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Original Research

Impact of neoadjuvant chemotherapy and pathological complete response on eligibility for breast-conserving surgery in patients with early breast cancer: A meta-analysis

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Abstract ***Purpose:*** We conducted a meta-analysis of randomised trials evaluating pathological complete response (pCR) and surgical outcomes after neoadjuvant systemic therapy (NST) in patients with early breast cancer (EBC).
Patients and methods: The primary outcome was breast-conserving surgery (BCT) rate. Secondary outcomes were pCR rate and association to BCT. Meta-analyses were performed using random effects models that use inverse-variance weighting for each treatment arm based on evaluable patients. Point estimates are reported with 95% confidence interval (CI), and $p < 0.05$ was considered statistically significant.
Results: Thirty-six studies were identified (N = 12,311 patients). We selected for the analysis 16 of 36 studies reporting both pCR and BCT for at least one treatment arm. Arms per study ranged from one to six; 42 independent units were available to evaluate the association between pCR and BCT. BCT rate ranged 5–76% across arms with an average BCT of 57% (95% CI 52–62%). Significant heterogeneity was observed among the trials (Cochrane Q = 787, $p < 0.001$, $I^2 = 97\%$). In the meta-regression model, BCT rates were not

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significantly associated with year of first patient-in (p = 0.89), grade (p = 0.93) and hormone-receptor status (p = 0.39). Clinical N-stage (p = 0.01) and human epidermal growth factor receptor (HER2) status (p = 0.03) were significantly associated with BCT. pCR rate ranged 3–60% across studies. The average pCR across all study arms was 24% (95% CI 19–29%). No association was observed between pCR rate in a study arm and the resulting BCT rate in a univariate model (p = 0.34) nor after adjusting for HER2 and clinical nodal status (p = 0.82). In the subset of 14 multi-arm studies, no significant association was seen between the differences in pCR and BCT between treatment arms (p = 0.27).
Conclusions: pCR does not increase BCT in patients receiving NST for EBC.

1. Introduction

Neoadjuvant systemic therapy (NST) achieves equivalent local recurrence, disease-free and overall survival outcomes as compared with adjuvant therapy in early breast cancer (EBC) [1,2]. Therefore, the neoadjuvant approach is an effective option, especially in BC subtypes with a clear indication to systemic therapy, such as human epidermal growth factor receptor 2 (HER2)–positive cancer and triple-negative breast cancer (TNBC) [3,4]. The main advantage of NST over adjuvant treatment is to provide active systemic treatment while surgically downstaging the cancer at presentation. NST often converts operable patients who were deemed not surgical candidates at the time of their diagnosis, as well as allows for breast-conserving surgery (BCT) in some patients initially considered candidates for mastectomy only [5]. In addition, NST offers the advantage of real-time assessment of sensitivity of the tumour to systemic therapy, along with the theoretical benefit of eradicating micrometastatic disease [6]. A major advantage in administering NST is that patients who achieve a pathological complete response (pCR) have an improved prognosis for long-term survival, especially those with HER2-positive and TNBC disease [5–8].

NST effect on surgical options varies according to the volume of disease at presentation, response to treatment both invasive and *in situ* disease, tumour subtype, pre- and post-NST imaging and clinical assessment and patient/surgeon preferences. In women, already candidates for breast conservation at diagnosis, NST may decrease the volume of surgical resection and/or axillary surgery. The ability of NST to downstage the axilla is becoming an increasingly important factor in proceeding with this approach as axillary dissection may be avoided in some patients who were initially N1 before the onset of NST. For those converted to clinical N0, sentinel node biopsy with or without radiation may be considered. Not all patients can be downstaged to BCT in the setting of NST; women with multicentric disease or diffuse suspicious microcalcifications suggestive of ductal carcinoma *in situ* should undergo mastectomy, and the patient may prefer a mastectomy or choose mastectomy and contralateral mastectomy for risk of hereditary BC. We postulate that pCR can be considered a surrogate for consideration of BCT.

More than two decades ago, many randomised and non-randomised prospective studies showed that NST allowed for BCT in some patients initially considered candidates for mastectomy only [2,9–15]. Based on various regimens and different eligibility criteria, between 13% and 83% of patients enrolled in different trials underwent BCT instead of mastectomy. Recently, the Early Breast Cancer Trialists' Collaborative Group published a meta-analysis of individual patient data from ten randomised trials with the aim of looking at long-term outcomes for neoadjuvant versus adjuvant chemotherapy in EBC [16]. Trial entry year for participants was 1983–2002. In this meta-analysis, patients treated with neoadjuvant chemotherapy (NACT) had an increased frequency of BCT as compared with patients treated with adjuvant chemotherapy (65% versus 49%, respectively) [16].

Despite the improvements in systemic therapies (including chemotherapy and targeted agents), several recent trials have shown lower rates in BCT than those in the past decade [17–20]. Surprisingly, the higher pCR rate achieved with new therapies did not translate into a higher rate of BCT. Therefore, there are factors besides response and eligibility for BCT that lead many patients to undergo mastectomy. The aim of the present study is to perform a meta-analysis of surgical outcomes in the context of prospective randomised neoadjuvant studies, identifying potential factors affecting the rate of BCT.

2. Patients and methods

2.1. Search strategy and selection criteria

We performed this meta-analysis in accordance with PRISMA guidelines [21].

To identify relevant studies, we searched Embase, MEDLINE (OvidSP), Web of Science, Scopus, PubMed Publisher, Cochrane and Google Scholar from 01