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Imaging performance in guiding response to neoadjuvant therapy according to breast cancer subtypes: A systematic literature review

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ABSTRACT

Monitoring therapeutic response to neoadjuvant chemotherapy(NAC) is likely to improve NAC effectiveness in breast cancer(BC). Imaging performance seems to vary per tumour subtype(by ER and HER2 status), therefore we performed a systematic review on subtype specific imaging performance in monitoring NAC in BC.

Abbreviations: BC, breast cancer; NAC, neoadjuvant chemotherapy; HER2, human epidermal growth factor 2; ER, oestrogen receptor; PR, progesterone receptor; TNBC, triple negative breast cancer; PET/CT, positron emission tomography computed tomography; pCR, pathologic complete response; PE, physical examination; US, ultrasound; MRI, magnetic resonance imaging; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; DW-MRI, diffusion-weighted magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating curve; AUC, area under the curve; QUADAS, quality assessment of diagnostic accuracy studies; TN, true negative; FN, False negative; TP, true positive; FP, false positive.

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Studies examining imaging performance in predicting pathologic complete response(pCR) during NAC in BC subtypes were selected. Per study, negative- and positive predictive value, sensitivity(se) and specificity(sp), AUC and accuracy were derived.
Fifteen/106 articles were included. Inter-study variability was revealed in: monitoring interval, response and pCR definitions. In ER-positive/HER2-negative BC, ^{18}1F FDG-PET/CT showed se/sp of 38%–89%/74%–100%, MRI showed se/sp of 35%–37%/87%–89%. In triple negative BC, ^{18}1F FDG-PET/CT showed se/sp of 0%–79%/95%–100%. ^{18}1F FDG-PET/CT showed in ER-positive/HER2-positive BC se/sp of 59%/80% and in ER-negative/HER2-positive 27%/88%.
Evidence on imaging performance in monitoring NAC according BC subtypes is lacking. Consensus should be reached in: definitions of pCR, response and monitoring interval before starting well-designed studies.

1. Introduction

In 2012, 1.7 million new cases of breast cancer were diagnosed worldwide. Despite research and improvements in breast cancer treatment, breast cancer is still: one of the most prevalent cancers overall, the most prevalent cancer among women, and one of the main causes of death (WHO, 2012). Research on new treatment approaches is thus of evident interest.

Neoadjuvant chemotherapy(NAC) showed to be at least equally effective as adjuvant chemotherapy (Mauri et al., 2005) while having additional advantages (Fisher et al., 1997; van der Hage et al., 2001), such as the ability to monitor therapeutic response during treatment (Gralow et al., 2008). Early therapeutic response assessed by imaging seems to be a predictor of pathologic complete response(pCR) (Marinovich et al., 2012), usually defined as absence of any residual invasive tumour cells in the original tumour bed and axilla (Kaufmann et al., 2006). PCR itself predicts long-term survival, especially in HER2-positive and triple negative(TN) tumours (Chollet et al., 2002; Von Minckwitz et al., 2012), monitoring early therapeutic response may be used to guide systemic treatment, which is called a response-guided NAC approach (von Minckwitz et al., 2013). Under this scenario, patients could be monitored after a specific number of NAC cycles, and according to their response at imaging, their further systematic treatment could be tailored, i.e. responders continue with the same initial treatment, and non-responders can be switched to a presumably non-cross-resistant regimen(Fig. 1) (von Minckwitz et al., 2013).

Currently, there is no definite guideline to assess response to NAC during treatment. Previous authors proposed physical examination plus mammography and ultrasound, but their performance seems to be limited (Yeh et al., 2005; Hamisa et al., 2015; Londero et al., 2004). Therefore, performance examination of more advanced techniques, i.e. magnetic resonance imaging(MRI) and PET—Computed Tomography(PET/CT) is of interest. So far, meta-analyses have shown sensitivities and specificities of 68% and 91% for dynamic contrast-enhanced(DCE)-MRI (Wu et al., 2012), 93% and 82% for diffusion-weighted(DW)-MRI (Wu et al., 2012) and 84% and 71% for ^{18}F FDG-PET/CT (Cheng et al., 2012) respectively. On the basis of these findings, MRI is currently the technique mainly used in clinical practice. While these techniques seem to already have better performance, recent studies have shown that breast cancer subtype affects imaging performance (Loo et al., 2011; Hayashi et al., 2013; Ko et al., 2013). Hence, personalizing the use of imaging techniques based on subtypes may further improve their performance in evaluating therapeutic response (Loo et al., 2011; Humbert et al., 2012).

As there is no subtype-specific guidance on imaging techniques to monitor therapeutic response during NAC to guide in further treatment regimen, this paper aims to create an overview of current knowledge on the performance of imaging techniques in breast cancer subtypes based on expression of ER and HER2.

2. Methods

We performed a systematic literature search to find studies reporting on the performance of imaging in assessing pCR during NAC for breast cancer subtypes.

2.1. Search strategy

For PubMed the terms: “breast cancer”(MeSH: Breast neoplasm); “imaging”(i.e. MRI, PET/CT); “outcome”(pathologic complete response, clinical response); “Neoadjuvant chemotherapy” and “breast cancer subtype”(oestrogen receptor(ER), progesterone receptor(PR), luminal, triple negative(TN) and human endocrine receptor 2(HER2)) were combined for the systematic search(Supplement 1). Snowballing was used to find additional relevant publications.

2.2. Selection criteria

The search was limited to studies written in English and published between January 2000 and March 2015. Case studies were excluded. Studies were included if performance data of the imaging technique(s) was reported: before and during NAC, specified to at least one receptor status(ER/HER2) and controlled with pCR as primary outcome. As secondary outcomes the neoadjuvant response index(NRI) (Rodenhuis et al., 2010) and residual cancer burden (Symmans et al., 2007) were accepted as response definition. Finally, studies using FDG-PET without CT were excluded, as this technology is no longer recommended in daily practice.

2.3. Data extraction

The first selection was performed based on abstract information and following the inclusion and exclusion criteria by two independent reviewers(AMC and ML). The selected studies were fully read by the same reviewers and were again assessed based on the inclusion and exclusion criteria. Disagreements were first discussed between the two reviewers, and if no agreement was reached, a third reviewer was approached(VR). For each article, the following items were extracted: author, sample size, study design, treatment regimen, breast cancer subtype, clinical stage, age, monitoring technique, cut-off value or response definition at imaging, interval time i.e. number of NAC cycles between baseline and response monitoring, technical settings, pCR definition: pCR or partial response, performance results, i.e. sensitivity, specificity, accuracy, negative and positive predictive values(NPV, PPV) and