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The underused potential of breast conserving therapy after neoadjuvant system treatment – Causes and solutions

André Pfob [a,b,*], Peter Dubsky [c,d]

[a] Department of Obstetrics & Gynecology, Heidelberg University Hospital, Germany
[b] National Center for Tumor Diseases (NCT), German Cancer Research Center (DKFZ), Heidelberg, Germany
[c] Breast Centre, Hirslanden Klinik St. Anna, Luzern, Switzerland
[d] Department of Surgery and Comprehensive Cancer Center, Medical University of Vienna, Austria

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ABSTRACT

Breast conserving therapy (BCT), consisting of breast conserving surgery and subsequent radiotherapy, is an equivalent option to mastectomy for women with early breast cancer. Although BCT after neoadjuvant systemic treatment (NAST) has been routinely recommend by international guidelines since many years, the rate of BCT worldwide varies largely and its potential is still underused. While the rate of BCT in western countries has increased over the past decades to currently about 70%, the rate of BCT is as low as 10% in other countries. In this review, we will evaluate the underused potential of breast conservation after NAST, identify causes, and discuss possible solutions. We identified clinical and non-clinical causes for the underuse of BCT after NAST including uncertainties within the community regarding oncologic outcomes, the correct tumor localization after NAST, the management of multifocal and multicentric tumors, margin assessment, disparities of socio-economic aspects on a patient and national level, and psychological biases affecting the shared decision-making process between patients and clinicians. Possible solutions to mitigate the underuse of BCT after NAST include inter-disciplinary teams that keep the whole patient pathway in mind, optimized treatment counseling and shared decision-making, and targeted financial support to alleviate disparities.

1. Introduction

Breast conserving therapy (BCT), consisting of breast conserving surgery and subsequent radiotherapy, has replaced mastectomy as the standard of care for women with early breast cancer [1,2]. Clinical trials demonstrated equivalent survival between BCT and mastectomy in the primary surgery as well as in the neoadjuvant setting [3–7]. BCT after neoadjuvant systemic treatment (NAST) poses unique opportunities but also challenges to patients and clinicians: On the one side, NAST allows for more BCT instead of mastectomy (associated with reduced surgical morbidity) [8–15] and in-vivo sensitivity testing of systemic treatment [16]. On the other side, BCT after NAST requires extensive multidisciplinary efforts to adequately diagnose the disease, initiate NAST, monitor treatment response, localize residual cancer, conduct surgery as well as radiotherapy, and meet patient expectations in terms of oncologic and aesthetic outcomes.

Although BCT after NAST has been routinely recommend by international guidelines since many years, the rate of BCT worldwide varies largely and its potential is still underused. While the rate of BCT in western countries has increased over the past decades to currently about 70%, the rate of BCT is as low as 10% in other countries [17–19]. Moreover, temporal trends of breast surgery after NAST indicate that the rate of bilateral mastectomy but not of breast conserving surgery has increased over the past decade despite increasing BCT eligibility, increasing use of NAST, and increasing complete response to NAST [20,21]. In this review, we will evaluate the underused potential of breast conservation after NAST, identify causes, and discuss possible solutions.

2. Causes for the underuse of breast conserving therapy after neoadjuvant systemic treatment

There are several clinical and non-clinical reasons for the underuse of breast conserving therapy after NAST.

* Corresponding author. Department of Obstetrics & Gynecology, Heidelberg University Hospital, Germany, Im Neuenheimer Feld 440, 69120, Heidelberg, Germany.
E-mail address: andre.pfob@med.uni-heidelberg.de (A. Pfob).

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1) Oncologic outcomes

The oncologic safety of BCT after NAST is of outmost importance. Several prospective, randomized controlled trials have demonstrated equal overall survival and distant-disease free survival of BCT after NAST compared to adjuvant treatment [5–7]. With respect to local recurrence, however, some meta-analysis suggest an increased risk of local recurrence after NAST compared to adjuvant treatment, while others do not [5,6]. The 2018 EBCTCG meta-analysis included 10 randomized controlled trials (n = 4756) comparing breast surgery in the neoadjuvant with the adjuvant setting [5]. The trials were conducted between 1983 and 2002 with a median follow-up of 9 years. Significantly higher rates of local recurrence for NAST compared to adjuvant treatment were reported after 10 and 15 years of follow-up (17.9% vs. 13.2% and 21.4 vs. 15.9%, respectively, log-rank $p < 0.001$). These findings led to much uncertainty regarding the use of NAST and management of subsequent surgery. Among the 10 trials included in the meta-analysis, there were two trials that did not perform any kind of surgery after NAST in case of clinical complete response (IB Bordeaux and Insitut Curie S6). Subgroup analyses showed that the risk of local recurrence after NAST compared to adjuvant treatment was greatest in these two trials (33.7% vs. 20.4% after 10 years, log-rank $p = 0.002$). However, also in the remaining eight trials with routine use of either mastectomy or BCT, there were significantly more local recurrences in the neoadjuvant groups (15.1% vs. 11.9% after 10 years, log-rank $p = 0.010$). Detailed analysis revealed significant differences in local recurrences among different surgical groups (planned vs. actual surgery): The risk of local recurrence was highest in patients initially planned for mastectomy but finally undergoing BCT, which raises concerns about adequate surgical planning (imaging, tumor localization etc.). Moreover, data on axillary surgery and radiotherapy were unknown. A similar meta-analysis, including 11 studies from 1983 to 2002 (n = 5041), stratified their findings into trials with optimal local treatment and inadequate local treatment (exclusive radiotherapy, no surgery). Increased risk of local recurrence after NAST compared to adjuvant treatment was seen only for patients with inadequate local treatment – no increased risk were seen for patients with optimal local treatment, also when they were initially planned for mastectomy but downstaged to BCT after NAST [6]. Additionally, a more recent meta-analysis, including 14 studies from 1980 to 2014 (n = 19,819), suggests that BCT is actually associated with significantly decreased risks of all-cause mortality (hazard ratio 0.78, 95% CI 0.69 to 0.89, $P < 0.001$), locoregional recurrence (0.64, 95% CI 0.48 to 0.85, $P = 0.002$), and distant recurrence (0.70, 95% CI 0.53 to 0.94, $P = 0.02$) compared to mastectomy in times of modern multi-modality treatment.

Thus, findings that breast surgery after NAST leads to higher risk of local recurrence may rather reflect inadequate locoregional management and illustrate the importance of adequate modern locoregional multi-modality treatment. However, modern multi-modality BCT requires high multidisciplinary team demands along the patient pathway: tumor localization and clipping, assessment of tumor multifocality/multicentricity, assessment of residual tumor extent, margin assessment, and patient preferences, which are discussed below.

2) Tumor localization and assessment of residual tumor extent

Compared to the primary surgery setting, pre-operative tumor assessment is more difficult in patients undergoing NAST: Depending on tumor biological and histological subtype, different response patterns exist (concentric tumor shrinkage vs. diffuse cell loss) and a radiological complete response is observed in a large proportion of patients after NAST [22]. Several meta-analyses showed that imaging after NAST (mammography, ultrasound, diffusion-weighted (DW) - MRI, contrast-enhanced (CE) - MRI, PET-CT) can be used to evaluate general response to NAST but that imaging is not accurate enough to definitely either confirm or exclude residual disease [23–25]. Sensitivity and specificity to detect residual disease are reported as 80% and 77% for mammography, 90% and 80% for ultrasound, 93% and 82% for DW-MRI, 68% and 91% for CE-MRI, and 84% and 71% for PET-CT [23–25]. Thus, patients who might be eligible for BCT require clipping of the tumor(s) prior to the initiation of NAST. The clip remains visible throughout the course of NAST and allows robust pre-operative localization of the tumor bed. As the clip itself is not visible during surgery, different techniques like wire or radioactive seed localization exist, to allow pre-operative tumor localization or intra-operative tumor identification.

In the past decade, MRI has been considered to be more sensitive in terms of response assessment to NAST and thus, in some countries, is considered the gold-standard for pre-operative tumor assessment after NAST in patients planned for BCT. However, more recent meta-analyses suggest that ultrasound and MRI show equivalent performance in both, detecting and excluding residual disease [25,26].

Adequate tumor localization and residual tumor assessment is crucial to enable BCT and must be considered prior to the initiation of NAST.

3) Multifocal or multicentric tumors

The breast surgical management of patients with multifocal (≥2 lesions in 1 breast quadrant) or multicentric (≥1 lesion in ≥2 breast quadrants) often leads to uncertainties for patients and clinicians, especially after NAST. Guidelines generally recommend mastectomy for patients with multicentric disease whereas BCT can be offered to patients with multifocal tumors [2,27]. These recommendations originate from data in the 1980s, suggesting that BCT in multifocal/multicentric patients results in local recurrence rates as high as 40% [28,29]. However, a more recent pooled analysis of 3 prospective clinical trials undergoing BCS after NAST (n = 6134) showed that LRFS, DFS, and OS of patients with multicentric or multifocal tumors were not inferior compared to patients with uni-focal tumors if clear margins can be obtained [30]. As multifocal or multicentric tumors tend to have an unfavorable breast-tumor ratio, BCT of these patients is rather limited by oncoplastic and cosmetic outcomes than oncologic outcomes. Recent and future advances in the field of oncoplastic breast surgery may enable good cosmetic outcomes despite resection of large breast tissue volumes [31]. Moreover, adequate pre-operative tumor localization (see above) is especially important for multicentric and multifocal tumors to obtain clear margins.

Patients with multifocal or multicentric tumors can undergo BCT if adequate tumor localization is ensured and clear margins as well as a satisfying cosmetic outcome can be obtained.

4) Margin assessment

Complete resection of the tumor while removing as little healthy breast tissue as possible is the aim of breast conserving surgery. The gold standard for the assessment of breast surgical margins is histopathologic evaluation of the surgical specimen. Positive margins (R1), defined as tumor touching ink, are associated with increased ipsilateral breast cancer recurrence and thus result in secondary surgical re-excision to obtain negative margins (R0), defined as no ink on tumor [32]. Re-excision rates following BCS are about 20% [33]. As some tumors, especially luminal and invasive lobular breast cancers, tend to show diffuse cell loss under NAST, there have been concerns regarding the safety of the “no ink on tumor” after NAST [22]. However, the safety of “no ink on tumor” has been demonstrated for BCS after NAST: In a single-center cohort of 382 patients undergoing NAST and subsequent BCS, no significant differences in OS, DFS, and LRFS were observed for different margin widths (>2 mm, 1–2 mm, <1 mm) [34]. To avoid secondary surgical procedures, several intra-operative margin assessment techniques exist to identify positive margins immediately, e.g. gross inspection [35], intra-operative ultrasound [36], margin shaving

[37], specimen radiography [38], and frozen sections [39]. Few of these procedures have been specifically evaluated for the use after NAST. For specimen radiography, evidence suggests less accurate assessments after NAST compared to the primary surgery setting (sensitivity 36.8% vs. 19.2%, specificity 86.8% vs. 89.2%) [38,40].

Although the safety of "no ink on tumor" for BCS after NAST has been demonstrated, some evidence suggests that the accuracy of intra-operative margin assessment to reduce secondary re-excisions might be impaired after NAST. Future research should focus on improving intra-operative margin assessment after NAST.

5) Socio-economic disparities in the use of breast conserving therapy

So far, we discussed technical and clinical uncertainties associated with BCT after NAST. However, in reality, socio-economic disparities on a patient and on a national level affect the use of BCT, too. A large evaluation of the National Cancer Database in the US from 1998 to 2011 (n = 727,927), revealed several patient-level, non-clinical factors to be associated with the use of BCT. Use of BCT was higher in patients with the highest level of education (OR 1.16, 95% CI 1.14–1.19), aged 50 years compared with younger patients (OR 1.14, 95% CI 1.12–1.15), treated in academic cancer programs compared with community programs (OR 1.13, 95% CI 1.11–1.15), and for patient residence within 28 km of a treatment facility compared with further away (OR 1.25, 95% CI 1.23–1.27). Use of BCT was lower in patients with the lowest median income (OR 0.92, 95% CI 0.90–0.94) [18]. These findings suggest that travel distance and low income, as a surrogate for patient ability or willingness to undergo BCS followed by radiotherapy, pose a relevant barrier to the receipt of BCT; patients without access to radiotherapy or for whom a longer time away from work is not acceptable economically, will opt for mastectomy, which has been demonstrated in other studies as well [41–43]. On a health system level, lower rates of BCT are observed in countries with scarce radiotherapy coverage and high rates of late-stage diagnosis. For example, in China, the rate of BCT is only about 10% compared with 60% in the US [18,19,44]. Lastly, observations that low income is associated with higher mastectomy rates are consistent with increased costs associated with NAST and radiotherapy [18]. Offering targeted financial support to patients at high risk of experiencing financial toxicity may help eliminating costs as a barrier to receive BCT.

In addition to clinical factors, socio-economic and psychological factors influence the use of BCT. Lacking access to multidisciplinary high-quality care is a major barrier to receive BCT.

6) Shared decision-making

The final treatment plan is determined during a shared-decision making process between the individual patient and the clinical care team, taking into account patient preferences and clinical counseling. The shared-decision making process can be a source of major biases if not adequately addressed by patients and clinicians. The findings of the National Cancer Database analysis mentioned above reflect the observation of increasing rates of contralateral prophylactic mastectomy in recent years, especially in younger patients, despite lack of survival benefit and increased surgical complications [45,46]. Although patient preferences are an important part of modern value-based health care and shared decision-making, it is also well-established that physicians with insufficient knowledge about risks of breast cancer recurrence offer prophylactic mastectomy more frequently. In addition, patients are much less likely to undergo a procedure if discouraged by their physician [47,48].

Overestimation of local recurrence risks in breast cancer occurs frequently: a cross sectional survey in Holland evaluated the average overestimation risk of individual local recurrence across different clinical professions; the average overestimation risk ranged from 15% (general practitioner, radiologist) to 3% (medical oncologist) [49]. Overestimation of local recurrence likely leads to higher patient anxiety levels which is a known risk factor for patients to opt for more aggressive treatment even when it is medically not beneficial. For example, among breast cancer patients eligible for BCT, those with high anxiety levels at the time of diagnosis are 9 times more likely to undergo unilateral or bilateral mastectomy compared to patients with low anxiety (37.3% vs. 18.3%; likelihood ratio 9.15; p = 0.002) [50].

Another emerging source of patient anxiety and lack of standardized clinical counseling is the clinical management of germline mutations. Prophylactic mastectomy is offered to women with BRCA1/2, PALB2, and TP53 mutations due to observed lifetime risks for breast cancer of 40–80% [51,52]. It must be noted, however, that the survival benefit of prophylactic mastectomy is substantial among young mutation carriers (age 25 years) but decreases rapidly when prophylactic surgery is performed later on [53]. These findings are likely linked to observations that BCT compared to mastectomy in BRCA mutation carriers already diagnosed with breast cancer results in equivalent risks of contralateral breast cancer, disease recurrence, and death (n = 3807, median follow-up 92 months) but increased risks of local recurrence after 15 years in patients treated with BCT (HR 4.19, 95% CI: 2.79–6.31, P < 0.001). Indeed, these findings would indicate an increased risk of secondary breast cancers rather than actual local recurrences [54].

While the clinical management of patients with high-risk germline mutations (BRCA1/2, PALP2, TP53, lifetime risk 40–80%) remains a challenge, local therapy discussions around low-risk germline mutations (ATM, BARD, RAD51C/D, CHEK2, lifetime risk 12–30%; general population risk 12%) may be even more confusing [51,52]. Treatment implications, either surgical or systemic ones, are unclear. However, increasing numbers of such low-risk mutations are reported in multigene panels, potentially leading to patient anxiety and insufficient counseling in clinical routine.

Behavioral science approaches have been suggested to help patients and clinicians understand their biases when opting for more aggressive treatment than justified by medical evidence [55]. Besides the awareness of psychological biases, the use of modern risk assessment tools may help to improve shared-decision making. The INFLUENCE nomogram, which is approved as medical device, is a risk assessment tool that allows accurate predictions of local recurrence for individual breast cancer patients based on 13,000 patients treated in the Netherlands [56]. Similar tools are currently developed for patients undergoing cancer-related mastectomy and breast reconstruction with respect to accurate predictions of patient-reported quality of life after surgery to facilitate individualized, informed decision-making [57,58].

In addition to clinical and socio-economic factors, psychological factors influence the use of BCT. Overestimation of local recurrence and increased patient anxiety during the shared decision-making process are a major barrier to receive BCT.

3. Solutions for the underuse of breast conserving therapy after neoadjuvant systemic treatment

We identified clinical and non-clinical causes for the underuse of BCT after NAST: uncertainties within the community regarding oncologic outcomes, the correct tumor localization after NAST, the management of multifocal and multicentric tumors, margin assessment, disparities of socio-economic aspects on a patient and national level, and psychological biases affecting the shared decision-making process between patients and clinicians.

Solutions to mitigate the underuse of BCT after NAST are illustrated in Fig. 1 and include.

1) Interdisciplinary teams that keep the whole patient pathway in mind.

BCT demands high interdisciplinary efforts from a multidisciplinary team. The multidisciplinary care team should consist of radiologists, surgeons, radiotherapists, medical oncologists, pathologists, specialized

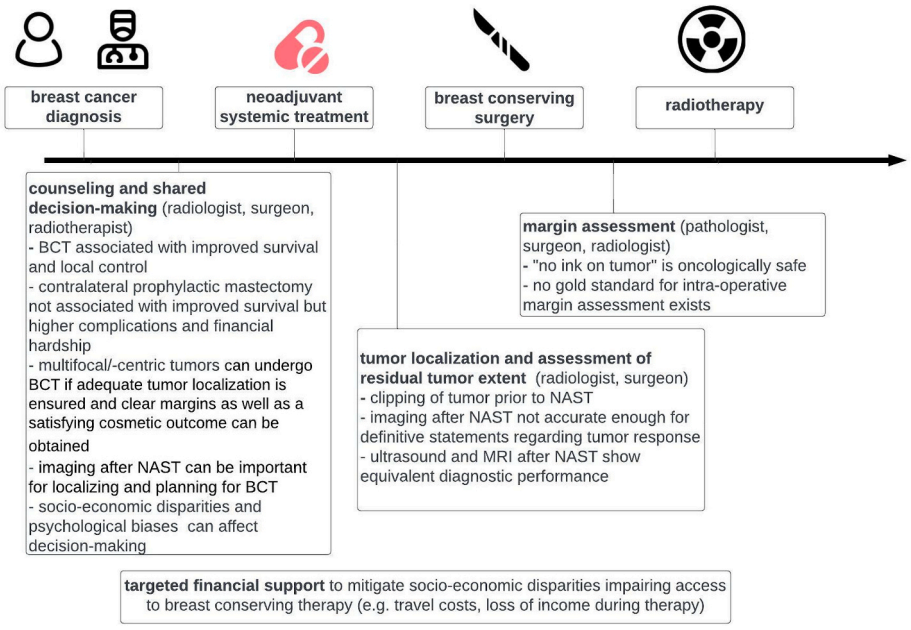

Fig. 1. Ideal patient pathway to enable breast conserving therapy after neoadjuvant systemic treatment.

nurses, psychologists, and administrative support staff. It is highly relevant to keep the whole patient pathway in mind during multidisciplinary care (e.g. clipping of all relevant tumor foci prior to NAST to enable BCS). The "Toolbox" initiative aims to provide detailed guidance for the multidisciplinary treatment team at all stages of the patient journey at a more granular level than clinical guidelines can ensure [59]. Such initiatives may help overcoming uncertainties in increasingly complex patient pathways.

2) Optimized treatment counseling and shared decision-making

As illustrated above, the uncertainties associated with BCT after NAST (within the clinical and patient community) in terms of oncologic outcomes, tumor localization, multifocality/-centricity, and margin assessment are evidently not justified. Clinicians must keep in mind that socio-economic and psychological biases (including patient anxiety due to insufficient counseling) can affect the shared decision-making process on both sides.

3) Financial support to mitigate disparities

Providing targeted financial support to mitigate socio-economic disparities on both, patient and national level, may help improving access to BCT (especially with respect to radiotherapy and early-stage diagnosis).

4. Outlook

BCT requires complex, multidisciplinary teamwork. Current research focusing on important interdisciplinary intersections of BCT (i.e. tumor localization and margin assessment) may help to reduce the complexity and facilitate easier implementation of tailored treatment after NAST. First, innovative strategies for intra-operative margin assessment via confocal laser scanning microscopes are currently evaluated, which may reduce the number of secondary re-excisions [60,61]. Second, machine learning algorithms have demonstrated potential to identify patients at high risk of experiencing financial toxicity during the course of their breast cancer treatment, which may enable targeted financial support [62]. Third, the concept of an intelligent vacuum-assisted biopsy recently opened new ways for tumor localization and response assessment to NAST by reliably identifying patients without residual cancer, which may enable the omission of breast and axillary surgery for these patients [63,64].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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