Letter to the editor on ‘Factors associated with surgical management following neoadjuvant therapy in patients with primary HER2-positive breast cancer: results from the NeoALTTO phase III trial’

Criscitiello et al. [1], reporting on the NeoAdjuvant Lapatinib and/or Trastuzumab Treatment Optimization (NeoALTTO) trial, elegantly analyse multiple factors which might account for why high objective clinical tumour response and pathological complete response (pCR) rates did not translate into higher breast-conserving surgery (BCS) and correspondingly lower mastectomy rates.

First, no information on baseline (i.e. pre-study) BCS rates for the recruiting centres was provided. As nearly half (46%) of the patients were treated in developing countries [1], lack of optimal radiotherapy resources was proposed as a possible contributory factor but this seems unlikely, as participation in NeoALTTO [2] would require an adequate radiotherapy service. However, lack of access could have influenced patients’ choices.

An additional factor was thought to be lack of multidisciplinary meetings implying surgical decision-making without dialogue between the radiology, oncology and surgical teams and regardless of clinical tumour response.

Many surgeons claim that excising the original tumour bed, i.e. the ‘footprint’ present before chemotherapy, with a margin is mandatory, on the basis of historic pre-trastuzumab studies demonstrating HR-ve, HER2+ tumours to have the highest local recurrence (LR) rates [3]. The use of targeted anti-HER2 therapy in combination with cytotoxics (especially taxanes) has mitigated the LR increase [4] although long-term data are still lacking.

Furthermore, there may be reluctance among surgeons to employ oncoplastic BCS techniques due to paucity of literature specifically addressing oncological safety in the neoadjuvant setting [5]. In developing countries, limited numbers of specialist breast surgeons and unfamiliarity with oncoplastic BCS techniques by general surgeons may be relevant.

In NeoALTTO, the mismatch between radiological response and extent of surgery may reflect the presence of DCIS beyond the invasive component. For the purposes of randomisation, T status is determined by the extent of invasive disease so any associated DCIS cannot be easily controlled for. While it is well recognised that anti-HER2 regimes including trastuzumab can cause regression of associated HER2+ DCIS, micro-calciﬁcations remain unchanged [6]. Perhaps final surgery was determined by the extent of micro-calciﬁcations rather than invasive tumour response. Despite pCR (deﬁned in NeoALTTO as complete disappearance of invasive tumour), the reason for mastectomy was possibly residual DCIS.

The disconnect between tumour response and final surgery is also exempliﬁed by the 25.8% conversion to mastectomy (n = 33) when BCS was planned at diagnosis, despite progressive disease by imaging criteria being documented in only 11 patients. Perhaps some of these patients had lobular histology (n = 17, all of whom ended up with mastectomy) and were incompletely staged at initial assessment (possibly due to lack of MRI access). Similarly, 75% of patients with multifocal/multicentric tumours at baseline who assessment underwent mastectomy (n = 36) may never have had surgical down-staging as the intended outcome.

For lobular histology, pCR rates are variable ranging from zero [7] up to 50% when adjusted for molecular subtypes such as HR-ve, HER2+ [8]. Clinician/surgeon scepticism regarding the utility of neoadjuvant therapy for lobular disease may account for the 100% mastectomy rate seen.

ER-negative status seemed to predict an increased likelihood of mastectomy even when controlled for all other known tumour factors. Paradoxically, as the authors note, this is despite a higher pCR rate for ER-veHER2+ [8]. Clinician/surgeon scepticism regarding the utility of neoadjuvant therapy for lobular disease may account for the 100% mastectomy rate seen.

ER-negative status seemed to predict an increased likelihood of mastectomy even when controlled for all other known tumour factors. Paradoxically, as the authors note, this is despite a higher pCR rate for ER-veHER2+ [8]. Clinician/surgeon scepticism regarding the utility of neoadjuvant therapy for lobular disease may account for the 100% mastectomy rate seen.

Finally, there is no mention of patient preference for mastectomy. Patient choice may not always relate to treatment response and should be recorded prospectively in all such trials where an end point is BCS rate.

Regular dialogue between pathology, radiology, oncology and surgical teams either in MDM’s or dedicated joint neoadjuvant clinics is crucial to optimise extent of surgery without compromising local control.

P. A. Barry1,2*, G. Schiavon1,2 & F. A. MacNeill1

1Breast Unit, The Royal Marsden NHS Foundation Trust, London;
2The Institute of Cancer Research, London, UK
(*E-mail: peter.barry@icr.ac.uk)

disclosure

The authors have declared no conflicts of interest.
Factors affecting surgical management following neoadjuvant therapy in patients with primary HER2-positive breast cancer: results from the NeoALTTO phase III trial

We thank Berry et al. [1] for their interest in our work. As we have mentioned in our manuscript [2], lack of radiotherapy services or multidisciplinary discussions in some centers participating in our study could partly explain the discordance between the high pathologic complete response (pCR) rates observed and the higher rates of breast conserving surgery (BCS) [3]. We also recognize that a multidisciplinary approach may be conducted differently in different countries, although the difference might be minor for patients within clinical trials. Unfortunately, besides observing these data, it is not possible—to date—to prove the reasons that might have influenced surgeons when deciding on the type of surgery. Hence, we thank Berry et al. for their speculations regarding such reasons.

We completely agree with Berry et al. on the potential causes they stated regarding the discordance between high pCR rates and low BCS rates including the presence of residual ductal carcinoma in situ (DCIS) component, presence of microcalcifications, and lobular component with multifocal/multicentric tumors. The authors also referred to the lack of MRI access as baseline staging as a reason for low BCS rates. However, we highlight the evidence supporting that the use of preoperative MRI has resulted in increasing mastectomy rates [4–7]. So, we are not sure that implementing routine MRI in our study would have resulted in increased breast conservation.

Another important issue is the lack of data on patients’ preference regarding surgical extent that was not prospectively collected within the NeoALTTO trial. This is indeed a limitation and since breast conserving rates are among the secondary end points of the study, prospective collection of patient choices should have been considered. With the advances in breast reconstruction evolving role of prophylactic mastectomies, capturing patients’ preferences could have refined our understanding to the factors associated with surgical management in our study.

Regarding the use of oncoplastic techniques that could eventually increase the BCS rates after neoadjuvant treatments, no data were gathered on what type of BCS was carried out and if oncoplastic procedures were done. Patients who do not respond to neoadjuvant treatments or have T3 tumors after neoadjuvant therapy have an increased risk of local recurrence (LR) [8], so even with the use of oncoplastic techniques, we consider that the main problem is the assessment and the correlation between the pre- and post-treatment in the surgical decision-making after neoadjuvant treatment.

Finally, Berry et al. stated on how the surgeon perception of historical data regarding the high rate of local recurrence in patients with ER+ HER2– play a vital role in their decision. This represents the core of the message that we convey which is the importance of discussions between different disciplines and clarification on how advances in systemic therapy have improved treatment outcome. This would call for revisiting the indications of mastectomy in these patients.

C. Criscitiello1*, H. A. Azim2, E. de Azambuja2 & I. T. Rubio3
1Department of Medical Oncology, Istituto Europeo di Oncologia, Milan, Italy
2ReEAST Data Centre and Department of Medicine, Clinical Oncology, Brussels, Belgium
3Breast Surgical Oncology Unit, Universitario Vall D’Hebron, Barcelona, Spain

(*E-mail: carmen.criscitiello@ieo.it)

disclosure
EdA received a travel grant from GlaxoSmithKline and Roche. ITR received honoraria from Myriad. All remaining authors have declared no conflicts of interest.

references