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EDITORIAL COMMENTARY

MRI and ^{18}F-FDG PET/CT in monitoring the response to neoadjuvant chemotherapy: is it necessary to appropriately select the patients?

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Neoadjuvant or preoperative chemotherapy (NAC) is considered the standard of care in the treatment of locally advanced breast cancer [1]. Its potential benefits include: (1) reduction in size of the primary tumour allowing conversion of mastectomy candidates to breast-conserving surgery candidates; (2) reduction in lymph node involvement allowing to conversion of patients requiring axillary dissection to candidates for sentinel node biopsy; (3) testing of tumour chemosensitivity to allow changes in therapy regimen, if needed; (4) correlation between achievement of a pathological complete response (pCR) on NAC completion and long-term prognosis; and (5) assessment of molecular changes during NAC as a means to assess response to specific chemotherapy and to discover of future possible drug targets [2]. Therefore, monitoring tumour response to NAC is useful from a clinical, diagnostic and prognostic point of view. It is usually evaluated by clinical and conventional imaging modalities, such as mammography and/or ultrasonography, although these are unreliable and inaccurate tools. There is evidence that contrast-enhanced MRI could be superior to standard clinical assessment methods in determining the prognostic response to NAC [3, 4]. Conversely, in recent years the role of PET/CT with ^{18}F-FDG in this setting has been the main end-point of many studies [5–7], but its utility should still be the subject of investigation. Moreover, breast cancer includes several molecular entities that differ in clinical behaviour, biological characteristics and outcome [8–10]. It is typically differentiated into three groups (basal-like or triple-negative, HER2-enriched, and luminal A and B) that are widely correlated with different response rates to NAC.

The study by Pengel et al. [11], published in the present issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, addresses the complementary role of MRI and PET/CT for the evaluation of response to NAC in 93 patients with locally advanced breast cancer. The authors evaluated the correlations among response to NAC, MRI and PET/CT parameters in this population of patients [11].

A recent meta-analysis by Houssami et al. [2] showed that different breast cancer subtypes show different pCR rates: positive for hormone receptor (HR)/HER2-negative 8.3 %, HER2-enriched/HR-positive 18.7 %, triple-negative 31.1 %, and HER2-enriched/negative HR-negative 38.9 %. These findings have clinical, biological and research implications: firstly, they can help clinicians select appropriate candidates for NAC versus adjuvant therapy; secondly, the majority of HR-positive/HER2-negative tumours are generally resistant to chemotherapy and therefore alternative approaches to treatment are necessary. This latter point suggests an interesting role for metabolic and functional imaging modalities to select appropriate candidates for NAC.

To date, four published studies have shown a correlation between MRI findings and response to NAC based on different breast cancer subtypes. Chen et al. [12] evaluated the predictive accuracy of MRI after NAC based on overexpression of HER2 and demonstrated that HER2-negative tumours have a high false-negative rate (6 out of 33 patients, 18 %). In the majority of patients (4/6, 66 %), nonmass-like enhancement was found on MRI. HER2-negative and HR-positive cancers and lesions showing nonmass-like enhancement are more likely to show residual disease as small foci or scattered cells after NAC, leading to underestimation of the extent of residual disease on MRI, and the diagnostic results of MRI should be used with caution in surgical planning [12]. The second study investigated the differences in MRI features

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between oestrogen receptor (ER)-negative and ER-positive breast cancers, but it was inconclusive about how accurate MRI is in detecting response of such tumours to NAC [13]. Loo et al. [14] found that the changes in MRI during NAC correlate well with pathology outcome in triple-negative and HER2-enriched tumours, but not in ER-positive/HER2-negative tumours. Finally, McGuire et al. [15] showed that MRI is significantly more likely to underestimate residual tumour size of luminal tumours than of triple-negative or HER2-enriched tumours after NAC.

Zucchini et al. [16] found that PET sensitivity for detecting pathological response to NAC was 100 %, although the highest specificity was found in ER-positive tumours. They concluded that PET has a role as an early marker of pCR in certain breast cancers with a high proliferative index such as triple-negative disease. Humbert et al. [6] found that the early metabolic response to NAC in HER2-enriched breast cancers is useful for differentiating responders from nonresponders. The aim of interim evaluation of response to NAC is to determine the possibility of switching to another effective therapy. On the contrary, evaluation of response to NAC at the end of therapy has an impact from a surgical point of view, being correlated with the surgical approach. Therefore, the benefits of PET/CT in the assessment of an early metabolic response to therapy can be translated into an advantage in therapeutic management. MRI could be useful for planning an appropriate surgical treatment, particularly in highly proliferative tumours.

As found by Pengel et al. [11], in ER-positive/HER2-negative tumours, (near) pCR is never achieved with relative reductions in SUVmax on PET/CT of less than 40 %, independent of the reduction in largest tumour diameter on MRI. Conversely, in triple-negative tumours, (near) pCR is related to relative reductions in SUVmax on PET/CT as well as relative reductions in largest diameter of initial and late enhancement on MRI. In multivariable analysis, both relative reduction SUVmax on PET/CT and largest diameter of late enhancement on MRI are independent predictors of (near) pCR, although the latter shows an association with higher statistical significance (OR 0.970, p=0.047, and OR 0.974, p=0.006, respectively). Data from the literature on the relationship between MRI parameters and response to NAC in breast cancer are discordant. The meta-analysis of Prevos et al. [17] showed that tumour diameter and volume on MRI cannot be used to differentiate between final responders and nonresponders to chemotherapy. In contrast, several studies have shown that observed changes in tumour diameter and/or volume after the first cycles of NAC are statistically significant and might help differentiate between these patient groups [18–21]. Loo et al. [22] suggested a diameter reduction of 25 % as a cut-off value between MRI examinations at baseline and at first follow-up. This large heterogeneity can be explained by the selection of patients, the majority of whom have invasive ductal cancer, invasive lobular cancer or mixed cancer and variable expression of hormone and HER2 receptors. In these different breast cancer subtypes, early and late responses to NAC may be overestimated or underestimated depending on the pattern of enhancement on MRI, such as mass-like or nonmass-like.

Pengel et al. [11] found that SUVmax on interim PET/CT and relative change in SUVmax on PET/CT are significantly associated with (near) pCR. In particular, 36.2 % of tumours with a reduction in SUVmax ≥50 % had a residual disease on pathology, which decreased to 26.3 % if a cut-off of ≥80 % reduction in SUVmax was used. SUVmax as a semiquantitative value was considered by the authors a reproducible parameter justifying its use for the evaluation of NAC response. To date, no homogeneity data are available for SUVmean, total lesion glycolysis (TLG), metabolic tumour volume (MTV) and other parameters for the assessment of response to NAC by PET. The majority of studies [7] have used SUVmax alone. On the contrary, a few studies have shown correlations with semiquantitative parameters other than SUVmax, including SUVmean, SUVavg, SUVpeak [7], TLG and MTV [5, 6],. Smith et al. [23] and Li et al. [24] used the dose uptake ratio and the tumour/normal uptake ratio, respectively, as semiquantitative PET measures. Tateishi el al. [25], in 142 patients who underwent quantitative PET/CT and dynamic contrast-enhanced-MRI at baseline and after two cycles of NAC, found that the %SUVmax, $\%K_{ep}$ and $\%AUC_{90}$ (the area under the time-intensity curve until over 90 s) were significant predictors of pCR. On the contrary, the predictive values of percentage change in longest diameter, %TLG, posttreatment K_{trans}, $\%K_{trans}$, posttreatment K_{ep} and posttreatment AUC_{90} did not reach statistical significance. This great variability, both in variables (i.e. SUVmax, TLG) and in threshold values for SUVs (ranged between 40 % and 88 % reduction) represents a great limitation to translating the clinical use of FDG PET/CT to the monitoring of the response to NAC, particularly when differentiation of response rates on the basis of breast cancer subtype is required.

Pengel et al. state that “a study involving monitoring of treatment response of lymph nodes and primary tumour using PET/CT and MRI may be an ideal setting to relate imaging findings to pCR” [11]. A future cost-effectiveness analysis is warranted because the association between two different and expensive methodologies should be justified. Can we consider referring for both MRI and FDG PET/CT only patients with an aggressive locally advanced breast cancer, such as a triple-negative or a HER2-enriched cancer? To date, no data about the cost-effectiveness of PET and MRI in the setting of NAC response is available. The findings of Schegerin et al. [26] on the cost of PET and MRI in breast cancer assessment were inconclusive. Conversely, the studies by Sloka et al. [27] and by Meng et al. [28] focused, respectively, on the cost-effectiveness of PET as compared axillary lymph node

dissection and on MRI and PET as compared to the assessment of axillary lymph node metastasis in patients with newly diagnosed early-stage breast cancer.

In recent years, neoadjuvant endocrine therapy has moved from being reserved for elderly and frail patients not considered candidates for chemotherapy to potentially being considered a primary therapeutic modality in selected patients, given the increasing evidence that NAC has a limited role in patients with ER-positive or progesterone receptor-positive, HER2-negative disease. PET/CT using radiopharmaceutical agents other than ^{18}F-FDG, such as ^{18}F-fluoroestradiol, will be able to determine the response to neoadjuvant endocrine therapy in patients with HR-positive/HER2-negative breast cancer more accurately than MRI. For this latter end-point, prospective comparative trials are necessary.

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