of Medical Sciences. Written informed consent was obtained from all patients. The study population were patients with breast cancer who received adjuvant therapy with full dose Tamoxifen (20mg, Daily) for at least 6 months and referred by the gynecologist for evaluation of endometrial pathologies to the radiology department of Imam Khomeini hospital from March 2012 to March 2014. Patients who had endometrial wall thickness of more than 4mm with transvaginal ultrasound were included in the study; and patients older than 70 years old, with vaginal infections, with positive βHCG results, and patients who did not take their medications regularly were excluded.

The variables recorded at the beginning were age, duration of Tamoxifen use and symptoms such as abnormal uterine bleeding (AUB) or vaginal discharge. First, a saline sonohysterography was performed (as described by Ogutcuoglu *et al.*[19]). Ten to twenty ml normal saline were infused through a foley catheter and transvaginal ultrasound was performed and ultrasonic endometrial findings were recorded including thickness, presence of hyperplasia, polyp, Adenomyosis, submucosal fibrosis, endometrial cancer signs, and adhesions in endometrial cavity.

Ultrasounds were done by Medison™ instrument and transvaginal endocavitary probes were used. Then symptoms such as AUB and pelvic pains were explained to the patients and they were encouraged for follow-up. Patients with positive saline sonohysterography finding was referred to gynecologist for hysteroscopy and biopsy was taken for pathologic examination.

Collected data were analyzed by SPSS software (IBM Inc.) v.19. Continuous variables were reported as mean ± standard deviation and categorical variables as absolute and relative frequency.

Results

After applying inclusion and exclusion criteria, 40 patients who were referred to ultrasound clinic for evaluation of endometrial pathologies after receiving Tamoxifen for more than 6 months, were included in the study. Mean age of patients was 46.5±7.8 (Range: 32-65, Median: 46.50).

Most the patients had at least two pregnancies in their lifetime, In fact, 42.5% of them had more than two, 40% of them had only 2 and only 7.5% just 1 pregnancy. Also 10% of patients didn't have history of prior pregnancy.

As demonstrated in table 1, most of the patients (62.2%) didn't have any symptoms. For the symptomatic patients, the most common symptom was abnormal discharge (16.66%) and abnormal uterine bleeding (11.9%). Other symptoms such as pelvic pain and mass palpation were only reported in two patients.

Regarding SIS findings, as reported in table 1, there was suspicious pathologic finding in most of the patients (14 patient, 34.14%). The most common

pathologic finding was endometrial polyp which was seen in 12 patients (29.26%) and after that adenomyosis in 5 patients (12.19%). Other findings such as hyperplasia, fibroid and adhesions were reported in fewer number of patients.

As shown in table 1, there were intrauterine lesions in 22 patients and they did not undergo hysteroscopy. Also, it was not performed for 2 more patients due to technical difficulties. For others, the most common pathologic finding was endometrial polyp which was found in 9 patients (21.41%). Also, endometrial hyperplasia was seen in 3 patients (7.14%) and other findings such as fibroid, leiomyoma, adenomyosis and adenomyoma were only seen in 1 patient. Two patients had simultaneous polyp hyperplasia and endometrial polyp. Biopsy was technically not possible in one patient because of multiple linear, fixed, bridging adhesion bands.

Nearly 75% of the patients who were referred to ultrasound clinic for evaluation of endometrial pathologies had been treated with Tamoxifen for less than 30 months. Mean duration of treatment was 13.985±18.4 months (Range: 6-56).

Table 1. Patients' Characteristics

	N (%)
Age (mean±SD)	46.5±7.818
Duration of Tamoxifen Treatment (mean±SD)	18.4 ±13.985
Pregnancy	
0	4 (10%)
1	3 (7.5%)
2	16 (40%)
>=3	17 (42.5%)
Symptoms	
Asymptomatic	25 (59.52%)
AUB	5 (11.90%)
Abnormal Discharge	7 (16.66%)
Pelvic Pain	2 (4.76%)
Mass	2 (4.76%)
Others	1 (2.38%)
Ultrasound	
Normal	14 (34.14%)
Hyperplasia	4 (9.75%)
Polyp	12 (29.26%)
Fibroid	2 (4.87%)
Adenomyosis	5 (12.19%)
Adhesion	1 (2.43%)
Others	3 (7.31%)
Pathology	
Not performed	22 (52.38%)
Polyp	9 (21.41%)
Hyperplasia	3 (7.14%)
Endometrium	1 (2.38%)
Fibroid	1 (2.38%)
Leiomyoma	1 (2.38%)
Adenomyosis	1 (2.38%)
Adenomyoma	1 (2.38%)
Inconclusive	1 (2.38%)
Technical Problem	2 (4.76%)

As shown in the table 2, in 16 patients both SIS, and histologic biopsy were done, which in 12 subjects (30% of total subjects) the results were concordant but in 4 subjects (10% of total subjects), they were incompatible. There were no indications for histologic biopsy in 24 subjects.

In table 3, sensitivity, specifity, positive predictive value (PPV) and negative predictive value (NPV) of SIS findings compared to pathology report (as the gold standard) are reported. SIS has the best accuracy for diagnosis of submucosal fibroma (97.5%) followed by hyperplasia (92.5%) and polyps (87.5%). Sensitivity of the test was the highest for submucosal fibroma (100%) and the lowest for endometrial hyperplasia (66.7%) but specifity of the test for diagnosis of three pathologies were rather similar (97.4% for submucosal fibroma and 94.6% for endometrial hyperplasia). Positive predictive value of the test for diagnosis of all three pathologies was less than 70%, but it had more than 95% negative predictive value for the diagnosis of all pathologies.

Table 2. Comparison of histopathologic and radiologic findings

	N (%)
Histopathologic finding the same as radiologic finding	12 (30%)
Histopathologic findings Different than radiologic findings	4 (10%)
No histopathologic report	24 (60%)
Total	40 (100%)

Table 3. Evaluation of the performance of saline sonohysterography per diagnosis

	Submucosal Fibroma	Endometrial Hyperplasia	Endometrial polyps p
Sensitivity	100%	66.7%	88.9%
Specificity	97.4%	94.6%	87.1%
Positive predictive value	50%	50%	66.7%
Negative Predictive Value	100%	97.2%	96.4%
Accuracy	97.5%	92.5%	87.5%

Discussion

In our study, as mentioned before, most of the patients who were referred to ultrasound clinic for evaluation of endometrial pathologies have been treated with Tamoxifen for 6-30 months (13.98±18.4). In the study by Fung, *et al.* 20 patients were treated with Tamoxifen for 48.2±27 months and in Elhelw *et al.* study patients received treatment for 12-28 months.[13,21]

Develioglu *et al.* reported that patients with an endometrial pathology had been treated with Tamoxifen for 30±16.9 months while patients without endometrial pathology had received treatment for 19.1±15.6 months.[22] These findings are verified by Franchi *et al.* and Ito *et al.* which reported that Tamoxifen consumption for 27 and 24 months (respectively) is associated with development of endometrial pathology.[23, 24] Yet, due to the limited number of subjects in our study it was not possible to find any association between duration of Tamoxifen treatment and endometrial pathologies.

Regarding number of pregnancies, almost half of our study population had a history of 3 pregnancies or more. Develioglu *et al.* study has showed that number of pregnancies in patients with intrauterine pathologies was 2.6 ±1.6 and this number for patients without pathology was 2.4 ±1.2 which the difference is not statistically significant.[22]

Our study showed most of the patients were asymptomatic. In a report by Yusefi *et al.* only 4.6% of the patients reported AUB and it appears that this finding is associated with increased endometrial thickness.[3] Jindal *et al.* evaluated the symptoms in patients using Tamoxifen and they found that 88% of the patients have no symptoms and AUB and abnormal discharge was reported in 8% and 4% of the patients respectively.[25] In Kochar *et al.* study 66% of the patients receiving Tamoxifen treatment were asymptomatic and 34% had a symptom and in another study by Gaber *et al.* on 247 patients receiving Tamoxifen, 175 had no symptoms, 52 had a suspicious finding in their endometrium and 20 patients presented with AUB.[26,27]

Endometrial polyp was the most common SIS finding in our study population. Deligdisch *et al.* reported that endometrial polyp is present in 23% of referrals, but Elhelw *et al.* reported than endometrial polyp was present in 45% of the patients, cystic irregularity in endo-myometrial junction and endometrial thinness were present in 41% and 13.6% of the patients, respectively.[21, 28] In some other studies, endometrial polyp prevalence was reported between 49-63% in patients receiving Tamoxifen treatment.[29-31] More importantly, Fong *et al.* reported SIS can thoroughly diagnose small polyps that are not detectable by transvaginal ultrasound or blind biopsy.[29]

In our study, the most common pathology finding was endometrial polyp. Of all the patients' biopsy samples, 22 patients were without any pathologic findings. The most common pathologic finding in others were endometrial polyp (9 subjects) and endometrial hyperplasia (3 subjects). In Yusefi *et al.* study endometrium was atrophic in 34.2% of the patients and there was no sufficient tissue for sampling.[3] In Fong *et al.* study endometrial pathologies were present in 40.2% of the patients receiving Tamoxifen and 38.5% had endometrial polyps.[29] Only 1.7% had submucosal fibroid. But Fung *et al.* reported significant changes were present in 32.3% of the patients which 5.3% were hyperplasia, 23.56% endometrial polyp and less than 5% endocervical polyp, atypical hyperplasia, adenocarcinoma or sarcoma.[20] Although in our study endometrial polyps were less frequent than others, but they are benign and have no significant clinical impact. For comparison in Elhelw *et al.* study, 10 endometrial polyps, 3 were hyperplasia and 1 was adenocarcinoma.[21] Also of 9 subjects with irregular endo-myo junction, 2 were hyperplasia. Overall, studies have shown than chronic consumption of Tamoxifen is associated with three times increase in risk of endometrial polyp and 5 times increase in endometrial hyperplasia, although duration and dosage of consumption should be considered.[32]

In comparison of SIS and pathologic findings, 16 patients had done both. In 12 subjects, pathologic evaluation confirmed the diagnosis of SIS and in 4 patients the diagnosis was different.

Hann *et al.* reported that from 28 endometrial polyps that were reported by SIS, 23 were confirmed by pathology and of 5 endometrial hyperplasia diagnosed by SIS, just 2 were confirmed by pathology.[30] Also in 19 patients who undergone endometrial biopsy first and no finding was reported by pathology, SIS evaluation found 10 polyps and 2 endometrial thickness. In another study by Hann group, in SIS of 50 patients, endometrial polyp was found in 32 subjects, yet, 81% of endometrial biopsies were normal, in 13% there was not enough sample and only in 6% endometrial polyp was reported.[31] In 4 patients, even with endometrial thickness of 5mm, endometrial biopsy was reported normal. Furthermore, endometrial biopsy was reported by endometrial biopsy in 4 patients but SIS was negative in 2 cases. It seems that this disagreement between pathology reports and SIS findings was due to insufficient endometrial sampling or movement of the stalk of the pedunculated polyps caused by curette.

In our study, we didn't find any cases of endometrial carcinoma or blood clots. But other studies have shown that chronic consumption of Tamoxifen is associated with increased risk of endometrial cancer.[31] Cohen *et al.* reported that in 3% of patients who were treated with Tamoxifen for a long period, there were some evidence of neoplastic changes in polyps but the incidence in control group was only 0.48%.[33] Yusefi *et al.* also estimated the prevalence of endometrial carcinoma in this patient group to be about 0.61% and reported a higher risk of cacncer development after 5 years of Tamoxifen consumption.[3] Per some epidemiologic studies, annual incidence of endometrial carcinoma in Tamoxifen users, some researchers believe that there's no need for screening in patients without clinical symptoms.[34]

As reported, in our investigation, SIS compared to gold standard (which is pathology biopsy) overall has high accuracy, sensitivity, specifciity and NPV in diagnosis of endometrial pathologies but not PPV. Several other studies, have assessed the results of SIS which we summarized them in table 4.[14, 19, 29, 35-42] Almost all their results are in concordance to our study showing more than 80% sensitivity and specificity and more than 90% NPV and accuracy for SIS. Only PPV is smaller in our study which might be due to small sample size.

In this report for evaluation of sensitivity and specificity of SIS, we used endometrial thickness of more than 5mm as cut-off point, but Develioğlu *et al.* used 9.5mm as the cut-off point and reported 89% sensitivity and 78% specificity.[22] Other studies have used 4-10mm as cut-off point and overall, whenever a smaller cut-off point has been used, false positive cases were more and subsequently sensitivity decreased.[16,43,44] The American College of Obstetricians and Gynecologists (ACOG) and the Society of Radiologists in Ultrasound (SRU) advise that either TVUS (with an endometrial thickness of ≤4 mm [ACOG] or ≤5 mm [SRU]) or endometrial sampling are recommended as a diagnostic tool in women with postmenopausal bleeding.[45,46]

Overall, our study showed that SIS evaluation has great negative predictive value for diagnosis of endometrial lesions which is important for a screening test and since this test is non-invasive and cheap, and without risk of radiation to the patient, we can recommend it as a screening test for patients receiving Tamoxifen for a long period.

Yet, since this test does not have great positive predictive value, it's better not to use it as a diagnostic test in this group of patients as many of the patients will be referred for endometrial biopsy eventually.

Although small sample size is a limitation of our study but overall, we conclude that SIS is an easy, non-invasive and inexpensive test and has great accuracy. Since chronic Tamoxifen consumption is associated with increased risk of endometrial carcinomas, these patients should be screened for endometrial pathologies. This study showed that SIS is a viable option for screening of these patients instead of endometrial biopsy because it has great negative predictive value, as 55% of the subjects in our study were ruled out of endometrial pathologies. But it doesn't have great positive predictive value for making the diagnosis, therefore it should be used by caution.

Table 2. Characteristics that have been shown to effect outcome of ECT treatment

		N	Sensitivity	Specificity	PPV	NPV	Accuracy
Our Study	Overall	40					
	Endometrial polyps		88.9%	87.1%	66.7%	96.4%	87.5%
	Endometrial Hyperplasia		66.7%	94.6%	50%	97.2%	92.5%
	Submucosal Fibroma		100%	97.4%	50%	100%	97.5%
Bingol *et al.*[35]	Overall	346	98%	83%	96%	91%	
	Endometrial polyps		100%	93%	90%	100%	
	Endometrial Hyperplasia		87%	100%	100%	95%	
Ogutcuoglu *et al.*[19]	Endometrial lesions	100	60%	96%	87.8%	83.8%	87%
Radwan *et al.*[14]	Endometrial polyps	241	97.3%	95.8%	91.1%	98.7%	96.27%
Luterek *et al.*[36]	Overall	40					
	Endometrial polyps		100%	100%	100%	100%	
	Submucosal Fibroma		75%	75%	75%	75%	
Kowalczyk *et al.*[37]	Overall	97	>72%	96%			
Erdem *et al.*[38]	Overall	133	97.7%	%82.4	93.5%	93.3%	93.4%
	Endometrial polyps		100%	91.8%	92.4%	100%	95.5%
	Submucosal Fibroma		95.7%	100%	100%	99%	100%
Jafari *et al.*[40]	Overall	99	%91.67	%86	%85.9	%85.7	
Ludwin *et al.*[39]	Overall	35	97%	90%			
	Endometrial polyps		100%	83%			
	Endometrial Hyperplasia		84%	95%			
Fong *et al.*[29]	Overall	104	89.7%	79.2%	76.1%	91.3%	
Kamel *et al.*[41]	Overall	106	64.5%	75.5%			
Kimiai *et al.*[42]	Endometrial Hyperplasia	100	83%	93%	83%	97%	
	Endometrial polyps		83%	95%	58%	98%	

References

1. Gao WL, Zhang LP, Feng LM. Comparative study of transvaginal ultrasonographic and diagnostic hysteroscopic findings in postmenopausal breast cancer patients treated with tamoxifen. Chin Med J (Engl) 2011; 124(15): 2335-9.
2. Chen JY, Kuo SJ, Liaw YP, Avital I, Stojadinovic A, Man YG, *et al.* Endometrial cancer incidence in breast cancer patients correlating with age and duration of tamoxifen use: a population based study. J Cancer 2014; 5(2): 151-5.
3. Yousefi Z, Homayie F, Rafei S. The evaluation of the endometrial thickness of amenorrhea breast cancer patients treated with tamoxifen. AMUJ. Arak Medical University Journal 2011; 14(5): 101–7.
4. Salazar EL, Paredes A, Calzada L. Endometrial thickness of postmenopausal breast cancer patients treated with tamoxifen. Gynecol Endocrinol 2005; 21(6): 312-6.
5. Fong K, Causer P, Atri M, Lytwyn A, Kung R. Transvaginal US and hysterosonography in postmenopausal women with breast cancer receiving tamoxifen: correlation with hysteroscopy and pathologic study. Radiographics 2003; 23(1): 137-50; discussion 51-5.
6. Lindahl B, Andolf E, Ingvar C, Ranstam J, Willen R. Adjuvant tamoxifen in breast cancer patients affects the endometrium by time, an effect remaining years after end of treatment and results in an increased frequency of endometrial carcinoma. Anticancer Res 2008; 28(2B): 1259-62.
7. Sinawat S, Chiyabutra T. Increased risk of endometrial abnormalities in breast cancer patients taking tamoxifen: the need for gynaecologic surveillance. Asian Pac J Cancer Prev 2004; 5(2): 183-7.
8. Decensi A, Gandini S, Serrano D, Cazzaniga M, Pizzamiglio M, Maffini F, *et al.* Randomized dose-ranging trial of tamoxifen at low doses in hormone replacement therapy users. J Clin Oncol 2007; 25(27): 4201-9.
9. Tepper R, Beyth Y, Altaras MM, Zalel Y, Shapira J, Cordoba M, *et al.* Value of sonohysterography in asymptomatic postmenopausal tamoxifen-treated patients. Gynecol Oncol 1997; 64(3): 386-91.
10. Markovitch O, Tepper R, Aviram R, Fishman A, Shapira J, Cohen I. The value of sonohysterography in the prediction of endometrial pathologies in asymptomatic postmenopausal breast cancer tamoxifen-treated patients. Gynecol Oncol 2004; 94(3): 754-9.
11. Aslam M, Ijaz L, Tariq S, Shafqat K, Meher Un N, Ashraf R, *et al.* Comparison of transvaginal sonography and saline contrast sonohysterography in women with abnormal uterine bleeding: correlation with hysteroscopy and histopathology. Int J Health Sci (Qassim) 2007; 1(1): 17-24.
12. Cepni I, Ocal P, Erkan S, Saricali FS, Akbas H, Demirkiran F, *et al.* Comparison of transvaginal sonography, saline infusion sonography and hysteroscopy in the evaluation of uterine cavity pathologies. Aust N Z J Obstet Gynaecol 2005; 45(1): 30-5.
13. Seshadri S, El-Toukhy T, Douiri A, Jayaprakasan K, Khalaf Y. Diagnostic accuracy of saline infusion sonography in the evaluation of uterine cavity abnormalities prior to assisted reproductive techniques: a systematic review and meta-analyses. Hum Reprod Update 2015; 21(2): 262-74.
14. Radwan P, Radwan M, Kozarzewski M, Polac I, Wilczynski J. Evaluation of sonohysterography in detecting endometrial polyps - 241 cases followed with office hysteroscopies combined with histopathological examination. Wideochir Inne Tech Maloinwazyjne 2014; 9(3): 344-50.
15. Hajishafiha M, Zobeiri T, Boroumandan F, Oroji R, Rajabpoor M. A comparative study of sonohysterography with diagnostic curettage in patients with abnormal uterine bleeding. The Journal Of Urmia University Of Medical Scinces 2006; 17(3): 181-7.
16. Mathew M, Gowri V, Rizvi SG. Saline infusion sonohysterography - an effective tool for evaluation of the endometrial cavity in women with abnormal uterine bleeding. Acta Obstet Gynecol Scand 2010; 89(1): 140-2.
17. Mehrabi E, Hajian S, Simbar M, Hoshyari M, Zayeri F. The Lived Experience of Iranian Women Confronting Breast Cancer Diagnosis. J Caring Sci 2016; 5(1): 43-55.
18. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst 1994; 86(7): 527-37.
19. Ogutcuoglu B, Karadag C, Inan C, Dolgun ZN, Yoldemir AT, Aslanova L. Diagnostic utility of saline infusion doppler sonohysterography in endometrial mass lesions. Pak J Med Sci 2016; 32(2): 284-8.
20. Fung MF, Reid A, Faught W, Le T, Chenier C, Verma S, *et al.* Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. Gynecol Oncol 2003; 91(1): 154-9.
21. Elhelw B, Ghorab MN, Farrag SH. Saline sonohysterography for monitoring asymptomatic postmenopausal breast cancer patients taking tamoxifen. Int J Gynaecol Obstet 1999; 67(2): 81-6.
22. Develioglu OH, Omak M, Bilgin T, Esmer A, Tufekci M. The endometrium in asymptomatic breast cancer patients on tamoxifen: value of

transvaginal ultrasonography with saline infusion and Doppler flow. Gynecol Oncol 2004; 93(2): 328-35.
23. Franchi M, Ghezzi F, Donadello N, Zanaboni F, Beretta P, Bolis P. Endometrial thickness in tamoxifen-treated patients: an independent predictor of endometrial disease. Obstet Gynecol 1999; 93(6): 1004-8.
24. Ito T, Katagiri C, Murata Y, Hamazoe R, Morita K. Indication for histological examination of endometrium in breast carcinoma patients receiving tamoxifen therapy. J Obstet Gynaecol Res 2001; 27(3): 141-5.
25. Jindal A, Mohi MK, Kaur M, Kaur B, Singla R, Singh S. Endometrial evaluation by ultrasonography, hysteroscopy and histopathology in cases of breast carcinoma on Tamoxifen therapy. J Midlife Health 2015; 6(2): 59-65.
26. Kochar S, Arora P, Chattopadhyay AB. Tamoxifen Therapy for Breast Cancer and Endometrial Pathology. Med J Armed Forces India 2005; 61(4): 313-5.
27. Gerber B, Krause A, Muller H, Reimer T, Kulz T, Makovitzky J, *et al.* Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. J Clin Oncol 2000; 18(20): 3464-70.
28. DeligdischL, Kalir T, Cohen CJ, de Latour M, Le Bouedec G, Penault-Llorca F. Endometrial histopathology in 700 patients treated with tamoxifen for breast cancer. Gynecol Oncol 2000; 78(2): 181-6.
29. Fong K, Kung R, Lytwyn A, Trudeau M, Chapman W, Nugent P, *et al.* Endometrial evaluation with transvaginal US and hysterosonography in asymptomatic postmenopausal women with breast cancer receiving tamoxifen. Radiology 2001; 220(3): 765-73.
30. Hann LE, Gretz EM, Bach AM, Francis SM. Sonohysterography for evaluation of the endometrium in women treated with tamoxifen. AJR Am J Roentgenol 2001; 177(2): 337-42.
31. Hann LE, Kim CM, Gonen M, Barakat R, Choi PH, Bach AM. Sonohysterography compared with endometrial biopsy for evaluation of the endometrium in tamoxifen-treated women. J Ultrasound Med 2003; 22(11): 1173-9.
32. van Leeuwen FE, Benraadt J, Coebergh JW, Kiemeney LA, Gimbrere CH, Otter R, *et al.* Risk of endometrial cancer after tamoxifen treatment of breast cancer. Lancet 1994; 343(8895): 448-52.
33. Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. Gynecol Oncol 2004; 94(2): 256-66.
34. Love CD, Muir BB, Scrimgeour JB, Leonard RC, Dillon P, Dixon JM. Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. J Clin Oncol 1999; 17(7): 2050-4.
35. Bingol B, Gunenc Z, Gedikbasi A, Guner H, Tasdemir S, Tiras B. Comparison of diagnostic accuracy of saline infusion sonohysterography, transvaginal sonography and hysteroscopy. J Obstet Gynaecol 2011; 31(1): 54-8.
36. Luterek K, Szymusik I, Bartkowiak R, Wielgos M. Sonohysterography in peri- and postmenopausal women with abnormal uterine bleeding or abnormal endometrial appearance. Neuro Endocrinol Lett 2014; 35(4): 297-300.
37. Kowalczyk D, Guzikowski W, Wiecek J, Sioma-Markowska U. Clinical value of real time 3D sonohysterography and 2D sonohysterography in comparison to hysteroscopy with subsequent histopathological examination in perimenopausal women with abnormal uterine bleeding. Neuro Endocrinol Lett 2012; 33(2): 212-6.
38. Erdem M, Bilgin U, Bozkurt N, Erdem A. Comparison of transvaginal ultrasonography and saline infusion sonohysterography in evaluating the endometrial cavity in pre- and postmenopausal women with abnormal uterine bleeding. Menopause 2007; 14(5): 846-52.
39. Ludwin A, Pitynski K, Szczudrawa A, Biernat I, Loster J. [Value of saline infusion sonohysterography and hysteroscopy in postmenopausal patient with persistent abnormal ultrasonographic images after endometrial curettage with normal histological results]. Ginekol Pol 2003; 74(9): 786-92.
40. Mohammad jafari R, Barati M, Najafian M, Saadati N, Shojaei K. Comparison of sensitivity & specificity of transvaginal sonography, saline infusion sonohysterography and hysteroscopy in evaluation of women with abnormal uterine bleeding. Journal Of Shahid Sadoughi University Of Medical Sciences And Health Services 2009; 17(4): 249-54.
41. Kamel HS, Darwish AM, Mohamed SA. Comparison of transvaginal ultrasonography and vaginal sonohysterography in the detection of endometrial polyps. Acta Obstet Gynecol Scand 2000; 79(1): 60-4.
42. Kimiaei P, Kalantari M. Efficacy of vaginal sonohystrography in the diagnosis of uterine abnormalities. Pejouhandeh Quarterly Research Journal 2000; 17(5): 77-83.
43. Gull B, Karlsson B, Milsom I, Granberg S. Can ultrasound replace dilation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer. Am J Obstet Gynecol 2003; 188(2): 401-8.
44. Litta P, Merlin F, Saccardi C, Pozzan C, Sacco G, Fracas M, *et al.* Role of hysteroscopy with endometrial biopsy to rule out endometrial

cancer in postmenopausal women with abnormal uterine bleeding. Maturitas 2005; 50(2): 117-23.
45. Langer JE, Oliver ER, Lev-Toaff AS, Coleman BG. Imaging of the female pelvis through the life cycle. Radiographics 2012; 32(6): 1575-97.
46. Alcazar JL, Errasti T, Zornoza A. Saline infusion sonohysterography in endometrial cancer: assessment of malignant cells dissemination risk. Acta Obstet Gynecol Scand 2000; 79(4): 321-2.

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.201634126-129

Axillary Nodal Examination in Breast Cancer: How Much Is Enough? Evidence for a New Minimum

S.G.D Gangadaran*[a]

[a] *Department of Medical Oncology, Government Royapettah Hospital, Chennai, India*

ARTICLE INFO

Received:
15 September 2016
Revised:
14 October 2016
Accepted:
8 November 2016

Keywords:
Axillary nodal yield, minimum nodes, breast cancer

ABSTRACT

Background: Axillary nodal spread is an established prognostic factor in breast cancer. Axillary nodal dissection and subsequent pathological examination is considered the gold standard technique of assessing the axilla for metastatic disease. A minimum of ten level I axillary nodes are required to be examined before an axillary specimen can be reliably labeled as disease free. This recommendation is based on a mathematical prediction model and such methodology has certain inherent limitations. In this study, we sought to revisit this concept of minimum nodes required to deem an axilla as true negative by using a linear correlation model.

Methods: Medical records of 165 consecutive breast cancer patients attending a medical oncology department for adjuvant therapy were assessed for inclusion. One hundred and forty-five breast cancer patients in clinical stages I-III met the inclusion criteria. Patients referred after neoadjuvant chemotherapy, breast conservation surgery, palliative mastectomy, and mastectomy for metastatic disease were excluded from the study. The study samples were segregated into groups of 1-5, 6-10, 11-15, 16-20, 21-25, and more than 25 nodes. A linear regression model was used to assess the association between the nodal positivity and nodal groups. The spearman rho with P value was calculated for the model. Factors influencing the nodal yield of an axillary specimen were selected from the published literature and the same variables were evaluated in the study cohort.

Results: A total of 1882 nodes were harvested from 145 axillary specimens and 320 nodes were positive for metastatic disease. The mean nodal harvest per axillary specimen was 11 nodes. The linear correlation model evaluating the association between nodal positivity and total nodal yield showed a spearman correlation coefficient of Rho = - 0.82 with P=0.04. To avoid bias due to the uneven sample size, the nodal ratio was calculated for each group and the linear association model reapplied to test the association with the total nodal harvest. A spearman rho of R = -0.94 with P=0.004 was obtained. The nodal groups tested for significance showed P= 0.0001 for the group 1-15 nodes. Evaluation of the factors likely to influence nodal yield showed that age (P=0.15) and obesity (P=0.67) had no effect on the nodal harvest. Tumor stage (P<0.001) and operating surgeon (P=0.0001) had a significant effect on the total nodal harvest.

Conclusions: The recommendation of a minimum of ten axillary nodes to be examined to determine true negativity of an axillary specimen needs reassessment. A new minimum of fifteen nodes is suggested before an axillary specimen is reliably deemed free of metastatic disease.

Address for correspondence:
S.G.D Gangadaran, MD., DM.
Address: Department of Medical Oncology, Govt Royapettah Hospital, Chennai, India
Email: sgd_gangadaran@rediffmail.com

Introduction

Axillary nodal involvement is an established prognostic determinant in breast cancer. A direct association between axillary nodal involvement and survival was well documented by Fischer *et al.* who demonstrated a five-year survival of 82.3%, 73%, 45%, and 28% for node negative, 1-3, 4-12, and more

than 13 involved axillary nodes, respectively.[1] Axillary nodal dissection and subsequent pathological examination has been the gold standard technique of assessing the axilla for metastatic disease.[2] Traditionally, axillary dissection is performed with staging, therapeutic, and prognostic goals in the management of breast cancers. The oncological reliability of sentinel node biopsy coupled with the necessity to reduce the high arm morbidity associated with a standard axillary dissection prompted a paradigm shift in axillary management of early breast cancers. In contemporary practice, the staging role of an axillary dissection has been eclipsed by the sentinel node biopsy technique and completion axillary dissection and primary axillary dissection reserved for pathologically proven nodes in the axilla.[3] Despite these changes in management principles, many patients with node negative early breast cancer are still subjected to a staging axillary dissection as the sentinel node biopsy technique is available only in selected oncology centers in India.

Axillary nodal dissection results in the assignment of a pathological nodal category based on the number of involved nodes. The nodal positivity has been shown to vary with the number of nodes examined and it has been recommended that a minimum number of ten level I axillary nodes should be examined before an axillary specimen can be reliably deemed as free of metastatic disease.[4] It is important to note this recommendation is based on a mathe-matical model that predicts the probability of a false negative axilla in a T1 tumor when all 11 examined nodes are negative is 6.14% with 90% certainty. This prediction model was developed from a data set of 1446 patients from the national cancer institute in Milan.[4] To adopt this approach universally may be fundamentally flawed as the nodal yield and positivity have been shown to vary with multiple disease, patient, or surgeon related factors. Somner *et al.* suggested a minimum of 16 nodes to be examined to ensure a negative axilla.[5] In this study, we sought to revisit this concept of minimum nodes required to deem an axilla as reliably negative for regional disease spread.

Methods

Medical records of 165 consecutive breast cancer patients attending a medical oncology department for adjuvant therapy were assessed for inclusion. The patients with a core biopsy proven diagnosis of breast cancer in clinical stages I-III who were surgically treated with a modified radical mastectomy were included in the study. The patients who were referred after breast conservation surgery, palliative mastectomy, and mastectomy for metastatic disease were excluded from the study. Axillary dissection included dissection of level I, II, and III nodes. Neo adjuvant chemotherapy is known to influence both the nodal positivity and the yield; hence, preoperative chemotherapy was a strict exclusion criterion.

The study included 145 evaluable patients. Basic demographic and disease-related data were collected. The post-operative pathology report was the main source of study information. All operative specimens were dissected by the surgeon for axillary nodes before transportation to the pathology lab in 10% formalin solution. The specimens were re dissected after fat clearance by a pathologist to further enhance the nodal yield and the final number harvested for that specimen by the summation of the surgeon's and the pathologist's nodal harvest. All nodes in a specimen were microscopically examined, initially by a single transverse section through the long axis. No further examination was done for positive nodes (> 0.2mm deposit); however, further sectioning of negative nodes was done to ensure true negativity. Immunohistochemistry based techniques were not used in this study to confirm negative nodes. The total nodal yield, nodal positivity, and nodal ratio were determined for each study specimen. For the purpose of this study, nodal ratio was defined as the ratio of positive nodes to the total nodal harvest.

The study samples were segregated into groups of 1-5, 6-10, 11-15, 16-20, 21-25, and more than 25 nodes. A linear regression model was used to assess the association between the nodal positivity and nodal groups. The spearman rho with P value was calculated for the model. Factors affecting the nodal yield of an axillary specimen were selected from published literature and the variables (age, obesity, tumor stage, and operating surgeon) were evaluated in the study cohort.[6-8] Age and tumor stage were analyzed with a linear regression test. The operating surgeon was previously reported as a variable affecting the nodal yield. The study participants were segregated into two groups based on the surgery performed by surgical oncologists or by general surgeons. The impact of the surgeon on the total nodal yield of an axillary specimen was analyzed as a categorical variable using the chi-square test. A P value less than 0.05 was considered significant.

Results

The baseline characteristics of the study patients are given in Table 1. A total of 1882 nodes were harvested from 145 axillary specimens and 320 nodes were positive for metastatic disease. The mean nodal harvest per axillary specimen was 11 nodes. The correlation model evaluating the association between nodal positivity and total nodal yield showed a spearman correlation coefficient of Rho = -0.82 with P=0.04 indicating a strong reverse association between the two variables (Figure 1). As the sample size in individual nodal groups was unbalanced, the nodal ratio was calculated for each

group and the linear association model reapplied to test for an association with the total nodal harvest (Figure 2). A spearman rho of R = -0.94 with P=0.004 was noted, indicating a strong reverse association between the nodal positivity yield and the increase in nodal examination. The nodal positivity increased from the group 1-5 nodes with the highest nodal positivity achieved in the nodal group 6-10 nodes; there was a steady decline in the yield of positive nodes despite the increase in nodal examination thereafter. The nodal groups tested for significance showed P= 0.0001 for the group 1 -15 nodes. The factors likely to influence the nodal yield were evaluated; age (P=0.15) and obesity (P=0.67) had no association with the nodal harvest. Tumor stage (P<0.001) and operating surgeon (P=0.0001) had a significant effect on the total nodal harvest. The mean nodal harvest for surgical oncologists was 14 nodes compared to 8 nodes for non-oncology trained surgeons.

Table 1. Baseline characteristics of the study cohort

	N=145
Age (mean)	52.5 years
Menopausal status	
Pre	53 (36%)
Post	92 (64%)
Histology	
Infiltrative ductal –NOS	140 (96.55%)
Lobular	3 (2.06%)
Medullary	1 (0.68%)
Metaplastic	1 (0.68%)
Tumor stage	
T1	27 (18.6%)
T2	85 (58.6%)
T3	31 (21.3%)
T4	1 (0.68%)
Stage	
I	15 (10.5%)
II	78 (53.7%)
III	52 (35.8%)
Pathological nodal stage	
N1	70 (48.3%)
N2	53 (36.5%)
N3	22 (15.2%)
Operating surgeon	
Oncologist	96 (66.2%)
Non-oncologist	49 (33.8%)

Discussion

Axillary dissection has staging and prognostic applications in node negative early breast cancer. The sentinel node biopsy technique has replaced the axillary dissection as a staging procedure in clinically node negative early breast cancer; however, it is still required as a staging procedure when the sentinel node technique is unavailable or otherwise contraindicated. The axillary nodal harvest has been suggested as a surgical quality

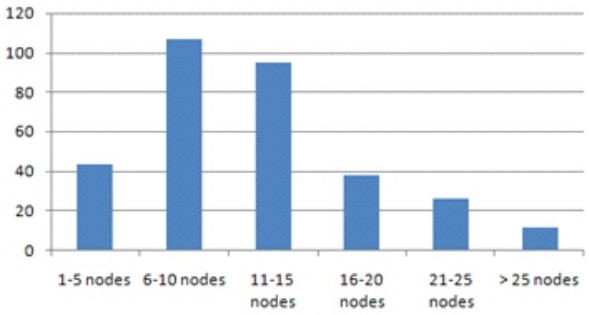


Figure 1. Relationship of nodal positivity with nodal groups

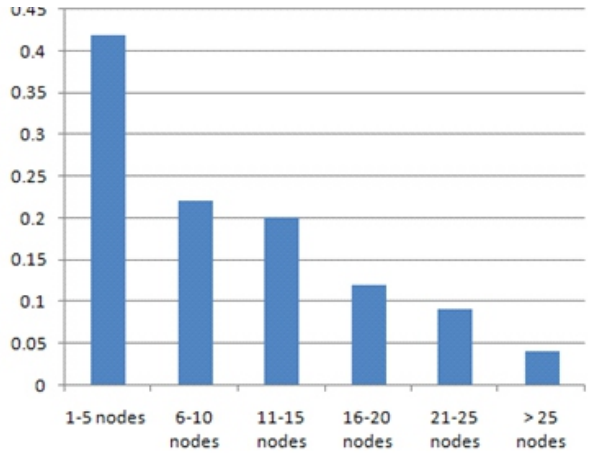


Figure 2. Relationship of nodal ratio with nodal groups

indicator. Pathological axillary staging requires a minimum of ten level I axillary nodes to be examined before a true negative axilla can be assumed. This criterion was determined based on a mathematical prediction model with data derived from patients treated between 1983 and 1986.[4] Our study suggests the minimum nodes required to be examined are 15.

Applying a linear correlation model, our study clearly showed that the nodal positivity declined with the increase in nodal examination (Rho= -0.82, P=0.04). The relationship was identical between the nodal ratio and the number of nodes examined (Rho=-0.94, P=0.004). A significant result (P=0.001) was obtained for nodal groups 1-15, indicating the nodal positivity rate does not increase significantly after examining 15 nodes. Somner *et al.* used an identical study methodology to evaluate 609 patients and suggested a minimum of 16 nodes to be examined to be confident of a disease negative axilla.[5] Blancas *et al.* conducted a study to determine whether the number of nodes removed at axillary dissection was associated with recurrence and concluded a minimum of 6 nodes was to be examined to be confident of a node negative status.[9] This study had 49% of the samples in T1 (< 20mm) category while the same (tumor size < 20mm) constituted only 18.6% of the samples in our study; as nodal positivity was significantly affected by the tumor size (P< 0.001), the noted differences could be explainable by more

samples with larger tumor sizes in our study. The Danish breast cancer cooperative group, based on the data of 31679 patients, reported that dissection of 20 nodes rather than 10-14 nodes increased the probability of nodal positivity by 7% for T1a, 9% for T1c, and 10% for T3 tumors.[10]

Several variables have been reported to influence the nodal yield of axillary dissection. Age and body mass index did not significantly affect the nodal yield in this study, which is in accordance with the results of a study reported by Lee *et al.*[11] Surgical training related factors (oncology vs. non-oncology) have been shown to alter nodal retrieval. This factor was a significant variable in our study (p=0.0001). In the present study, 34% of the axillary dissections were performed by non-oncologists and the mean nodal harvest for this group was 8 nodes. It is probable that this factor resulted in a lower mean nodal harvest observed in this study; but it is unlikely to have influenced the analysis of the primary study objective as a linear correlation model, and not to a probability based model, was used for assessing the minimum nodes required to deem an axilla negative for metastatic disease.

This study has a few limitations. The sample size was small and the dependent nature of the observations (lymph nodes) may be considered as a design limitation for the linear regression model. The minimum number of histological sections required to confirm a disease free nodal status was left to the pathologist's discretion and keratin immune histochemistry was not used in this study to confirm a true negative result. The nodal yield has been shown to vary with the pathologist examining the specimen; however, such data were unavailable due to the retrospective nature of this study. Survival and recurrence data (follow-up) were not incorporated into the study design to assess whether the new proposed minimum of 15 nodes translates to a clinical benefit.

This study demonstrates that the prevailing standard of a minimum of ten axillary nodes to be examined to assign pN0 category needs revision. A new minimum of fifteen nodes is suggested before an axillary specimen is reliably deemed free of metastatic disease. The implications on the cost, resources, and disease recurrence of this new recommendation remain unknown.

References

1. Fisher B, Bauer M, Wickerham DL, Redmond CK, Fisher ER, Cruz AB, *et al.* Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. An NSABP update. Cancer 1983; 52(9): 1551-7.
2. Wang Y, Dong H, Wu H, Zhang L, Yuan K, Chen H, *et al.* Improved false negative rate of axillary status using sentinel lymph node biopsy and ultrasound-suspicious lymph node sampling in patients with early breast cancer. BMC Cancer 2015; 15: 382.
3. Gnant M, Thomssen C, Harbeck N. St. Gallen/Vienna 2015: A Brief Summary of the Consensus Discussion. Breast Care (Basel) 2015; 10(2): 124-30.
4. Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with breast carcinoma. Cancer 1992; 69(10): 2496-501.
5. Somner JE, Dixon JM, Thomas JS. Node retrieval in axillary lymph node dissections: recommendations for minimum numbers to be confident about node negative status. J Clin Pathol 2004; 57(8): 845-8.
6. Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, *et al.* Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 2003; 21(7): 1205-13.
7. Cil T, Hauspy J, Kahn H, Gardner S, Melnick W, Flynn C, *et al.* Factors affecting axillary lymph node retrieval and assessment in breast cancer patients. Ann Surg Oncol 2008; 15(12): 3361-8.
8. Boughey JC, Donohue JH, Jakub JW, Lohse CM, Degnim AC. Number of lymph nodes identified at axillary dissection: effect of neoadjuvant chemotherapy and other factors. Cancer 2010; 116(14): 3322-9.
9. Blancas I, Garcia-Puche JL, Bermejo B, Hanrahan EO, Monteagudo C, Martinez-Agullo A, *et al.* Low number of examined lymph nodes in node-negative breast cancer patients is an adverse prognostic factor. Ann Oncol 2006; 17(11): 1644-9.
10. Axelsson CK, Mouridsen HT, During M, Moller S. Axillary staging during surgery for breast cancer. Br J Surg 2007; 94(3): 304-9.
11. Lee MC, Plews R, Rawal B, Kiluk JV, Loftus L, Laronga C. Factors affecting lymph node yield in patients undergoing axillary node dissection for primary breast cancer: a single-institution review. Ann Surg Oncol 2012; 19(6): 1818-24.

Original Article Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.201634130-134

Comparison of the Accuracy of Frozen Section in Morning and Afternoon Working Hours for Axillary Lymph Node Biopsy

Fezzeh Elyasinia[a], Mohammad Reza Keramati*[a], Farham Ahmadi[a], Mohammad Ashouri[a], Vahid Moghadas[a], Fahimeh Elyasinia[a], Maryam Yaghoubi[a], Armita Aboutorabi[b], Ahmad Kaviani[a, b]

[a] *Department of Surgery, Tehran University of Medical Sciences, Tehran, Iran*
[b] *Kaviani Breast Diseases Institute (KBDI), Tehran, Iran*

ARTICLE INFO

Received:
20 October 2016
Revised:
4 November 2016
Accepted:
16 November 2016

Keywords:
Breast cancer,
frozen section,
working hour,
lymph node dissection

ABSTRACT

Background: The role of diagnostic pathology has become more prominent. This study aimed to compare the accuracy of frozen section compared with permanent section in the morning and afternoon working hours.

Methods: In this cross-sectional study, 99 patients with stage 1 and 2 breast cancer who underwent sentinel and non-sentinel lymph node biopsy between 2013 and 2015 were included.

The results of frozen section and permanent pathology of the lymph nodes were compared with one another. The time of pathologic evaluation including morning (before 2pm) and afternoon (after 2 pm) was also considered in the comparative analysis.

Results: The mean age of the patients was 48.58±8.96 years. The accuracy of frozen section biopsy of the sentinel lymph node was 79.80%, 81.0%, and 78.0% in general, before 2 pm, and after 2 pm, respectively. The accuracy of frozen section biopsy of the non-sentinel lymph node was 62.32%, 65.1%, and 57.7% in general, before 2 pm, and after 2 pm, respectively.

Conclusions: There was no difference in the accuracy of the frozen section biopsy before and after 2 pm for the sentinel or non-sentinel lymph node biopsy.

Introduction

Breast cancer is the most common cancer among women and the second leading cause of cancer death among women. Due to screening programs, it is very important to find patients in the early stages of this cancer for breast conservation surgery. Therefore, the results of the intraoperative frozen section have a crucial role in determining the surgical approach.[1-3]

Intraoperative pathologic frozen section evaluation of the tissue samples was introduced in 1891 by William M. Welsh.[4] This technique can be used by surgeons to gain good information in a short time for decision making and choosing proper approaches.[5-12] However, important diagnostic errors might occur based on wrong pathologic results.[13-19] The frozen section method is widely used in breast surgery for detection of underlying malignancy within margins of the surgical resection during a surgical procedure. Several studies have been done to determine the efficiency and accuracy of frozen section results in breast surgery. In these articles, many factors affecting the accuracy of this method have been also assessed.[6,20,21]

Working time arrangement has been mentioned as a key issue because it links the human capacity with production means. Due to the development of new technologies requiring continuous human assistance and control 24 hours a day, this issue has

Address for correspondence:
Mohammad Reza Keramati, MD
Address: Department of Surgery, Imam Khomeini Complex Hospital, Keshavarz Blvd., Tehran, Iran
Tel: +98 9121147406
Fax: +98 21 66581657
Email: dr_morezak@yahoo.com

become increasingly important. Therefore, the daytime work difference might affect human processes such as pathologic evaluation of surgical samples.

This study aimed to evaluate and compare the accuracy of frozen section in relation to the results of the permanent section in the morning (before 2 pm) and afternoon (after 2 pm) working hours.

Methods

In this cross-sectional analytic study, patients suffering from early breast cancer with a breast mass smaller than 5 cm (T1 or T2) and no palpable mass on examination or diagnostic imaging in the visible region of the axilla were included. This study was conducted at a tertiary and referral university hospital between 2013 and 2015. Sampling was done using the convenience sampling method.

The exclusion criteria were multifocal breast cancer, inflammatory breast cancer, history of previous mastectomy or oncologic breast surgery, pregnancy, or ductal carcinoma in situ (DCIS).

Demographic data and information related to clinical findings and diagnostic imaging were collected. The results of the frozen section taken from the margin of the tumor in cases who underwent Sentinel Lymph Node Biopsy (SLNB) in addition to the results of the frozen section study of the lymph nodes were also recorded. Data were analyzed using SPSS version 20.0. Quantitative data are demonstrated as mean and standard deviation, and qualitative data are shown as frequency and percentage. A p-value of less than 0.05 was considered statistically significant.

Results

In this study, 99 patients were studied. The mean age of the participants was 48.58± 8.96 years (range: 28 – 76 years). The mean body mass index (BMI) of the patients was 26.98±3.59 kg/m^2. Seventy-one patients (71.7%) had a BMI above 25.0 kg/m^2. The mean tumor size was 2.35 ± 0.93 mm. Moreover, 56.7% of the masses were detected in the right breast, and 43.3% were in the left breast. A total of 58 tissue samples were taken (58.6%) within the morning working hours (before 2 pm) and 41 samples (41.4%) were taken during the afternoon working hours (after 2 pm). All samples were sent for both frozen section and permanent pathologic evaluation afterwards.

Of the 99 pathologically evaluated sentinel node samples evaluated by frozen section, 46 patients (46.5%) had malignant tissues and 53 (53.5%) had no proof of malignancy. Of the 99 permanent pathologic samples of the sentinel node, 66 cases (66.7%) had evidence of malignancy while 33 cases (33.3%) had no signs of malignancy. Of the 69 non-sentinel lymph node samples evaluated by frozen section, 16 cases (23.2%) had evidence of malignancy and 53 (76.8%) had no signs of malignancy. Of 69 non-sentinel lymph node samples as a permanent section, 40 patients (58.0%) had malignant tissues while 29 cases (42.0%) had no signs of malignancy.

The sensitivity and specificity of frozen section in the diagnosis of sentinel lymph node involvement was 69.70% (CI = 57.15% to 80.41%) and 100% (CI = 89.42% to 100.00%), respectively. The positive and negative predictive value of the frozen section in the diagnosis of sentinel lymph node involvement was 100% (CI = 92.29% to 100.00%) and 62.26% (CI = 47.89% to 75.21%), respectively. In general, the accuracy of frozen section in the diagnosis of sentinel lymph node samples was 79.80%. The sensitivity and specificity of frozen section in the diagnosis of non-sentinel lymph node samples was 37.50% (CI = 22.73% to 54.20%) and 96.55% (CI = 82.24% to 99.91%), respectively. The positive and negative predictive value of frozen section in the diagnosis of non-sentinel lymph node samples was 93.75% (CI = 69.77% to 99.84%) and 52.83% (CI = 38.64% to 66.70 %), respectively. The accuracy of frozen section in the diagnosis of non-sentinel lymph node samples was 62.32%.

Of the samples taken from sentinel lymph nodes, 58 samples (58.6%) were taken before 2 pm and 41 samples (41.4%) after 2 pm. The frozen section results of 47 samples taken before 2 pm and 32 samples taken after 2 pm were concordant with the results of permanent section. Therefore, the accuracy of frozen section for sentinel lymph node samples before and after 2 pm was 81.0% and 78.0%, respectively. There was no significant relationship between the results of frozen and permanent section and the time of pathologic evaluation before and after 2 pm (P value = 0.716). Of the samples taken from non-sentinel lymph nodes, 43 samples (62.3%) were taken before 2 pm and 26 samples (37.7%) were taken after 2 pm. Of these samples, the results of 28 and 15 frozen section samples taken before and after 2pm matched the results of permanent section. So, the accuracy of frozen section for non-sentinel lymph node samples before and after 2 pm was 57.7% and 65.1%, respectively. No significant relationship was detected between the results of frozen and permanent section at the time of pathologic evaluation (P value = 0.537).

Comparison of the results of permanent and frozen section is demonstrated in Table 1.

Table 1. Results of frozen section and permanent section evaluation of samples

		Permanent section	
		Sentinel nodes	
		with malignancy	without malignancy
Frozen section	with malignancy	46 (46.5%)	0
	without malignancy	20 (22.2%)	33 (33.3%)
		Non-sentinel nodes	
		with malignancy	without malignancy
	with malignancy	15 (21.7%)	1 (1.4%)
	without malignancy	25 (36.2%)	28 (40.6%)

The results of frozen section and permanent section according to the time of sentinel and non-sentinel lymph node biopsy are depicted in Table 2.

Table 2. Results of frozen and permanent section evaluation in each working shift for sentinel and non-sentinel lymph node biopsy

	Time of sentinel lymph node biopsy	
Frozen section versus permanent section	Before 2 pm	after 2 pm
Match	47 (47.5%)	32 (32.3%)
Miss match	11 (11.1%)	9 (9.1%)
	Time of non-sentinel lymph node biopsy	
Frozen section versus permanent section	Before 2 pm	after 2 pm
Match	28 (40.6%)	15 (21.7%)
Miss match	15 (21.7%)	11 (15.9%)

Discussion

According to clinical experience, there is a relationship between working time, work shift duration, and fatigue with the final outcome of procedures. Hospital staff may make medical errors due to fatigue.[22-29] In most studies, fatigue can increase the error rate over the working time.[30-32]

Studies have shown the important role of frozen section in determining the surgical approach. The intraoperative frozen section can also be of help in axillary dissection.[1-3,20] Therefore, effective communication between the pathologist and surgeon is important, as well. In this study, the accuracy of the frozen and permanent pathologic evaluation of sentinel and non-sentinel lymph node biopsy specimens was investigated.

According to our analysis, the accuracy of frozen section results of sentinel lymph node biopsy specimens was 79.80%, 81.0%, and 78.0% in general, before 2 pm, and after 2 pm, respectively. There was no significant difference in the accuracy of the results of the frozen section before and after 2 pm in this study (P value = 0.716). Moreover, the accuracy of frozen section evaluation of non-sentinel lymph node biopsy specimens was 62.32%, 65.1%, and 57.7% in general, before 2 pm, and after 2 pm, respectively. There was no significant difference in the accuracy of frozen section results before and after 2 pm (P value = 0.537). Considering the higher sensitivities reported in some other previous studies compared to our study, more studies are required to clarify the reasons.[33,34]

In a study of Rogers *et al.*, the frozen section results of 1414 samples matched the results of permanent pathology.[35] The accuracy of frozen section in the diagnosis of malignant cells in this study is similar to other similar studies, including a study by Weiser *et al.*, and a study by Van Diest *et al.*[3,36]

Previous studies have proposed that repetitive processes may be affected more than other procedures by fatigue during shift times.[21, 37-42] In a study by Sanaka *et al.*, the time of performing colonoscopy was an independent predictor for detection of adenoma.[38] In another study by Sanaka *et al.*, performing colonoscopy in the afternoon compared to the morning was an independent predictor of incomplete colonoscopy.[39] According to a study by Parsaei *et al.*, breast surgery with a later start time might have a lower quality.[43] These reports are in contrast to our findings. However, Mehta *et al.*, showed that doing ERCP in the morning or in the afternoon did not seem to affect the cannulation success, procedure completion rate, length of the procedure, or adverse events.[37] This result is similar to our findings.

According to our findings and analyses, there is no difference in the accuracy of the results of frozen section analysis for sentinel and non-sentinel biopsy before and after 2 pm. However, further studies with more cases are recommended.

References

1. Weber S, Storm FK, Stitt J, Mahvi DM. The role of frozen section analysis of margins during breast conservation surgery. The cancer journal from Scientific American 1996; 3(5): 273-7.
2. Sotiriou C, Neo S-Y, McShane LM, Korn EL, Long PM, Jazaeri A, *et al.* Breast cancer classification and prognosis based on gene expression profiles from a population-based study. Proceedings of the National Academy of Sciences 2003; 100(18): 10393-8.
3. Weiser MR, Montgomery LL, Susnik B, Tan LK, Borgen PI, Cody III HS. Is routine intraoperative frozen-section examination of sentinel lymph nodes in breast cancer worthwhile? Annals of surgical oncology 2000; 7(9): 651-5.
4. Wright JR. " William Osler Medal Essay": The Development of the Frozen Section Technique, The Evolution of Surgical Biopsy, and the Origins of Surgical Pathology. Bulletin of the History of Medicine 1985; 59(3): 295.
5. Algaba F, Arce Y, Lopez-Beltran A, Montironi R, Mikuz G, Bono A. Intraoperative frozen section diagnosis in urological oncology. European urology 2005; 47(2): 129-36.
6. Kubinski DJ, Clark PE, Assimos DG, Hall MC. Utility of frozen section analysis of resection margins during partial nephrectomy. Urology2004; 64(1): 31-4.
7. Shaha A, DiMaio T, Webber C, Jaffe B. Intraoperative decision making during thyroid surgery based on the results of preoperative needle biopsy and frozen section. Surgery 1990; 108(6): 964-7; discussion 70-1.
8. Wong Z, Muthu C, Craik J, Carter J, Harman CR. Role of intraoperative frozen section in the management of thyroid nodules. ANZ journal of surgery 2004; 74(12): 1052-5.
9. Riedl O, Fitzal F, Mader N, Dubsky P, Rudas M,

Mittlboeck M, *et al*. Intraoperative frozen section analysis for breast-conserving therapy in 1016 patients with breast cancer. European Journal of Surgical Oncology (EJSO) 2009; 35(3): 264-70.
10. Prey MU, Vitale T, Martin SA. Guidelines for practical utilization of intraoperative frozen sections. Archives of Surgery 1989; 124(3): 331-5.
11. Borrego AF, Martínez FM, Parra JLC, Grañeda DS, Crespo RG, Stern LL-D. Diagnosis of infection in hip and knee revision surgery: intraoperative frozen section analysis. International orthopaedics 2007; 31(1): 33-7.
12. Goharderakhshan RZ, Sudilovsky D, Carroll LA, Grossfeld GD, Marn R, Carroll PR. Utility of intraoperative frozen section analysis of surgical margins in region of neurovascular bundles at radical prostatectomy. Urology 2002; 59(5): 709-14.
14. Renshaw AA, Gould EW. Measuring errors in surgical pathology in real-life practice. American journal of clinical pathology 2007; 127(1): 144-52.
14. Raab SS, Grzybicki DM, Janosky JE, Zarbo RJ, Meier FA, Jensen C, *et al*. Clinical impact and frequency of anatomic pathology errors in cancer diagnoses. Cancer 2005; 104(10): 2205-13.
15. Saltzstein SL, Nahum AM. Frozen section diagnosis: accuracy and errors; uses and abuses. The Laryngoscope 1973; 83(7): 1128-43.
16. Raab SS. Improving patient safety by examining pathology errors. Clinics in laboratory medicine 2004; 24(4): 849-63.
17. Furness P, Lauder I. A questionnaire-based survey of errors in diagnostic histopathology throughout the United Kingdom. Journal of clinical pathology 1997; 50(6): 457-60.
18. Safrin RE, Bark CJ. Surgical pathology signout: routine review of every case by a second pathologist. The American journal of surgical pathology 1993; 17(11): 1190-2.
19. Howanitz PJ, Renner SW, Walsh MK. Continuous wristband monitoring over 2 years decreases identification errors: a College of American Pathologists Q-Tracks Study. Archives of pathology & laboratory medicine 2002; 126(7): 809-15.
20. Giuliano AE, Dale PS, Turner RR, Morton DL,Evans SW, Krasne DL. Improved axillary staging of breast cancer with sentinel lymphadenectomy. Annals of surgery 1995; 222(3): 394.
21. Rogers C, Klatt EC, Chandrasoma P. Accuracy of frozen-section diagnosis in a teaching hospital. Arch Pathol Lab Med 1987; 111(6): 514-7.
22. Gaba DM, Howard SK. Fatigue among clinicians and the safety of patients. New England Journal of Medicine 2002; 347(16): 1249-55.
23. Fisman DN, Harris AD, Rubin M, Sorock GS, Mittleman MA. Fatigue increases the risk of injury from sharp devices in medical trainees results from a case-crossover study. Infection Control & Hospital Epidemiology 2007; 28(01): 10-7.
24. Smith-Coggins R, Rosekind MR, Hurd S, Buccino KR. Relationship of day versus night sleep to physician performance and mood. Annals of emergency medicine 1994; 24(5): 928-34.
25. Van Dongen H, Dinges DF. Circadian rhythms in sleepiness, alertness, and performance. Principles and practice of sleep medicine 2005; 4: 435-43.
26. Samkoff JS, Jacques C. A review of studies concerning effects of sleep deprivation and fatigue on residents' performance. Academic Medicine 1991; 66(11): 687-93.
27. Spath PL. Reducing errors through work system improvements. Error Reduction in Health Care: A Systems Approach to Improving Patient Safety 2000: 199-234.
28. Lockley SW, Barger LK, Ayas NT, Rothschild JM, Czeisler CA, Landrigan CP. Effects of health care provider work hours and sleep deprivation on safety and performance. The Joint Commission Journal on Quality and Patient Safety 2007; 33(Supplement 1): 7-18.
29. Jones G, Hocine M, Salomon J, Dab W, Temime L. Demographic and occupational predictors of stress and fatigue in French intensive-care registered nurses and nurses' aides: A cross-sectional study. International journal of nursing studies 2015; 52(1): 250-9.
30. Mehta PP, Sanaka MR, Parsi MA, Zuccaro G, Dumot JA, Lopez R, *et al*. Effect of the time of day on the success and adverse events of ERCP. Gastrointestinal endoscopy 2011; 74(2): 303-8.
31. Sanaka MR, Deepinder F, Thota PN, Lopez R, Burke CA. Adenomas are detected more often in morning than in afternoon colonoscopy. The American journal of gastroenterology 2009; 104(7): 1659-64.
32. Chan MY, Cohen H, Spiegel BM. Fewer polyps detected by colonoscopy as the day progresses at a Veteran's Administration teaching hospital. Clinical Gastroenterology and Hepatology 2009; 7(11): 1217-23.
33. Tan J, Joblin L, Davenport E. Accuracy of frozen sections for breast cancer sentinel lymph node biopsies within a peripheral New Zealand hospital. N Z Med J 2016; 129(1431): 46-50.
34. SomashekharSP, Naikoo ZA, Zaveri SS, Holla S, Chandra S, Mishra S, *et al*. Intraoperative Frozen Section Evaluation of Sentinel Lymph Nodes in Breast Carcinoma: Single-Institution Indian Experience. Indian J Surg 2015; 77(Suppl 2): 335-40.
35. Rogers C, Klatt EC, Chandrasoma P. Accuracy of frozen-section diagnosis in a teaching hospital.

Archives of pathology & laboratory medicine 1987; 111(6): 514-7.
36. Van Diest PJ, Torrenga H, Borgstein PJ, Pijpers R, Bleichrodt RP, Rahusen FD, *et al.* Reliability of intraoperative frozen section and imprint cytological investigation of sentinel lymph nodes in breast cancer. Histopathology 1999; 35(1): 14-8.
37. Mehta PP, Sanaka MR, Parsi MA, Zuccaro G, Dumot JA, Lopez R, *et al.* Effect of the time of day on the success and adverse events of ERCP. Gastrointest Endosc 2011; 74(2): 303-8.
38. Sanaka MR, Deepinder F, Thota PN, Lopez R, Burke CA. Adenomas are detected more often in morning than in afternoon colonoscopy. Am J Gastroenterol 2009; 104(7): 1659-64; quiz 65.
39. Sanaka MR, Shah N, Mullen KD, Ferguson DR, Thomas C, McCullough AJ. Afternoon colonoscopies have higher failure rates than morning colonoscopies. Am J Gastroenterol 2006; 101(12): 2726-30.
40. Chan MY, Cohen H, Spiegel BM. Fewer polyps detected by colonoscopy as the day progresses at a Veteran's Administration teaching hospital. Clin Gastroenterol Hepatol 2009; 7(11): 1217-23; quiz 143.
41. Tan PJ, Xu M, Sessler DI, Bashour CA. Operation timing does not affect outcome after coronary artery bypass graft surgery. Anesthesiology 2009; 111(4): 785-9.
42. Switzer JA, Bennett RE, Wright DM, Vang S, Anderson CP, Vlasak AJ, *et al.* Surgical time of day does not affect outcome following hip fracture fixation. Geriatr Orthop Surg Rehabil 2013; 4(4): 109-16.
43. Parsaei R, Elyasinia F, Aboutorabi A, Saberi F. Does Time of Day Affect Quality of Breast Cancer Surgery? Arch Breast Cancer 2014; 1(2): 59-63.

Case Report Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.201634135-138

Anaplastic Large Cell Lymphoma Associated with Saline Breast Implant

Grace Ng*[a], Rupa K. Patel[a], LaNette Smith[b], Guido Sclabas[a]

[a] *Department of Surgery, School of Community Medicine, University of Oklahoma, Oklahoma, USA*
[b] *Breast Surgery of Tulsa, Oklahoma, USA*

ARTICLE INFO

Received:
10 September 2016
Accepted:
4 October 2016

Keywords:
Seroma,
breast implant,
breast lymphoma

ABSTRACT

Background: Breast implant associated anaplastic large T- cell lymphoma is a rare type of non-Hodgkin lymphoma, with a reported incidence of 0.3% per 100,000 women with breast prosthesis per year. It presents most commonly as a peri-implant seroma, but may also present as a capsular mass, tumor erosion through skin, in a regional lymph node, or found incidentally during revision surgery.

Case presentation: We report a 68-year-old female patient who presented with a four month history of marked pain and swelling of the right breast, who upon implant removal and right sided capsulectomy, revealed pathology consistent with ALK negative, CD 30 positive anaplastic large T- cell lymphoma.

Conclusion: Breast implant associated anaplastic large cell lymphoma, although a rare clinical occurrence is of clinical significance. Prognosis is favorable in the majority of reported cases. Definitive treatment guidelines have yet to be determined after review of long-term follow-up data.

Introduction

Breast implant-associated anaplastic large cell lymphoma (ALCL) is a rare entity with a reported incidence of 0.3% per 100,000 women with breast prosthesis per year.[1,2] It is a rare type of non-Hodgkin lymphoma (NHL) typically found in the capsule surrounding breast implants.[3] It most often presents as a unilateral breast swelling related to late peri-implant seroma, but may also present as a capsular mass, tumor erosion through skin, in a regional lymph node, or an incidental finding during revision surgery.[4] The average age of presentation is approximately 50 years old and appears to be a late complication as symptoms can develop up to 10 years post-surgery.[4] The first cases of ALCL were thought to be associated with breast implants and were published in 1997 by Keech and Creech.[5] Since then, the growing number of cases reported has encouraged an association between the presence of implants and the development of ALCL.[6] A recent systemic review by Brody *et al* in 2014 revealed a total of 79 cases reported in literature.[7] Since then, there has been an addition of five more cases reported in published literature, totaling 84 cases to date.[1,8,9]

We present a case of a textured saline breast implant associated ALCL, adding to the current literature, and review the pathogenesis, presentation, and current recommendations for the management of this disease.

Address for correspondence:
Grace Ng, MD
Address: 4502 East 41st Street, Tulsa, OK 74135-2512, USA
Tel: +1 915 3464049
Email: grace-ng@ouhsc.edu

Case Presentation

A 68-year-old female presented with a four month history of intense right sided breast pain and swelling. The patient reported a history of bilateral

subcutaneous mastectomies with subsequent placement of subpectoral saline implants greater than ten years ago. On exam, the right breast appeared swollen and markedly tender. There was no evidence of a suspicious mass, skin dimpling, or nipple discharge. On ultrasound, a large peri-implant fluid collection was seen. About 300cc of fluid was initially aspirated and sent for cytology and cultures. Cultures returned negative; however, cytology revealed scattered, single, highly atypical cells with irregular and convoluted nuclei suspicious for malignancy. Breast magnetic resonance imaging (MRI) revealed a thickened and enhanced fibrous capsule with a large right sided peri-implant intracapsular fluid collection, without evidence of implant rupture bilaterally (Figure 1). The patient underwent surgical exploration of the right breast that revealed a well formed single capsule and an intact implant. A right sided capsulectomy was performed and the implant was removed. The contralateral left implant was intact and was also removed but without a capsulectomy. The implants were not replaced. Final pathology confirmed features consistent with ALK negative, CD30+, anaplastic large T-cell lymphoma, without evidence of capsular invasion (Figure 2A and 2B). Post-operatively, the patient recovered well. The patient will maintain close follow-up with no further plans for further intervention at this time.

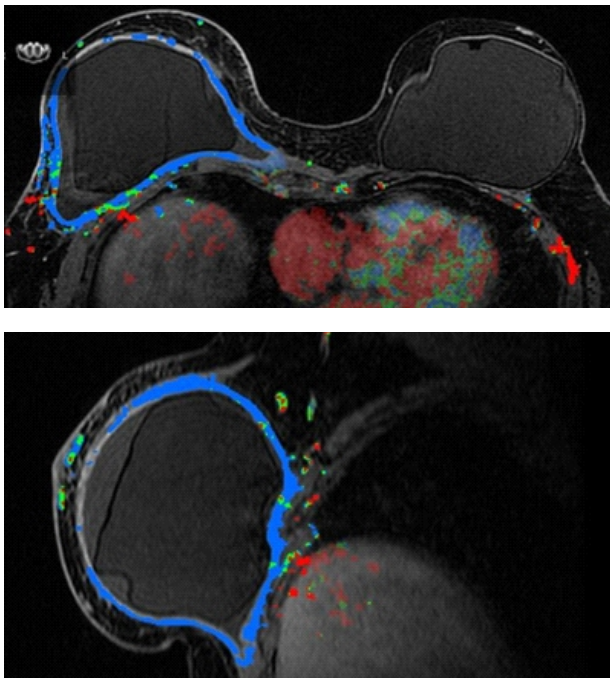


Figure 1. Breast magnetic imaging shows bilateral intact subpectoral saline implants. Large collection of intracapsular fluid surrounds a deformed implant on the right. Thickened and enhanced fibrous capsule with high intensity signal in capsule as well as surrounding skin and subcutaneous fat of the right breast. Absence of lymphadenopathy.

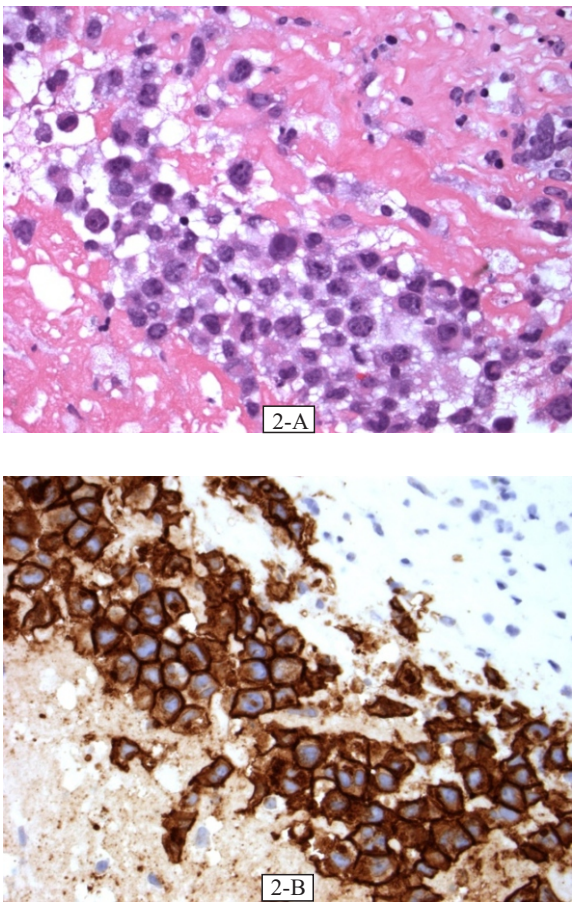


Figure 2. A) Presence of multinucelated cells, presence of "hallmark" cells with horseshoe like nuclei and abundant cytoplasm B) Anaplastic cells exhibiting immunoreactivity of CD30 and CD4 staining.

Discussion

Primary non-Hodgkin lymphoma (NHL) accounts for less than 1% of all breast malignancies. Most NHLs involving the breast are of B-cell origin. Less than 10% are of T-cell origin. ALCL is a rare T-cell lymphoma, accounting for only 3% of adult NHLs and 6% of breast NHLs.[10-13] Different types of ALCL include: systemic ALCL that is either anaplastic lymphoma kinase (ALK) positive or ALK negative, cutaneous ALCL (c-ALCL), ALCL of the breast (non-implant associated), and ALCL (implant associated).[1,3,12] Many authorities argue that implant-associated ALCL is not a disease of the breast parenchyma itself, but rather a disease of the fibrous capsule surrounding the implant as a result of chronic inflammation.[10] It has not yet been determined, however, if disease confined to the capsule will progress to a more advanced stage if left untreated.[14]

Breast implant associated ALCL is typically ALK negative, and is recognized to have a more indolent course secondary to its confinement to the peri-implant capsule, although there are reports of more aggressive presentations.[8, 9, 15, 16] It is noted to affect bilateral breasts equally, whereas primary breast lymphomas have a predilection for the right breast.[3-5, 10, 13, 14, 17] Its onset is often late and can present up to 10

years post implantation.[3,8] Although typical presentations include breast swelling (secondary to seroma or effusion), it can alternately present with constitutional B symptoms such as fever, weight loss, night sweats, general malaise, and lethargy.

It may also present as a palpable mass, or with axillary lymphadenopathy.[6, 9] Histopathologic diagnosis is typically found in microscopically neoplastic cells within the effusion or lining the fibrous capsule surrounding the implant rather than in a gross tumor.[9] Analysis of the neoplastic cells in implant associated ALCL reveals "hallmark" lymphoma cells which feature eccentric, horseshoe, or kidney-shaped nuclei with a paranucelar eosinophilic region, and positive cell surface and cytoplasmic staining for CD30 (Figure 2A and 2B).[3,8]

Definitive guidelines for the management of breast implant associated ALCL have yet to be set forth; however, a recent article published by Kim *et al* compiled recommendations from a multidisciplinary panel based on their interpretation of published evidence. There was universal agreement that seromas occurring more than 1 year after breast implantation should be aspirated and sent for culture, cytology, flow cytometry, cell block, immunohistochemical analysis, and T cell receptor gene rearrangement. With positive cytology, surgical intervention should include removal of the affected implant with total capsulectomy. This alone, is considered adequate treatment. In those with disease confined to the capsule. There is no consensus on contralateral breast implant removal or capsulectomy. All patients should also undergo workup for systemic disease with CT scan of the chest, abdomen, and pelvis, PET scan and occasionally bone marrow biopsy. The addition of chemotherapy and radiation to all patients with breast implant associated ALCL remains debatable, but in the literature, it has typically been reserved for those with a mass, systemic disease, or local, regional or metastatic disease (i.e. stage IE).[8, 14] It is usually not recommended in women with disease confined to the capsule.

Recall, this disease can also present as a mass or with axillary lymphadenopathy. Those presenting with a mass have been shown to have an overall worse survival and higher risk of treatment failure or relapse. For these patients, all suspicious tissue should be excised and sent as a fresh specimen.[8,9] In a case report of a patient exhibiting ALCL with axillary nodal involvement published by Estes *et al*, the addition of radiation therapy and chemotherapy has provided a favorable outcome to date.[9] Radiation therapy has shown some benefit in those with disease extending beyond the capsule, localized recurrent disease, persistent disease after surgery, or patients in whom surgery is not an option.[14] However, a study by Miranda *et al* showed no overall survival benefit in patients who received chemotherapy.[6] It is clear that the modes of treatment and effectiveness of each varies based on presentation; however, capsulectomy, radiation, and chemotherapy are available options for the treatment of breast associated ALCL. Continued surveillance following treatment is also paramount to long term survival. The multidisciplinary panel compiled by Kim, *et al* recommends clinical follow up at least every 6 months for 5 years and annual ultrasound for 2 years. Those with reimplantation of a breast prosthesis may require continued surveillance beyond 5 years.[14]

Breast implant associated anaplastic large cell lymphoma, although a rare clinical occurrence is of clinical significance. It is a diagnosis that can be swiftly identified and adequately treated. Patients presenting with a late forming seroma status post implant placement should undergo prompt ultrasound evaluation with fluid aspiration and cytologic analysis. As seen in the literature, prognosis is favorable in the majority of reported cases. Definitive treatment guidelines have yet to be determined after review of long term follow up data; however, the consensus is clear to perform a total capuslectomy with implant removal of the affected breast, evaluate for disseminated disease, and close follow up.

Conflict of Interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

References

1. Hwang MJ, Brown H, Murrin R, Momtahan N, Sterne GD. Breast implant-associated anaplastic large cell lymphoma: a case report and literature review. Aesthetic Plast Surg 2015; 39(3): 391-5.
2. Farace F, Bulla A, Marongiu F, Campus GV, Tanda F, Lissia A, *et al.* Anaplastic large cell lymphoma of the breast arising around mammary implant capsule: an Italian report. Aesthetic Plast Surg 2013; 37(3): 567-71.
3. Ye X, Shokrollahi K, Rozen WM, Conyers R, Wright P, Kenner L, *et al.* Anaplastic large cell lymphoma (ALCL) and breast implants: breaking down the evidence. Mutat Res Rev Mutat Res 2014; 762: 123-32.
4. Jewell M, Spear SL, Largent J, Oefelein MG, Adams WP, Jr. Anaplastic large T-cell lymphoma and breast implants: a review of the literature. Plast Reconstr Surg 2011; 128(3): 651-61.
5. Keech JA, Jr., Creech BJ. Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. Plast Reconstr Surg 1997; 100(2): 554-5.
6. Miranda RN, Aladily TN, Prince HM, Kanagal-Shamanna R, de Jong D, Fayad LE, *et al.* Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. J Clin Oncol 2014; 32(2): 114-20.

7. Brody GS, Deapen D, Taylor CR, Pinter-Brown L, House-Lightner SR, Andersen JS, *et al.* Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. Plast Reconstr Surg 2015; 135(3): 695-705.
8. Locke MB, Lofts J. Variable presentation of anaplastic large-cell lymphoma in patients with breast implants. ANZ J Surg 2015:
9. Estes CF, Zhang D, Reyes R, Korentager R, McGinness M, Lominska C. Locally advanced breast implant-associated anaplastic large-cell lymphoma: a case report of successful treatment with radiation and chemotherapy. Front Oncol 2015; 5: 26.
10. Xu J, Wei S. Breast implant-associated anaplastic large cell lymphoma: review of a distinct clinicopathologic entity. Arch Pathol Lab Med 2014; 138(6): 842-6.
11. Talwalkar SS, Miranda RN, Valbuena JR, Routbort MJ, Martin AW, Medeiros LJ. Lymphomas involving the breast: a study of 106 cases comparing localized and disseminated neoplasms. Am J Surg Pathol 2008; 32(9): 1299-309.
12. Miranda RN, Lin L, Talwalkar SS, Manning JT, Medeiros LJ. Anaplastic large cell lymphoma involving the breast: a clinicopathologic study of 6 cases and review of the literature. Arch Pathol Lab Med 2009; 133(9): 1383-90.
13. de Jong D, Vasmel WL, de Boer JP, Verhave G, Barbe E, Casparie MK, *et al.* Anaplastic large-cell lymphoma in women with breast implants. Jama 2008; 300(17): 2030-5.
14. Kim B, Predmore ZS, Mattke S, van Busum K, Gidengil CA. Breast Implant-associated Anaplastic Large Cell Lymphoma: Updated Results from a Structured Expert Consultation Process. Plast Reconstr Surg Glob Open 2015; 3(1): e296.
15. FDA Medical Device Safety Communications: Reports of Anaplastic Large Cell Lymphoma (ALCL) in Women with Breast Implants 2011. http://www.fda.gov/medicaldevices/safety/alertsandnotices/ucm240000.htm (accessed August 11 2016).
16. Aladily TN, Medeiros LJ, Amin MB, Haideri N, Ye D, Azevedo SJ, *et al.* Anaplastic large cell lymphoma associated with breast implants: a report of 13 cases. Am J Surg Pathol 2012; 36(7): 1000-8.
17. Kim B, Roth C, Chung KC, Young VL, van Busum K, Schnyer C, *et al.* Anaplastic large cell lymphoma and breast implants: a systematic review. Plast Reconstr Surg 2011; 127(6): 2141-50.

Case Report Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.201634139-143

Radioguided Occult Lesion Localisation (ROLL) for Excision of Non-Palpable Breast Lesions, a Personal Experience in a Patient with Multifocal Breast Cancer

Abdolali Assarian*[a], Sanaz Zand[b]

[a] Department of Surgery, Tehran University of Medical Sciences, Tehran, Iran
[b] Kaviani Breast Disease Institute (KBDI), Tehran, Iran

ARTICLE INFO

Received:
3 September 2016
Revised:
4 October 2016
Accepted:
21 October 2016

Keywords:
Multifocal,
non-palpable,
wire-guided localization,
breast conservation therapy,
radioguided occult lesion localization

ABSTRACT

Background: Breast conservation therapy (BCT) is the standard of care for early stage breast cancer. The procedure can be a challenge for the surgeon if the lesion is non-palpable. For excision of non-palpable breast lesions, they should be localized precisely before surgery. There are different techniques such as the WGL (Wire Guided Localization), ROLL (Radio-guided Occult Lesion Localization), etc. Some centers consider ROLL as the gold standard technique for excision of non-palpable breast lesions.

Case presentation: A 44-year-old woman with multifocal breast cancer presented to the breast clinic. Her imaging including MRI scan confirmed the presence of three tumors in the left breast and malignant looking nodes in the left axilla. Under ultrasound guidance, Core Needle Biopsy (CNB) of the breast lesions and Fine Needle Aspiration (FNA) of two lymph nodes in the left axilla were performed. Pathology of all three masses confirmed Invasive Ductal Carcinoma (IDC) and FNA of the lymph nodes was suspicious for malignancy. She was treated with breast conserving surgery using the ROLL technique. All three tumors were excised with adequate margins and axillary lymph node dissection was performed. The cosmetic results were satisfactory.

Conclusion: The ROLL technique is simple to perform and has several advantages compared to the WGL. We recommend this procedure, especially in multifocal non-palpable lesions.

Introduction

Breast conservation therapy (BCT) is the standard of care for early stage breast cancer.[1] The goal of breast conserving surgery is complete excision of lesions with negative margins to optimize the surgical outcome. Many studies have compared BCT and mastectomy but did not find any significant differences in "Overall Survival" (OS) and "Disease Free Survival" (DFS).[2,3]

Address for correspondence:
Abdolali Assarian, MD, FRCSEd
Address:
Tel/Fax:
Email:aliassarian@yahoo.com

The procedure can be a challenge for the surgeon if the lesion is non-palpable. More than 25% of breast lesions which are detected on mammography, ultrasound scan, and MRI scan are non-palpable clinically.[4-6] For excision of non-palpable breast lesions, they should be localized precisely before surgery. There are different techniques such as WGL (Wire Guided Localization), ROLL (Radio-guided Occult Lesion Localization), RSL (Radio-guided Seed Localization), IOUS (Intra-Operative Ultrasound), CAL (Cryoprobe-Assisted Localization); and HUG (Hematoma-directed Ultrasound Guided).[7] The WGL and ROLL are the two techniques widely used for excising non-palpable breast lesions nowadays.

ROLL has been used since 1996 when it was introduced by European Institute of Oncology in

Milan. Some centers consider it as the gold standard technique for excision of non-palpable breast lesions.[8] In the ROLL technique, about 4 to 6 hours before surgery, a small dose (0.2-0.5 mCi) of a solution containing a high molecular weight radioactive tracer and albumin colloid radio-labelled with 99m-Technetium (^{99m}Tc) is injected with a needle into the center of the lesion under stereotactic or ultrasound scan guidance. In the operating room, a handheld Gamma probe is used during the operation to guide surgical resection.[4,6,9-12]

By definition, the lesions are multicentric when two or more malignant lesions are in different quadrants or more than 5 cm apart. Multifocal lesions are in the same quadrant or less than 5 cm apart.[1,2]

BCT is not an absolute contraindication in multifocal cancers provided that negative margins can be achieved after excising all lesions with reasonable cosmetic results. Although WGL is widely used in surgical practice, there are some data showing ROLL may be more effective and reliable.[8]

We hereunder report a patient with multifocal breast cancer who underwent the ROLL technique for localizing the lesions.

Case presentation

A 44-year-old woman with a family history of breast cancer in her cousin was referred to breast clinic with a lump in her left breast. On examination, there was a 2.5 cm mobile firm mass in the upper central area of the left breast with palpable mobile lymph nodes in her left axilla.

We referred her for an ultrasound scan and the radiologist reported three masses: 1) An irregular hypoechoic mass in the upper outer quadrant (2 o'clock) measured 27*27 mm (BIRAD 5) 2) A microlobulated hypoechoic mass in the upper outer quadrant (3 O'clock) measured 9*7 mm (BIRADs 4b) 3) A microlobulated hypoechoic mass in the upper inner quadrant (10 O'clock) measured 7*6 mm (BIRADs 4a). Ultrasonography also showed suspicious lymph nodes with cortical thickening in the left axilla. She therefore had one palpable tumor (top lesion in Figure 1) and the other two lesions were not palpable (lower lesions in the same figure).

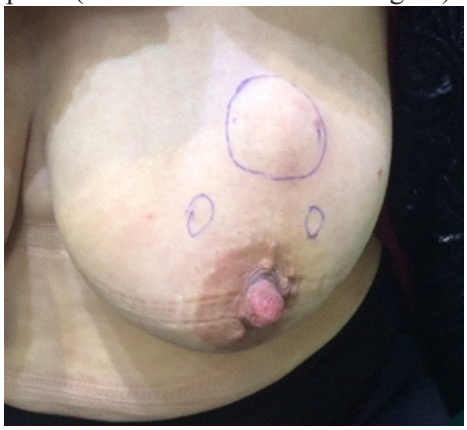


Figure 1. Three lesions in the upper part of the left breast

Mammography showed a speculated mass in the upper outer quadrant of the left breast (BIRADS 5) (Figure 2).

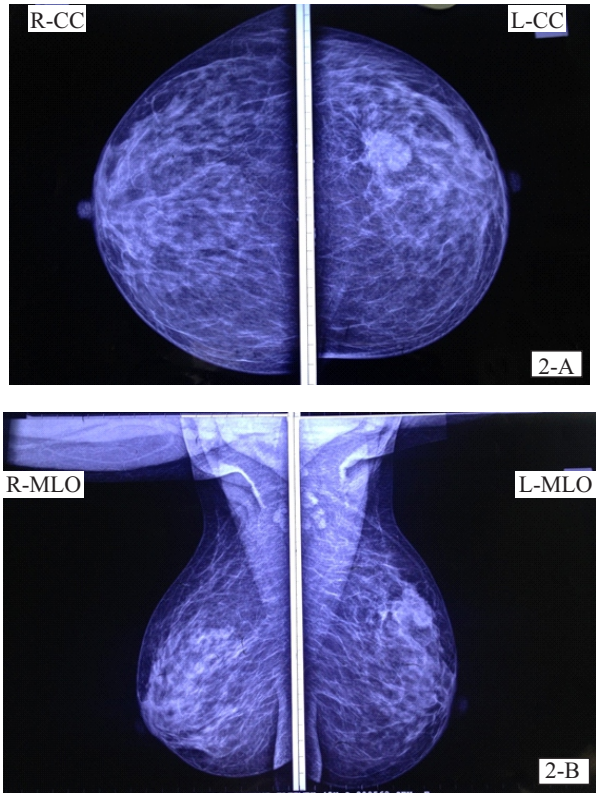


Figure 2. A- Right and left craniocaudal view of both breasts on mammography. B- Right and left medio lateral view of both breasts on mammography

MRI scan confirmed the presence of three tumors in the left breast and malignant looking nodes in the left axilla. Under ultrasound guidance, Core Needle Biopsy (CNB) of the breast lesions and Fine Needle Aspiration (FNA) of two lymph nodes in left axilla were performed. Pathology of all three masses confirmed Invasive Ductal Carcinoma (IDC), and FNA of the lymph nodes was suspicious for malignancy.

As MRI scan did not show any other lesions, breast conserving surgery was planned using the ROLL technique. The two non-palpable masses were injected with a small dose (0.2-0.5 mci) of Technetium (TC)-99m with a needle into the center of the tumor under ultrasound scan in the morning of the surgery. During the surgery with the guide of a gamma probe, all three masses were excised and axillary lymph node dissection was performed. Specimens were sent for definite pathological diagnosis.

Pathology reported all three masses were excised with adequate margins. The closet margin of the three tumors was 7mm, 14mm, and 5mm and skin was free of tumor. From 20 lymph nodes resected, 7 were involved by the tumor.

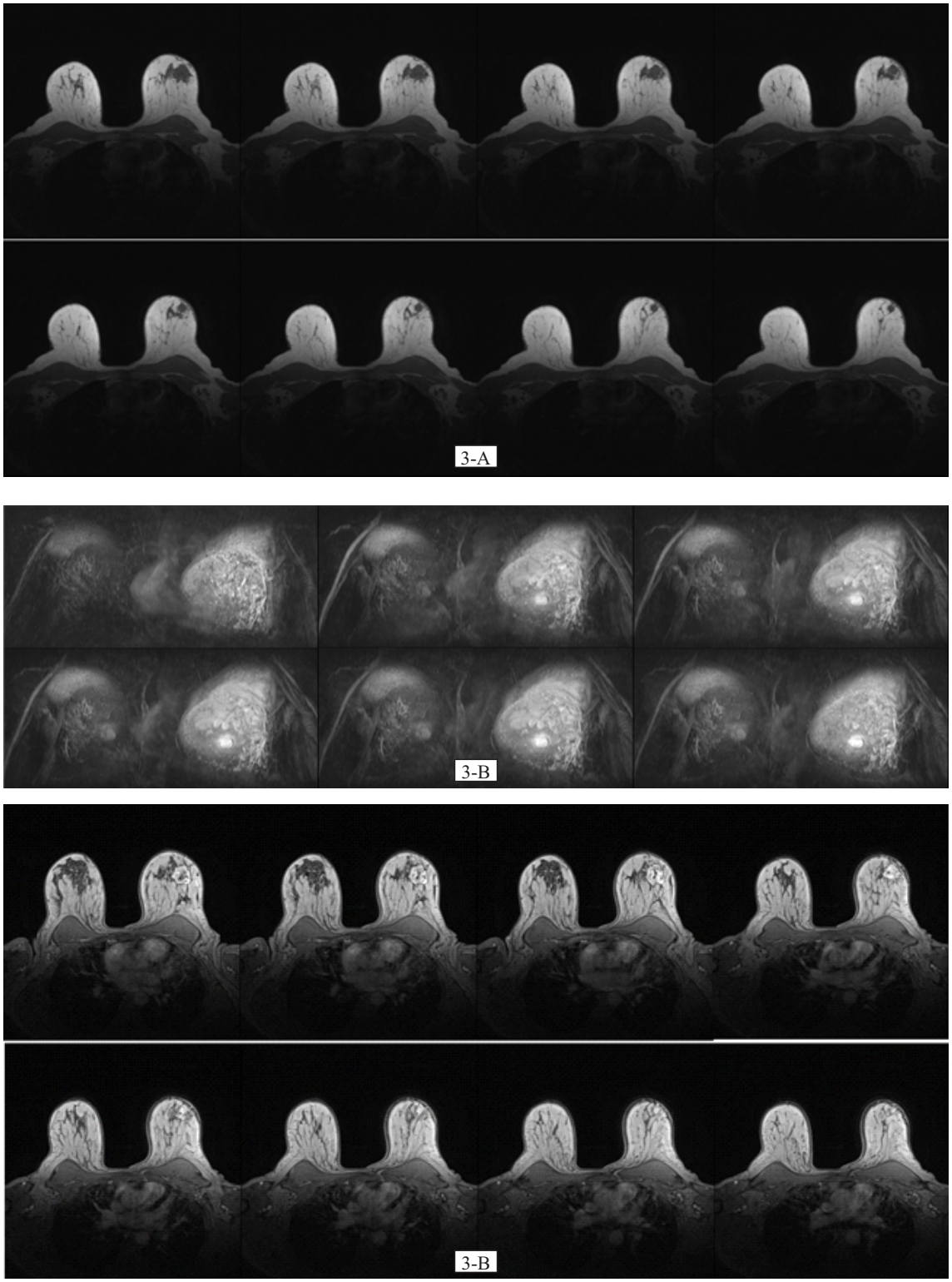


Figure 3. Dynamic MRI scan of both breasts without (3-A) & with (3-B) contrast showing enhanced masses in the upper outer quadrant of the left breast

Discussion

The goal of breast conserving surgery is complete excision with negative margins to optimize the surgical outcome. The procedure can be a challenge for the surgeon in non-palpable lesions. Although wire localisation is widely used in practice, it has several drawbacks. In a significant number of patients, there is a long distance from the entry point of wire to the lesion which can complicate the surgery, including long incisions and difficulties to reach the lesion. There are cases when wire breaks during the operation and causes a lot of stress for the surgeon and potentially compromises the surgery. The tip of the wire is not always obvious during the surgery; therefore, the surgeon sometimes performs a wider excision to make sure the lesion has been

removed, which means extra breast tissue loss. Specimen X-ray is necessary to confirm excision but this facility is not available in most centres and can take up to thirty minutes.

ROLL is another popular technique which overcomes most of these shortcomings. Most hospitals in Iran have a radioisotope department to provide the material and an ultrasound scan device to guide the injection. With the help of the same gamma probe which is used for sentinel biopsy, the breast lesion can be easily detected and removed. There are some data which indicate less tissue loss after this technique compared to wire guided excision. Confirmation of the lesion removal can be easily made with the same probe.

WGL has been the gold standard for many years but its disadvantages, such as displacement and repositioning of the wire, limited incision site, painful placement of the wire, the need for skilled radiologist, small risk of pneumothorax, and increased risk of needle stick injury to the surgeon and pathologist, have shifted some surgeons toward using the ROLL technique.[1-3,5,11,13]

Some reports have shown that ROLL reduces the volume and weight of tissue removal, creates better cosmetic outcomes, and reduces the operation time and also the re-operation rate.[4,9]

Van der Ploeg *et al*. in 2007 reviewed ROLL for non-palpable breast lesions. They found ROLL was more radical than WGL, its localization was more accurate and faster, excision of the lesion was more elegant and simpler, and the cosmetic results were better. They recommended ROLL as the preferred technique in the management of non-palpable lesions.[4]

In 2012, in a large multi-center randomized clinical trial study called "ROLL trial", Postma *et al*. compared the efficacy of ROLL with WGL in breast conserving surgery for non-palpable breast tumors and concluded that ROLL was comparable to WGL in terms of complete tumour excision and re-excision rate. ROLL, however, leads to excision of larger tissue volumes. Therefore, ROLL cannot replace WGL as the standard of care.[14]

In a study in Hungary in 2012, Takacs *et al*. compared ROLL and WGL in the treatment of non-palpable masses in two groups of patients (ROLL=321, WGL=69) and reported no significant differences in the operating time, removed specimen volume and pathological tumour size, presence of positive resection margins, and occurrence of postoperative wound infection. They reported a higher rate of clear margin in ROLL but it was not statistically significant. The localization time was significantly reduced in ROLL but there was no difference in the duration of excision. Finally, they recommended ROLL as the preferred technique because of the shorter localization time and simpler technique.[8]

A systematic review in 2013 by Ahmed *et al*. compared the differences of WGL and RGL (radio-guided localization: ROLL & RSL) in the treatment of non-palpable breast cancers and reported that RGL reduced the operation time but with increased as accompanied volume of the excised tissue and therefore could not be recommended as the standard of care.[5]

Based on our search in PubMed and Scopus, we only found one article using ROLL for multicentric lesions in both breasts without previous biopsy. In the report by Paredes *et al*., ROLL was used in a case of bilateral multifocal breast cancer. They suggested the use of different size radiocolloids to allow proper evaluation of each lesion and to avoid more radical surgery. They used 99m Tc-nanocolloidal and albumin macroaggregates (99mTc-MAA) for suspicious lesions of both breasts to distinguish lesions in the same breast.[15] However, we had no problem with just using TC(99m) since the gamma probe is able to distinct lesions with a sufficient distance.

The ROLL technique is simpler to perform and has more advantages. There are conflicting data in the literature regarding the resected volume. We would recommend this procedure especially in multifocal non-palpable lesions when WGL can be quite challenging. The final result of our case is shown in Fig 4. We suggest an RCT (Randomized Control Trial) study to compare ROLL vs. WGL in non-palpable multifocal breast cancer when mastectomy is not planned.

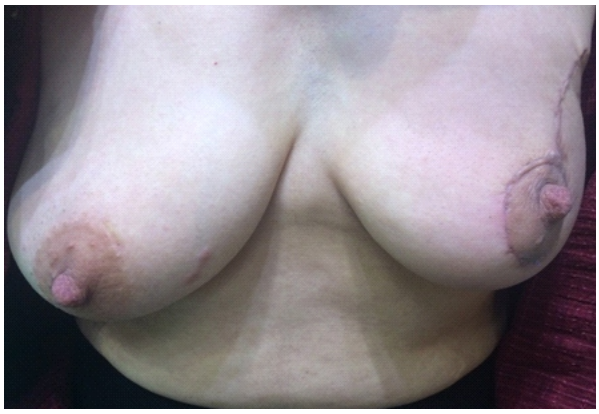


Figure 4. Final result after surgery

References

1. Nijenhuis MV, Rutgers EJ. Conservative surgery for multifocal/multicentric breast cancer. Breast 2015; 24 Suppl 2: S96-9.
2. Houvenaeghel G, Tallet A, Jalaguier-Coudray A, Cohen M, Bannier M, Jauffret-Fara C, *et al*. Is breast conservative surgery a reasonable option in multifocal or multicentric tumors? World J Clin Oncol 2016; 7(2): 234-42.
3. Pedersen L, Gunnarsdottir KA, Rasmussen BB, Moeller S, Lanng C. The prognostic influence of

multifocality in breast cancer patients. Breast 2004; 13(3): 188-93.
4. van der Ploeg IM, Hobbelink M, van den Bosch MA, Mali WP, Borel Rinkes IH, van Hillegersberg R. 'Radioguided occult lesion localisation' (ROLL) for non-palpable breast lesions: a review of the relevant literature. Eur J Surg Oncol 2008; 34(1): 1-5.
5. Ahmed M, van Hemelrijck M, Douek M. Systematic review of radioguided versus wire-guided localization in the treatment of non-palpable breast cancers. Breast Cancer Res Treat 2013; 140(2): 241-52.
6. Lovrics PJ, Cornacchi SD, Vora R, Goldsmith CH, Kahnamoui K. Systematic review of radioguided surgery for non-palpable breast cancer. Eur J Surg Oncol 2011; 37(5): 388-97.
7. Chan BK, Wiseberg-Firtell JA, Jois RH, Jensen K, Audisio RA. Localization techniques for guided surgical excision of non-palpable breast lesions. Cochrane Database Syst Rev 2015; (12): Cd009206.
8. Takacs T, Paszt A, Simonka Z, Abraham S, Borda B, Ottlakan A, *et al*. Radioguided occult lesion localisation versus wire-guided lumpectomy in the treatment of non-palpable breast lesions. Pathol Oncol Res 2013; 19(2): 267-73.
9. van Esser S, Hobbelink MG, Peeters PH, Buskens E, van der Ploeg IM, Mali WP, *et al*. The efficacy of 'radio guided occult lesion localization' (ROLL) versus 'wire-guided localization' (WGL) in breast conserving surgery for non-palpable breast cancer: a randomized clinical trial - ROLL study. BMC Surg 2008; 8: 9.
10. Belloni E, Canevari C, Panizza P, Marassi A, Rodighiero M, Tacchini S, *et al*. Nonpalpable breast lesions: preoperative radiological guidance in radioguided occult lesion localisation (ROLL). Radiol Med 2011; 116(4): 564-74.
11. Nadeem R, Chagla LS, Harris O, Desmond S, Thind R, Titterrell C, *et al*. Occult breast lesions: A comparison between radioguided occult lesion localisation (ROLL) vs. wire-guided lumpectomy (WGL). Breast 2005; 14(4): 283-9.
12. Dua SM, Gray RJ, Keshtgar M. Strategies for localisation of impalpable breast lesions. Breast 2011; 20(3): 246-53.
13. Landman J, Kulawansa S, McCarthy M, Troedson R, Phillips M, Tinning J, *et al*. Radioguided localisation of impalpable breast lesions using 99m-Technetium macroaggregated albumin: Lessons learnt during introduction of a new technique to guide preoperative localisation. J Med Radiat Sci 2015; 62(1): 6-14.
14. Postma EL, Verkooijen HM, van Esser S, Hobbelink MG, van der Schelling GP, Koelemij R, *et al*. Efficacy of 'radioguided occult lesion localisation' (ROLL) versus 'wire-guided localisation' (WGL) in breast conserving surgery for non-palpable breast cancer: a randomised controlled multicentre trial. Breast Cancer Res Treat 2012; 136(2): 469-78.
15. Paredes P, Vidal-Sicart S, Santamaria G, Zanon G, Pons F. [Application of the ROLL technique in a case of bilateral multifocal breast cancer]. Rev Esp Med Nucl 2008; 27(6): 436-9.

Author Guidelines

Archive of Breast Cancer (ABC) considers the following types of article for publication: original article, review article, letter to the editors and short communication.

All contributions must be written in English. Papers must be submitted on the understanding that they have not been published elsewhere (except in the form of an abstract or as part of a published lecture, review, or thesis) and are not currently under consideration by another journal. The corresponding author is responsible for ensuring that the article's publication has been approved by all the other coauthors.

Authorship

To qualify as an author, one should contribute substantially to the intellectual content of the submitted manuscript. This consists of 1) contributions to the conception or design of the work; or the acquisition, analysis, and interpretation of data for the work; 2) Drafting the work or revising it critically; 3) Final approval of the version to be published.

Permissions

Authors wishing to include figures, tables, or passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online formats and to include evidence that such permission has been granted. Any material received with submitting papers without such evidence will be assumed to originate from the authors.

Online Submission

Manuscripts should be submitted and tracked to final decision at www.archbreastcancer.com. The instructions for authors should be closely followed. Manuscripts that do not comply with these instructions will not be sent for external review.

Preparation of manuscripts

- ***Original article***

Original articles must not exceed 5,000 words, including references, figure legends and tables. The number of tables, figures and references should be appropriate to the manuscript content. Authors whose first language is not English are requested to have their manuscripts checked carefully before submission.

Abbreviations of standard SI units of measurement should be used.

Sections of the manuscript

Papers should be divided into the following sections: (1) Title page, (2) Abstract (3) Keywords, (4) Introduction, (5) Methods, (6) Results, (7) Discussion, (8) Acknowledgements, (9) Conflict of Interests, (10) References, (11) Figure legends, (12) Tables and (13) Figures.

General format

Please prepare your manuscript text using Word processing software (in .doc or .docx format). Submissions of text in the form of PDF files are not accepted. Manuscripts should be double-spaced, including text, tables, legends and references.

Number each page. Please avoid footnotes; instead, and as sparingly as possible, use parentheses. Enter text in the style and order of the journal. Use the TAB key once for paragraph indents. Where possible, use ***Times New Roman***for the text font and ***Symbols*** for the Greek and special characters.

1) Title page

- Full title
- Complete names of the all authors and with their highest academic degree(s) and their affiliations;
- Corresponding author's name should be followed by an asterisk;
- Mailing address, telephone, fax, and e-mail for correspondence;
- Running title of no more than 20 characters;
- Indicate the number of words in the abstract and manuscript.

2) Abstract

- All abstracts may not contain more than 250 words;
- Do not cite references in the abstract;
- The abstract should be self-explanatory without reference to the main text;
- Limit use of acronyms and abbreviations;
- The structure includes Background, Methods, Results and Conclusions.

3) Key Words

- Provide 3 to 5 key words t for indexing purposes. Keywords found in the Medical Subject Headings List (MeSH) of Index Medicus (see www.nlm.nih.gov) are preferable.

4) Introduction

- State clearly the aim and objectives of the study;
- Should indicate the main reasons for doing the work;
- A detailed review of the literature is not recommended;
- The content should be accompanied with relevant references.

5) Methods

- Mention the type of the study;
- Describe the methods, tools, and procedures employed with sufficient details to allow others to

reproduce the results without the need to communicate with the authors;

- Describe the intervention and control groups;
- Mention the type of statistical tests used;
- Describe rationale for use of specific statistical tests, when it would be necessary;
- State statistical significance when appropriate;
- The authors should state that their study complies with the Declaration of Helsinki, that the locally appointed ethics committee has approved the research protocol and that informed consent has been obtained from the subjects (or their guardians).

6) Results

- State findings of the study in the text, tables, or figures and not repeat the same findings in tables and figures and the text;
- Be precise and do not include material that is appropriate for the discussion e.g. explanation of findings;
- Units, quantities, and formulas should be mentioned according to the System International (SI units);
- All measurements should be presented in metric units.

7) Discussion

- State the original and important features of the study. Do not repeat all the finding presented within the results section;
- Contain the significance of the findings and the relevance to previously published studies;
- State only the conclusions that are supported by the study;
- Mention the limitations and applications of the results.

8) Acknowledgments

All contributors who do not meet the criteria for authorship as defined previously should be listed in acknowledgements section. Examples include a department chairperson who provided only general support, a person who provided purely technical help or writing assistance.

9) Conflict of Interest

- State all funding sources, and the names of companies, manufacturers, or external organizations providing technical or equipment support.

10) References

- Accuracy of reference details is the responsibility of authors;
- Personal communications, unpublished observations, and submitted manuscripts are not accepted references;
- In the main text, references should be entered consecutively by superscript Arabic numerals. The reference list should be organized in numerical order according to the order appearing in the text. *Examples of* acceptable reference formats are as follow:
- *Reference to a journal publication:*

1. Chavez LR, Hubbell FA, McMullin JM, Martinez RG, MiShra SI. Structure and meaning in models of breast and cervical cancer risk factors: a comparison of perceptions among Latinas, Anglo women, and physicians. Med Anthropol Q 1995; 9(1): 40-74.
2. Fitoussi AD, Berry MG, Fama F, Falcou MC, Curnier A, Couturaud B, *et al*. Oncoplastic breast surgery for cancer: analysis of 540 consecutive cases [outcomes article]. Plast Reconstr Surg 2010; 125(2): 454-62.

- *Reference to a book:*

1. Strunk Jr W, White EB. The elements of style. 3rd ed. New York: Macmillan; 1979.

- *Reference to a chapter in an edited book:*

1. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. Introduction to the electronic age, New York: E-Publishing Inc; 1999, p. 281-304.

- If there are 7 or more authors, list the first 6 ones and then insert "*et al.*"

11) Figure legends

Each figure should have a concise caption (legend) describing accurately what the figure depicts. Figure legends should be mentioned at the end of the manuscript file and not in the figure file. Figure legends should begin with the term Fig. in bold type, followed by the figure number also in bold type (e.g. Fig 1).

12) Tables

Tables should be presented in a separate file. For each table, a short descriptive title should appear above. Please make sure that each table is cited in the text and is numbered using Arabic numerals. For previously published material as tables, indicate the original source in the form of a reference at the end of the table caption. Asterisks (*) for significance values and other statistical points should be included beneath the table body.

13) Figures

Figures should be limited to the number necessary for clarity and must not duplicate data given in tables or in the text. Submissions should have no more than 8 total figures and tables. Any number exceeding this should be designated as supplementary material for online access only. Figures must be suitable for high quality reproduction and should be submitted in the desired

final printed size so that the quality of the figure would not be affected after being printed. Figures should be no larger than 125 (height) x 180 (width) mm (5 x 7 inches) and should be submitted in a separate file from that of the manuscript. Figures should be saved in TIFF format at a resolution of at least 300 pixels per inch at the final printed size for colour figures and photographs, and 1200 pixels per inch for black and white line drawings. Although some other formats can be translated into TIFF format by the publisher, the conversion may alter the tones, resolution and contrast of the image. Therefore, PDF is not acceptable as a source file for figures and illustrations.

- ***Short Communication***

A small-scale study that includes important new information may be published as a short communication. It usually carries an abstract up to 150 words, text up to 800 words, up to two tables or figures, and essential references.

- ***Letters to the Editor***

Letters commenting on articles published recently (within the past 4 issues)of Archive of Breast Cancer Journal or expressing views on relevant topics will be considered for publication.

- ***Case Report and Series***

Case reports include case report/studies of patient(s) that describe a novel situation or add important insights into mechanisms, diagnosis or treatment of a disease. Case reports are limited to 1,500 words including references. The body of a case report manuscript should include: title page, structured abstract (including: background, case presentation, conclusion), key words, introduction, case presentation, discussion, acknowledgments, references and illustrations (if applicable).

- ***Review Article***

Authors are encouraged to contact the Editor-in-Chief (akaviani@tums.ac.ir) before preparing an unsolicited review article to avoid duplication of other works already in progress. Review articles are limited to 7,000 words including references and should include the following sections: title page, abstract, main text, acknowledgments, references, figure legends, tables and figures.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The submission has not been previously published, nor is it before another journal for consideration.
2. The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines, which is found in About the Journal.
3. To ensure blinding review, the authors are asked to prepare the title page (including name and affiliations of all authors) and main manuscript file (containing abstract, instruction, methods, results, discussion, references and tables) separately.
   Please upload the main document of manuscript in "step 2. upload submission" and upload your title page in step 4 as a supplementary file.

Privacy Statement

The names and email addresses entered in this journal site will be used exclusively for the stated purposes of this journal and will not be made available for any other purpose or to any other party.

Call for manuscripts

The special issue in Archives of Breast Cancer (Supplement 2017) on "Medical Ethics and Professionalism in Screening, Management and rehabilitation of breast cancer"

Archives of Breast Cancer plans to publish a special issue on **Medical Ethics and Professionalism in patient-physician communication, screening, management, and rehabilitation of breast cancer** from different points of view. All types of manuscripts in this field will be welcome (commentary, original, short communication, review and case presentations).

All the manuscripts submitted before the end of 2017 will be assessed and peer-reviewed for publication. The special issue is planned to be published in 2018.

For more information regarding the journal scope and style, please visit ABC website at:

ARCHBREASTCANCER.COM

amoena
For you, like no other

The Original
since 1975
Hand made in Germany

We are the world's **leading supplier** of products for women following breast cancer.
We provide inspiration, information and innovation, encouraging confidence in women's lives.

Germany DE
Tel.: +49 (8035) 871
www.amoena.eu
amoena@amoena.com

Iran IR
Tel.: + 98 (21) 88198450
www.vazinteb.com
info@vazinteb.com

DO I NEED CHEMOTHERAPY?

An individual question...

...An individual answer

oncotype DX® Breast Cancer Assay

INFORMING LIFE DECISIONS

- The ONLY multi-gene assay that helps to identify patients at risk of distant recurrence[1,2] and patients who are likely, or unlikely, to benefit from chemotherapy[3,4]
- Intended for newly diagnosed patients with early-stage, ER-positive, HER2-negative invasive breast cancer that is node negative or with 1-3 positive nodes[1,2]

Visit us at **www.oncotypeDX.com**

References

1. Paik S et al. *N Engl J Med* 2004; 351: 2817-2826; **2.** Dowsett M et al. *J Clin Oncol* 2010; 28: 1829-1834; **3.** Paik S et al. *J Clin Oncol* 2006; 24: 3726-3734; **4.** Albain KS et al. *Lancet Oncol* 2010;11: 55-65.

NEWBRIDGE PHARMACEUTICALS

ROUGINE DAROU

3rd Floor, No.2, Kimia Bldg., End of Anahita St., 1st Peyvand St., Eastern side of Farhang Sq., Saadat Abad, Tehran, Iran
Postal Code: 1997744415
Phone: +98 21 27605000 Fax: +98 21 22140568
www.rouginedarou.com info@rouginedarou.com

Genomic Health®

GHI10448_0215_EN_INT

AryoTrust™

Trastuzumab

Our Ambition, Your Trust

ARYOGEN

Orchid Pharmed