Editorial

Routine use of preoperative breast MRI for patients considered for intraoperative radiotherapy

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Abstract: This editorial comments on the study by Tallet *et al*. which reported on the incidence of ipsilateral second breast cancers (BC) detected by preoperative magnetic resonance imaging (MRI) in patients being considered for intraoperative radiotherapy (IORT). Any second BC was detected in 7% of patients; an ipsilateral BC was detected in 4% of patients, precluding them from IORT. The authors comment that in view of detection of a substantial rate of ipsilateral BCs by preoperative MRI, this exam should be used routinely for staging patients being considered for IORT.

Keywords: Breast cancer (BC); magnetic resonance imaging (MRI); intraoperative radiotherapy (IORT); accelerated partial breast irradiation (APBI)

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In patients with early stage breast cancer (BC), breast conserving therapy with lumpectomy followed by whole breast irradiation (WBI), is considered the standard of care, resulting in equivalent survival compared to mastectomy alone (1-6). The Early Breast Cancer Trialists' Collaborative Group meta-analysis has shown that, compared to lumpectomy alone, the addition of WBI improves 5-year local recurrence from 26% to 7% and, for every four local recurrences prevented at 10 years, one death from BC is avoided at 15 years (7).

Standard adjuvant radiotherapy after lumpectomy generally includes 5- to 5.5-weeks (25- to 28-fractions) of WBI followed by a 5- to 8-fraction boost to the lumpectomy cavity, all delivered via external beam technique. Hypofractionated radiotherapy, also a standard for early stage BC, includes 3 weeks of WBI, often followed by a 5-fraction lumpectomy cavity boost. WBI eradicates microscopic disease within the lumpectomy cavity and remote to the index cancer (multicentric disease) (8). The boost gives further dose to the lumpectomy cavity to eradicate any residual disease at the lumpectomy cavity that may remain after surgical excision, as the majority of recurrences have been shown to occur at or in the area of the tumor bed (3,9-12).

The protracted nature of standard adjuvant radiotherapy is related to the WBI phase. Accelerated partial breast irradiation (APBI), or irradiation of only the region of the tumor bed, omits the WBI phase. APBI can be delivered over 1 day to 2 weeks, depending on the technique (high- or low-dose rate interstitial brachytherapy, external beam radiotherapy, or intracavitary intraoperative radiotherapy (IORT) via photons or electrons), thus, significantly shortening treatment time and potentially reducing health care costs. Furthermore, dose and toxicity to adjacent normal structures, including the heart, chest wall, and contralateral breast, may be reduced significantly by decreasing the volume of irradiated tissue. The majority of prospective trials that have investigated the replacement of WBI with APBI have demonstrated local control rates in the breast comparable to those observed after conventional WBI (13-16). Patient selection is key, and the American Society for Radiation Oncology has published consensus statements to guide patient selection criteria and best practices for the use of APBI outside of a clinical trial (17,18).

IORT, using 50-kV X-rays, is an attractive APBI

approach because it delivers the entire radiation treatment during surgery. The randomized IORT-APBI trial, TARGIT-A, reported that, in select patients, targeted IORT (TARGIT) concurrent with lumpectomy was non-inferior to WBI (16). The selection criteria included women ≥45 years old with invasive ductal carcinoma that was unifocal on examination and imaging. Magnetic resonance imaging (MRI) was not required, and only 5.6% of patients in the trial had an MRI performed. A risk-adapted approach was used, meaning that if unpredicted pre-specified adverse features were shown on final pathology report, WBI was added to TARGIT, in which case TARGIT served as the tumor bed boost. Fifteen percent of patients in the TARGIT arm received WBI due to adverse features noted on final pathology. At median follow-up of 2 years and 5 months, 5-year risk for local recurrence was 3.3% for TARGIT *vs*. 1.3% for WBI for all-comers. In the two thirds of patients in the prepathology stratum, i.e., when TARGIT was delivered during the initial lumpectomy, the risk of local recurrence was 2.1% *vs*. WBI 1.1% (P=0.31).

Patient selection is key when using the APBI approach for breast conserving therapy. Multifocality and multicentricity are exclusion criteria for APBI since non-index lesions could be outside of the clinical target volume for radiation. Preoperative breast MRI can detect additional ipsilateral and contralateral tumor foci that may not have been detected by conventional imaging workup and thereby change operative management in a clinically relevant number of cases

In a single institution retrospective study, Tallet *et al*. reported on the incidence of ipsilateral second BC found with the use of preoperative MRI in patients considered for APBI with IORT (19). One hundred seventy-nine patients with early stage BC who met the Inca's criteria for APBI were offered IORT. Eligibility criteria were based on physical exam, mammography, ultrasound, and biopsy, and included: post-menopausal women ≥55 years old with T1N0, hormonal-receptor-positive, HER2-negative, invasive non-lobular epithelioma, without extensive intraductal component, without fast-growing tumor, without lymphovascular invasion, without criteria for adjuvant chemotherapy. MRI was used as part of preoperative staging in 79% of patients. The main reasons for not undergoing MRI are cited as surgeon's preference, MRI contraindication, or patient refusal. Of those undergoing MRI, ACR3–4 new abnormalities (ACR3 = probably benign; ACR4 = suspicious) were noted in 31%, either in ipsilateral or contralateral breast or both. Targeted ultrasound then led to biopsy of 21% total (15% ipsilateral and 13% contralateral). If second-look ultrasound did not confirm an MRI detected abnormality, the lesion was considered invalid. Biopsy led to diagnosis of a second ipsilateral BC in 4% and a contralateral BC in 4.3%. IORT was cancelled for the 4% patients with a second ipsilateral BC. Breast density was 2 in most of these cases. Two of the cases were multifocal but classified as bicentric based on distance of >40 mm between the two. Three of the cases were multicentric. The authors conclude that preoperative MRI should be used routinely for staging of patients who are candidates for APBI by conventional imaging.

Similar results have been reported in other series evaluating the impact of preoperative MRI on patient selection for APBI, with patient selection for APBI altered in up to 10% of cases because of MRI information (20-23).

MRI has been shown to have added diagnostic value for local staging in particular patient subgroups, including those with mammographically dense breasts; unilateral multifocal/multicentric cancer or a synchronous bilateral cancer; with invasive lobular cancer; at inherited high risk for BC; or with cancer showing a size discrepancy of >1 cm between mammography and sonography (24). Adding preoperative MRI, however, can alter clinical management in potentially harmful ways, for example, increased ipsilateral mastectomies, increased prophylactic contralateral mastectomies, increased workup, increased costs, and delayed definitive surgical management. Furthermore, the clinical significance of the MRI-detected lesions is not known. With standard breast conservation, additional tumor foci detected by MRI may be controlled by adjuvant WBI. A recent study showed no differences in local failure rates, overall survival, cause-specific survival, freedom from distant metastases, or contralateral BC between patients with or without preoperative MRI and resection of additional tumor foci, suggesting that surgical removal of tumor foci that are occult on conventional diagnostic workup does not improve outcomes in patient receiving WBI (25).

To conclude, a retrospective analysis to assess the impact of preoperative MRI on patient eligibility for APBI by Tallet *et al*. is in line with a number of similar studies that call for routine use of preoperative MRI in the workup of these patients (19). Preoperative MRI appears to alter management in 4–10% of cases. However, the clinical significance of the change is unknown, particularly when, based on prospective data, the 5-year risk for local recurrence is just 3.3% for APBI generally without

preoperative MRI. This is a very intriguing question that merits further investigation, preferably in the setting of a prospective randomized clinical trial. For now, the report by Tallet *et al*. can only serve as hypothesis-generating without definitive guidelines or recommendations to be drawn. Until more long-term data addressing long-term clinical outcomes and cost-effectiveness are available, selective use of preoperative MRI in APBI candidates may be more appropriate, such as in patients with mammographically dense breasts or with cancer showing a size discrepancy on conventional imaging modalities. Changes in therapy planning resulting from preoperative MRI should be decided in a multidisciplinary setting.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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