We note the discussion generated by Vaidya *et al*[1] following their recent article, and agree such issues should be debated openly and scientifically. They suggest that neoadjuvant chemotherapy to treat breast cancer is an over-utilised treatment modality, and that this approach should be reduced. While the authors raise some valid considerations around this subject there are several issues around the surgical management of these patients which merit further review.

The authors’ comment that avoiding surgical excision of the original tumour bed in patients with an apparent pathological complete response (pCR) leads to higher local recurrence illustrates the importance of correctly defining response to treatment. In these studies pathological response was not assessed and surgery omitted on the basis of clinical/radiological assessment of response to treatment. However, these are inaccurate tools with which to determine pathological response, with accuracy reported as ranging from 54-80%[2]. Although MR imaging in these patients has greater sensitivity than other modalities for predicting pCR, there currently remains no tool to predict pCR with sufficient accuracy to safely omit surgery following neoadjuvant chemotherapy[3]. It is not realistic to classify patients having no surgery to the pCR group, as a proportion will not in fact have had pCR - hence the increased LR rate seen in these patients. As McPherson et al correctly acknowledge, when these patients are excluded in the EBCTCG meta-analysis there is an absolute increase of only 3.2% in local recurrence rates[4]. Ongoing studies are evaluating the ability of tumour bed biopsies to predict pCR, in both the US [5] and in the UK with the Pre-NOSTRA trial. It is possible that this approach may identify patients where surgery can potentially be safely omitted, although this is not acknowledged by Vaidya *et al*. However, this approach will require robust evaluation in prospective clinical trials prior to its use in clinical practice.

Surgery following neoadjuvant chemotherapy may indeed be technically more difficult as it involves the excision of impalpable disease - however, other breast cancers, including in situ disease, treated with primary surgery may also be impalpable and can be successfully treated with breast conserving surgery. This is not an argument for primary surgery for all, but rather for good multidisciplinary working in neoadjuvant setting, to allow pre-treatment marking of tumours with accurate localisation of marker clips and painstaking pathological assessment of margins, and surgical re-excision where appropriate. In their response to comments, Vaidya *et al* comment that surgical precision is difficult, and this is true, but is applicable to many surgical situations apart from this context. Furthermore, the technical difficulty of axillary dissection is not determined by the palpability of lymph nodes as this procedure is an *en bloc* dissection, which does not rely on the palpation and removal of individual lymph nodes. However, it can be influenced by regression of disease and scarring within nodes and the axilla. It is important to note that there may be a differential response to neoadjuvant chemotherapy in the breast and axilla, with complete resolution of nodal disease being seen in 42% of patients without a breast pCR and 89% of those with a breast pCR[6]. This suggests that there may well be patients in whom axillary conservation can be considered, although we concur that this will also require evaluation in randomised trials.

The POSH study does not demonstrate a survival benefit from bilateral mastectomy within 1 year of diagnosis [7], but to suggest that knowing BRCA status would not benefit this patient group is to miss a key point of mutation testing during neoadjuvant chemotherapy, which is to further inform surgical decision-making. Importantly, BRCA negative patients may be reassured, and BRCA mutation carriers may opt for early bilateral mastectomy following neoadjuvant chemotherapy to possibly allow avoidance of radiotherapy or to allow bilateral DIEP flap reconstruction.

The caveat that patients should be informed of the risk of non-response applies to all patients treated with neoadjuvant chemotherapy, and not just this subgroup. Where randomised studies have shown that sequencing of chemotherapy and surgery does not influence overall survival it is entirely conceivable that those who progress on neo-adjuvant chemotherapy would also fare poorly with adjuvant therapy. The lack of differential seen in overall survival between the two approaches does not support the concept that resistant clones are more likely to develop with neo-adjuvant therapy. Furthermore, neoadjuvant treatment provides additional information regarding chemosensitivity that can not be obtained after surgery, and we are only now beginning to understand how to exploit this to the advantage of our patients. Pathological response toneoadjuvant treatment may prove a valuable selection tool for the application of more aggressive post-operative treatment, and may identify groups who can benefit from additional adjuvanttherapy {Masuda, 2017} . As Vaidya and colleagues point out in their response to discussion, therethere is currently limited evidence that response-adapted neoadjuvant therapy is associated with improved outcomes {von Minckwitz, 2013}, our ability to fine tune treatment selection based upon response has to date been inadequately explored, but is an area of active interest, and needs to be throughly explored in well-designed prospective studies.

The approach of using neoadjuvant treatment for breast cancer should certainly be examined critically, and the benefits and risks, including the apparent elevated risk of local recurrence, discussed with patients. A small increase in local recurrence risk in the absence of a survival disadvantage may be acceptable to some patients in the context of potentially downstaging surgery, and indeed this is the premise on which breast conservation is based.

It is certainly true that, whilst pCR rates have increased with the development of systemic therapies, these have not necessarily yet translated into similar increases in breast conservation[8], and further work is required to address this. Both clinical treatment and trials are best delivered in a multidisciplinary fashion and surgical endpoints should be well defined and given due prominence in clinical trials of novel agents in the neoadjuvant setting, in order to assess how best to translate improvements in pCR into increased rates of breast conservation whilst minimising local recurrence rates and optimising oncological outcomes. As ever, there will be no “one size fits all” treatment for breast cancer and the focus should be on optimising patient selection for neoadjuvant treatment and refining the multidisciplinary management of this patient group (radiological, surgical and pathological), in the context of a better understanding of tumour biology. This is preferable to indiscriminately disregarding a treatment approach likely to have significant benefit for a proportion of patients.

Stuart A McIntosh

Clinical Senior Lecturer in Surgical Oncology, Queen’s University Belfast

Ramsey I Cutress

Associate Professor in Breast Surgery, University of Southampton

Professor Malcolm Reed,

Dean, Brighton and Sussex Medical School

Professor Dan Rea,

Professor of Medical Oncology, University of Birmingham

Chair, NCRI Breast Clinical Studies Group.

1. Vaidya, J.S., et al., *Rethinking neoadjuvant chemotherapy for breast cancer.* BMJ, 2018. **360**: p. j5913.

2. Croshaw, R., et al., *Accuracy of clinical examination, digital mammogram, ultrasound, and MRI in determining postneoadjuvant pathologic tumor response in operable breast cancer patients.* Ann Surg Oncol, 2011. **18**(11): p. 3160-3.

3. Fowler, A.M., D.A. Mankoff, and B.N. Joe, *Imaging Neoadjuvant Therapy Response in Breast Cancer.* Radiology, 2017. **285**(2): p. 358-375.

4. Asselain, B., et al., *Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials.* The Lancet Oncology.

5. Kuerer, H.M., et al., *A Clinical Feasibility Trial for Identification of Exceptional Responders in Whom Breast Cancer Surgery Can Be Eliminated Following Neoadjuvant Systemic Therapy.* Ann Surg, 2017.

6. Tadros, A.B., et al., *Identification of Patients With Documented Pathologic Complete Response in the Breast After Neoadjuvant Chemotherapy for Omission of Axillary Surgery.* JAMA Surg, 2017. **152**(7): p. 665-670.

7. Copson, E.R., et al., *Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study.* The Lancet Oncology.

8. Criscitiello, C., et al., *Breast conservation following neoadjuvant therapy for breast cancer in the modern era: Are we losing the opportunity?* Eur J Surg Oncol, 2016. **42**(12): p. 1780-1786.