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Real-time Detection of Cellular Metabolism: a New Trend for Intra-Operative Diagnosis of Cavity Margins

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During decades of breast cancer management, the clear surgical margin in breast cancer surgery has saved its importance even after considerable improvements in adjuvant therapies.[1] It has a significant independent impact on the treatment outcome, especially the local control of the disease.[2] Traditionally, wide surgical margins (more than 2cm) were the standard of care in breast cancer surgery. Improving the surgical techniques, adding radiation as a local adjuvant therapy, systemic therapies such as chemotherapy, hormonal therapy and targeted therapy allowed the surgeons to modify their surgical treatment to accept closer margins. Nowadays, "no ink on tumor" for most invasive and 2mm safe margin for in situ carcinomas (DCIS) are accepted according to most protocols and recommendations.[3]

On the other hand, by introducing breast conservative surgery (BCS), intraoperative evaluation of the margins was a part of management protocols. For many years, assessments of the margins using frozen section and touch prep and specimen mammography have helped the surgeons to perform more precise resections.[4,5] Still, their false positive and false negative reports and low accuracy as well as the fact that they are time-consuming have limited their routine usage. In fact, the omission of intraoperative assessment was due to the low sensitivity and specificity of the methods and their shortage of accurate assessment.[4] Obviously, a potentially accurate method for the intraoperative assessments of margins can help surgical oncologists to make the best decisions to properly define the extent of the resection of tissue from all around the tumor. The precise resection after an accurate assessment of the tumor margins is more crucial in situations where returning to the surgical field to remove the positive margin is challenging, e.g., after oncoplastic repair, intraoperative radiotherapy or when immediate breast reconstruction is planned after mastectomy.[6] Also, intraoperative assessment of the margins is more critical in the surgery of patients who receive neoadjuvant systemic therapy or suffer from more extensive forms of DCIS.[7]

To sum up, although many attempts have been put into the intraoperative evaluation of the surgical margins in breast cancer treatment, the precise assessment of the tumor cavity for evaluation of the remaining high-risk cells in the tumor bed is still challenging. Recently, some new technologies (MassPen, Margin Probe, etc.) have been developed for the precise real-time checking of excision and cavity side margins.[8]

In this article, the authors summarize the mechanism and results of a new technology working on the theoretical basis of hypoxia glycolysis. One of the most important distinctive differences between a normal or a malignant cell, especially in epithelial carcinomas, is changing the cellular metabolism from Oxidative Phosphorylation (OXPH) to anaerobic/aerobic glycolysis (during cancerous transformation steps) named hypoxia glycolysis. Hence, the real-time probing of the metabolism in the cavity side margins of a resected neoplastic tumor could be particularly helpful to prevent tumor recurrence.

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The main characteristic of glycolysis is releasing ROS/H_2O_2 from the cells during metabolism. In other words, cancer cells produce a lower amount of ATP in each cycle of glycolysis while they run a much larger number of metabolic cycles. Pyruvic acid and ROS/H2O2 are the most important agents released during these cycles. On the other hand, normal cells produce about 32 ATP in each OXPH cycle but the number of metabolic cycles is much lower in them. Totally, the amount of glucose consumption by cancer cells is much more than that of the normal cells. If these cells with the ability of H2O2/ROS releasement remained in the cavity side margins after tumor resection, these reactive non-stable molecules could be lively traced by biochemical, electrochemical or immune fluorescent assays. Thus, we can achieve a real-time margin checking approach during the surgery.

As the newest achievement, researchers from the University of Tehran (UT), Tehran University of Medical Sciences (TUMS), MOTAMED cancer research center, and Shahid Beheshti Medical University (SBMU) developed an electrochemically smart needle to check and scan cavity margin regions by recording the concentration of ROS/H_2O_2 agents in real-time.

The system which has been named Cancer Diagnostic Probe (CDP) has been applied for intra-operative real-time evaluation of cavity side margins after breast tumor resection (Figure 1). This system detects the presence of high-risk neoplastic cells in tumor bed based on electrochemical tracing of hypoxia glycolysis and/or aerobic glycolysis as the distinct metabolic parameters of breast cells from atypical hyperplasia neoplasia to invasive neoplasia.[8,9]

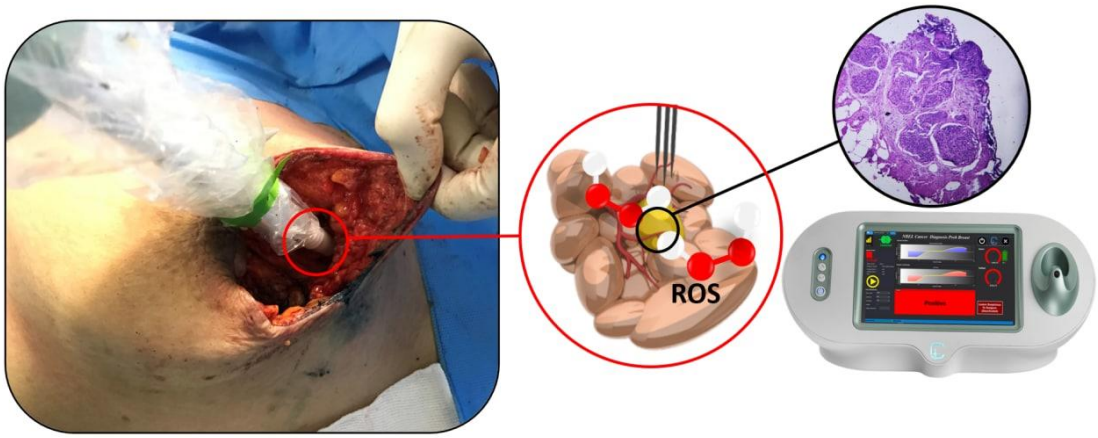

Figure 1. Cancer Diagnostic Probe (CDP) would check the cavity side margins intraoperatively, after tumor resection, in real-time. The mechanism of detecting involved lesions is tracing ROS released from remaining neoplastic cells, due to their glycolysis metabolism, by electrochemical approach based on specific nanostructures decorated on the needles. The CDP scores about the involvement or clearance of the margins were calibrated by pathological categorization of WHO. Permanent pathology (H&E) of the scored lesions was gold standard for evaluation of CDP responses. Sensitivity of CDP for both non-neoadjuvant and neoadjuvant cases were more than 90%.

Safe biocompatible nanostructure decorated needles record the electrochemical peak of reactive oxygen species (ROS) released by the remaining neoplastic cells in the tumor bed in less than 30 seconds. Pathological calibration of CDP responses is another significant ability achieved based on clinical trials on breast-conserving surgery (BCS) cases (either Neoadjuvant or Adjuvant), showing that CDP reduced the margins involved, some of which even have been missed in permanent pathology of tumor side. Detailed data could be found in papers released by the same authors.[10,11,12] The published sensitivity and specificity of CDP in human trials of BC patients in the Neoadjuvant setting were 91% and 89%, while in the non-Neoadjuvant setting, the figures were 93% and 91%, respectively, which is completely acceptable allowing the surgeons to apply the device in the clinical practice.[11,12,13]

In summary, intra-operative cavity side margin evaluation seems to be the next trend in BCS, which can drastically reduce the remaining neoplastic cells in the tumor bed. Among the methods presented for this purpose, metabolic evaluation of the tumor bed cells is interesting due to the distinct metabolism differences between normal and pre-neoplastic/neoplastic cells. CDP, as a real-time handheld diagnostic tool, can evaluate the cavity side margin by electrochemically tracing the hypoxia glycolysis. Many successful studies and trials reveal the efficacy of this tool even in the presence of frozen section in breast-conserving surgery.

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ETHICAL CONSIDERATIONS

There is no ethical issue for this paper.

CONFLICTS OF INTEREST

Nothing to declare.

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REFERENCES

1. Glorioso JM, Gonzalez Juarrero AB, Rodysill BR, Harmsen WS, Habermann EB, Carter JM, et al. Margin Proximity Correlates with Local Recurrence After Mastectomy for Patients Not Receiving Adjuvant Radiotherapy. *Annals of surgical oncology*, (2017) 24(11), 3148–56. doi: 10.1245/s10434-017-5968-2.
2. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Clin Oncol*. (2014) 32(14), 1507–1515. doi: 10.1200/JCO.2013.53.3935.
3. Pilewskie M, Morrow M. Margins in breast cancer: How much is enough? *Cancer*, (2018) 124(7), 1335–1341. doi:10.1002/cncr.31221.
4. Versteegden DPA, Keizer LGG, Schlooz-Vries MS, Duijm LEM, Wauters CAP, Strobbe LJA. Performance characteristics of specimen radiography for margin assessment for ductal carcinoma in situ: a systematic review. *Breast Cancer Res Treat*. 2017 Dec;166(3):669-679. doi: 10.1007/s10549-017-4475-2.
5. Surace A, Gentile S, Raponi A, Pasquero G, Tota D, Baù MG. Surgical Margins Status Assessment After Breast Conserving Surgery: Is There a Difference Between Surgeon and Radiologist Evaluation?. *Arch Breast Cancer*, (2021) 8,1:16-20. doi: 10.32768/abc.20218116-20.
6. Najafi M, Salmon R, Kaviani A. Oncological Outcome of Oncoplastic Breast Surgery: A Review of the Literature. *Arch Breast Cancer*, (2015) 2(1):5-14. doi: 10.19187/abc.2015215-14.
7. Elahi A, Toogeh G, Mahmoodzadeh H, Jahanbin B, Shahi F, Kalaghchi B, et al. Ductal Carcinoma In Situ Close to the Inked Margin: A Case Presented in Multidisciplinary Session With Clinical Discussion and Decision Making. *Arch Breast Cancer*, (2018) 2:58-62. doi: 10.19187/abc.20185258-62.
8. Miripour ZS, Abbasvandi F, Aghaee P, Shojaeian F, Faramarzpour M, Mohaghegh P, et al. Human study on cancer diagnostic probe (CDP) for real-time excising of breast positive cavity side margins based on tracing hypoxia glycolysis; checking diagnostic accuracy in non-neoadjuvant cases. *Cancer medicine*, (2022) 10.1002/cam4.4503. Advance online publication. doi: 10.1002/cam4.4503.
9. Dabbagh N, Abbasvandi F, Miripour ZS, Hoseinpour P, Jahanbakhshi F, Moradi A, et al. Accuracy of cancer diagnostic probe for intra-surgical checking of cavity side margins in neoadjuvant breast cancer cases: A human model study. *The international journal of medical robotics + computer assisted surgery: MRCAS*, (2022) 18(1), e2335. doi: 10.1002/rcs.2335.
10. Mahdavi R, Mehrvarz S, Hoseinpour P, Yousefpour N, Abbasvandi F, Tayebi M, et al. Intraradiological pathology-calibrated electrical impedance spectroscopy in the evaluation of excision-required breast lesions. *Medical physics*, (2022) 10.1002/mp.15481. doi:10.1002/mp.15481
11. King ME, Zhang J, Lin JQ, Garza KY, DeHoog RJ, Feider C, et al. Rapid diagnosis and tumor margin assessment during pancreatic cancer surgery with the MasSpec Pen technology. *Proceedings of the National Academy of Sciences of the United States of America*, (2021) 118(28), e2104411118. doi: 10.1073/pnas.2104411118
12. Dabbagh N, Abbasvandi F, Miripour ZS, Hoseinpour P, Jahanbakhshi F, Moradi A, et al. Accuracy of cancer diagnostic probe for intra-surgical checking of cavity side margins in neoadjuvant breast cancer cases: A human model study. *Int J Med Robot*. 2022 Feb;18(1):e2335. doi: 10.1002/rcs.2335.
13. Miripour ZS, Abbasvandi F, Aghaee P, NajafiKhoshnoo S, Faramarzpour M, Mohaghegh P, et al. Electrochemical tracing of hypoxia glycolysis by carbon nanotube sensors, a new hallmark for intraoperative detection of suspicious margins to breast neoplasia. *Bioengineering & translational medicine*, (2021) 7(1), e10236. doi: 10.1002/btm2.10236.

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