Invited Commentary Open Access

Archives Of Breast Cancer

DOI: 10.19187/abc.2017411-3

Optimal Timing of Surgery after Neoadjuvant Chemotherapy of Breast Cancer

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During recent decades, our understanding of the characteristics of breast cancer has improved, leading to improvements in individualized treatment methods historically, neoadjuvant chemotherapy (NAC) was limited to inoperable breast cancer[1], however, according to the results of several studies in some centers around the world this method has become the routine practice in almost all stages of breast cancer (except for the very early ones). Initially, theories suggested that NAC may result in more rapid eradication of micrometastatic disease increasing overall survival (OS). Although studies could not confirm this theory, NAC has led to an increase in the rates of breast conserving therapy (BCT), a decrease in the extent of local treatment (e.g. axillary dissection) and as a result, better cosmetic outcomes.[2] Other benefits of NAC that made this method popular include providing prognostic and therapeutic information based on in vivo tumor response, turning inoperable tumors into operable ones and providing enough time for genetic testing and breast reconstruction.[3]

Not only has NAC been helpful in the treatment of patients but its use has led to major advances in the field of cancer research.[4]

As an example, if considering pathologic response as a surrogate for survival, compared to the past, we may wait shorter to witness the results of clinical trials on new systemic therapies. In contrast, we still need the very survival curves to assess outcomes in studies on locoregional treatments which require long-term follow-ups to show meaningful differences. Thus, it is not surprising that many guidelines of locoregional treatment are not based on recent and prospective clinical evidence, but often have roots in retrospective or earlier studies.

NAC, per se, has opened new questions and issues that have not existed before, some include the accuracy and timing of sentinel lymph node biopsy in this setting[5], indications of radiotherapy and the extent of the radiation field[6], and further adjuvant chemotherapy in patients with inadequate response. An important question that we would like to address here is the optimal timing of surgery after NAC and its impact on survival.

The time of surgery after NAC is an ongoing issue. Large randomized trials demonstrating benefits of NAC (NSABP B18 & B27, EORTC 10902) along with several following studies made no mention of the timing of surgery.[7,8] Moreover, many single institution studies addressing this issue did not evaluate its impact on treatment outcome. Although, according to an accepted unwritten rule and also the information extrapolated from adjuvant chemotherapy studies, in current practice, the operation is performed as soon as the patient is fit. This usually is possible around 6 to 8 weeks after the completion of NAC.

In contrast to neoadjuvant chemotherapeutic series, there is substantial data on optimal interval after surgery for adjuvant chemotherapy. A meta-analysis demonstrated that increasing the time window could lead to decreased survival especially in patients with advanced, triple negative (TNBC) or Her2+ breast cancer[9]. Although according to biologic models of preclinical studies, a shorter time period from surgery to adjuvant chemotherapy would result in better outcomes[10], there is no such biologic model in the setting of NAC.

There are too few studies, all retrospective, addressing time interval after completion of neoadjuvant chemotherapy for breast cancer. In 2014, Gabordi *et al.*, presented results of a study at

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the annual meeting of the American Society of Breast Surgeons, demonstrating that patients undergoing surgery within 40 days after completion of NAC show greater reductions in final Ki-67, a marker of proliferative activity, which was associated with decreased recurrence rates.[11] In this study, 83 patients undergoing NAC and surgery during 2012 and 2013 were evaluated retrospectively. The decline rate of Ki-67 in the group having surgery within 40 days of NAC was 41% compared to 23% in the group who underwent surgery later (P = 0.038).

Recently, two other retrospective articles emerged on this topic. In a study by Sanford *et al*., published in 2015 in Annals of Surgical Oncology journal, 1101 patients with stage I-III breast cancer who were treated with NAC in MD Anderson Center during 1995-2007 were identified and divided into 3 groups according to the interval between chemo and surgery: ≤4 weeks, 4-6 weeks, and 6-24 weeks.[12] There was no difference in 5-year recurrence-free survival (RFS) or locoregional recurrence-free survival (LRFS). In multivariate analysis, compared with an interval of ≥4 weeks, patients who underwent surgery at 4–6 or >6 weeks had equivalent overall survival (OS), LRFS, and RFS; a sensitivity analysis suggested worse OS in patients who underwent surgery at >8 weeks. The authors concluded that patients with maximal 8-week neoadjuvant chemotherapy to surgery interval had equivalent OS, RFS, and LRFS.

In the study by Omarini *et al.*, a study published recently in the European Journal of Surgical Oncology, 319 patients with breast cancer were evaluated Who were treated in an Italian institute from 1991 to 2015.[13] The study consisted of two groups according to the timing of surgery after chemotherapy: ≤3 weeks, and >3 weeks. OS and RFS were significantly worse in the latter group, with a hazard ratio of 3.1 (95% CI, 1.1-8.6 P = 0.03) and 3.1 (95% CI, 1.3-7.1 P = 0.008), respectively. Multivariate analysis confirmed that time to surgery (TTS) was an independent prognostic factor in term of OS (P = 0.03) and RFS (P = 0.01). Interestingly, even in the subgroup of patients with pathologic complete response (pCR), TTS continued to be an independent prognostic factor for both OS and RFS (P = 0.05 and P = 0.03).

The retrospective nature of these studies makes interpretation of results difficult. In addition, the small sample size in both studies, heterogeneity of their patients and the fact that patients received different treatment protocols are all the reasons why we cannot make a firm conclusion. It is worth mentioning that some of the patients in these studies were treated more than 20 years ago. In the Sanford study, the <4weeks interval group compared to other two groups had higher percentage of stage III and high-grade tumors. Additionally, the reason for delayed surgery was not mentioned in this study. In Omarini's study the percentage of pCR in the group with TTS <3 weeks was higher than the other one (30% vs. 19%, although not statistically significant, P = 0.07) and a higher proportion of patients with TTS <3 weeks had positive hormonal receptors (48% vs. 35%). The total duration of chemotherapy in different groups of these studies was not mentioned, and the interval between diagnosis /initiation of chemotherapy and surgery is not clear. Although we know that the time from diagnosis to surgery in the adjuvant setting has an impact on survival, still there is no study evaluating the impact of this timing in the neoadjuvant setting.

It should be noted that in practice several factors could influence the timing of surgery after NAC leading to difficulties in performing the surgery in a preplanned schedule. These factors include complications of chemotherapy, age and comorbidities of patients, preference of both patient and surgeon, and the facilities of that center.

Overall, it seems that there cannot be a definite conclusion based on available evidence, however, this reminds us that it is prudent to be on the safe side and perform surgery as soon as the general condition and complications of chemotherapy allow us to do so. Defining the true impact of time to surgery after NAC needs randomized prospective trials, even though such studies have some practical and ethical issues. At present, there is a need for more prospective studies with larger sample sizes, and more thorough information about patients and treatments in order to better understand the impact of TTS after NAC in treatment outcomes.

Conflict of interests

The authors declare no conflict of interests.

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