Perspective

Patient selection for partial breast irradiation by intraoperative radiation therapy: can magnetic resonance imaging be useful?—perspective from radiation oncology point of view

Marco Krengli[1,2], Carla Pisani[1,2], Letizia Deantonio[1,2]

[1]Division of Radiotherapy, University Hospital Maggiore della Carità, Novara, Italy; [2]Department of Translational Medicine, University of "Piemonte Orientale", Novara, Italy

Correspondence to: Marco Krengli, MD. Chair of Radiotherapy, University of "Piemonte Orientale", Via Solaroli, 17 - 28100 Novara, Italy.
Email: marco.krengli@med.uniupo.it.

Abstract: The guidelines of the European and American Societies of Radiation Oncology (GEC-ESTRO and ASTRO) defined the selection criteria to offer partial breast irradiation (PBI) after lumpectomy in patients with low risk breast cancer regardless pre-operative staging. A recent publication by Tallet *et al.* explored the impact of preoperative magnetic resonance imaging (MRI) on patient eligibility for PBI. From their study, an ipsilateral BC was detected in 4% of patients, excluding these patients from intraoperative radiotherapy (IORT). The authors suggested that preoperative MRI should be used routinely for patient's candidate to IORT, because of the rate of ipsilateral breast cancer detected. In view of Tallet's article, we analyzed some aspects of this issue in order to envisage some possible perspective on how to better identify those patients who could benefit from PBI, especially using IORT. From historical studies, the risk of breast cancer recurrence outside index quadrant without irradiation is in the range of 1.5–3.5%. MRI sensitivity for detection of invasive cancer is reported up to 100%, and it is particularly useful in dense breast. Other imaging technique did not achieve the same sensibility and specificity as conventional MRI. Of note, none of randomized trials published and ongoing on PBI included preoperative MRI as part of staging. To perform a preoperative MRI in PBI setting is an interesting issue, but the available data suggest that this issue should be preferably studied in the setting of prospective clinical trials to clarify the role of MRI and the clinical meaning of the discovered additional foci.

Keywords: Partial breast irradiation (PBI); intraoperative radiotherapy (IORT); magnetic resonance imaging (MRI); patient selection

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Introduction

After breast-conserving surgery, radiotherapy (RT) plays an essential role to reduce local recurrences in the residual breast and to improve cancer-specific and overall survival (1). Recent studies concentrated on tailoring RT to the patient's individual risk according to pathological and bio-molecular prognostic factors, in order to reduce the volume and the duration of complementary RT in selected patients (2-4). In fact, irradiation of a smaller volume, i.e., the tumour bed with a safety margin, allows an increase of the daily dose by hypofractionation without increasing the risk of late toxicity. The concept and the role of partial breast irradiation (PBI) were recently analyzed in three prospective randomized clinical studies using brachytherapy or intraoperative radiation therapy (IORT) (5-7).

The rationale for PBI is that, in the large majority of the cases, ipsilateral breast cancers recurrences occur close to the site of lumpectomy. From the historical trials, the risk of breast cancer recurrence outside index quadrant without breast irradiation is in the range of 1.5–3.5% (8,9). PBI

can be delivered over 1 day to 2 weeks, depending on the technique, i.e., IORT, interstitial brachytherapy, or external beam RT. The IORT represents a very convenient PBI modality since it does not require any further radiation treatment for the patients after the surgical procedure and reduces the workload of the RT department.

The main challenge of PBI is the appropriate patient selection. Upon literature data, European and American Societies of Radiation Oncology (GEC-ESTRO, ASTRO) published consensus statements regarding these criteria (10,11). According to these documents, the most suitable patients for PBI are older than 60 years with invasive ductal cancer, unicentric T1 lesion, positive oestrogen receptor status, absence of lymph vascular space invasion and negative surgical margins (10,11). Multifocal and multicentric lesions are exclusion criteria for PBI because of the high risk of tumour relapse in the other quadrants. With this perspective, the use of the most appropriate diagnostic imaging is a key point for patient selection to identify small unicentric lesions.

In this regard, a recent publication by Tallet *et al*. (12) explored the impact of preoperative magnetic resonance imaging (MRI) on patient eligibility for PBI by IORT. One hundred 75 patients meeting the international selection criteria were planned for surgery with IORT. Seventy-nine percent of them underwent breast MRI as part of the preoperative assessment. The reasons for not undergoing MRI were surgeon's opinion, MRI contraindication, and patient's refusal. The supplemental foci defined as ACR3-4 (ACR3 = probably benign, ACR4 = suspicious) underwent a second ultrasound, and if the suspicious was confirmed patients underwent biopsy. The supplemental foci defined as ACR5 (ACR5 = cancer) were immediately submitted to biopsy. Ipsilateral suspicious lesions were identified in 33 patients (23%) and 21 (15%) underwent a biopsy. A second ipsilateral tumour was detected in 4% of the patients with a change of treatment strategy. Moreover, a contralateral breast cancer was found in 4.3% of the patients. In the conclusion, the authors propose the routine use of MRI for the staging of patients who are candidates for PBI.

This concept can be applied to any PBI modality but it is more crucial for PBI with IORT when no additional imaging procedure is done to identify the radiation target.

In relation with the Tallet's article, we analyzed and discussed the use of MRI for the identification of the patients who could benefit the most from PBI, especially using IORT.

MRI and other imaging modalities

Conventional MRI by T1 (with contrast) and T2 weighted images has a superior sensitivity compared to mammography in detecting ipsilateral multifocal or multicentric breast cancers (13). The sensitivity for detection of invasive cancer is reported up to 100%. The advantage of MRI has been shown to be non-significant in fatty breasts, while significant in fibro glandular and heterogeneous or very dense breasts (14-16). However, MRI with conventional sequences is limited in the detection of pre-invasive lesions (i.e., *in situ* ductal cancer), because it is unable to detect micro calcifications. In such a case, sensitivity is between 60% and 90% (17).

Some authors analyzed the role of MRI in PBI setting and found that 5–10% of the patients initially considered for PBI resulted unsuitable because of MRI findings (18-21). Houssami *et al*. (22) analyzed 19 studies and observed that MRI can detect additional disease in the affected breast in the 16% of women with breast cancer, while 66% of these findings are confirmed as malignant at histology, during surgery or biopsy. In women with multicentric neoplastic foci, the meta-analysis showed that conversion from lumpectomy to mastectomy, according to MRI findings, occurred in 11.3% of cases.

The clinical significance of detecting these additional sites of disease was reported by a German group in a retrospective review of 346 patients who were preoperatively staged with (n=121) or without (n=225) MRI (23). At a mean follow-up of 40 months, the in-breast tumour recurrence rate in patients treated with breast conservative therapy and staged with MRI was 1.2% (1/86) compared with 6.5% (9/138) of the patients staged without preoperative MRI (P<0.001). The authors underlined that some in-breast recurrences appear to correlate with cancer that was already present at the time of diagnosis. In the German study, all new foci underwent a biopsy with a negative result in 61.2% of cases (23). Such a procedure could be considered invasive and stressful for patients and resulted worthless in 61% of them.

In this regard, the study by Tallet *et al*. (12) adopted a less invasive approach for managing the MRI false positive foci: after positive (ACR3-4) preoperative breast MRI, all patients were subsequently studied with a second look ultrasound, and only the confirmed ultrasound suspicious foci underwent fine needle biopsy.

In the era of justification of every single procedure, any diagnostic process should be justified in terms of indication

and optimized in terms of potential risks for patients. The concept of "optimization" in diagnosis is well described for the use of ionizing radiations by the EURATOM Directives using the "ALARA" principle: the radiation dose should be kept at the level as low as reasonably achievable taking into account social and economic factors.

This definition, by analogy, could be applied also for other diagnostic modalities not using ionizing radiations but having potential risks for the patients and costs for the society. By applying this concept, the use of breast MRI could be limited because it is a time-consuming technique; its availability is limited and costly. On the other hand, its use could be justified by the potential benefits. A possible clinical scenario could be the implementation of MRI in a subgroup of patients at higher risk. With regard to this concept, a multidisciplinary working group included preoperative MRI as a recommendation for PBI (24). Upon the available literature data, this panel estimated that about 5–10% of patients eligible at standard assessment would be ineligible after MRI imaging. In this regard, a recent meta-analysis by Di Leo *et al*. (25) reviewed the articles analyzing the ineligibility for PBI after MRI. Out of 3,136 patients, 11% of initially eligible for PBI resulted ineligible after MRI. Of interest, the authors observed as predicting factors of ineligibility after MRI: the invasive tumours at stage pT2 or higher, the invasive lobular histology pattern and the premenopausal status. In the single institution retrospective study by Tallet *et al*. (12), the authors used the eligibility criteria proposed by the ESTRO guidelines. With strict adherence to them, they observed a lower incidence of second ipsilateral cancer (4%) compared to the Di Leo's data.

The challenge of the occult additional lesions detected by MRI is the real clinical implication, and it is not clear if these lesions could be indolent or aggressive lesions. In the literature, there are a few studies trying to predict the aggressiveness of the tumour foci by using the apparent diffusion coefficient (ADC) value of diffusion weighted (DW)-MRI and the standardized uptake value (SUV) of the [18F]FDG-PET. In a sample of 70 breast cancer patients, Karan *et al*. found that the median ADC value was significantly associated with vascular invasion (P=0.008). The maximum SUV (SUVmax) was also significantly correlated with tumour size (P=0.001), histological grade (P=0.001), lymph node status (P=0.0015), oestrogen receptor status (P=0.010), and human epidermal growth factor receptor 2 status (P=0.020) (26). With a similar purpose, Molinari *et al*. observed that lower ADC values are associated with elevated Ki67 proliferation index in 115 breast cancer lesions (27). The association of ADC and Ki67, that could be considered a marker of aggressiveness, may help for understanding also the clinical value of occult foci detected by MRI. On the other hand, Soussan *et al*. evaluated the association of Ki67 with PET SUVmax in a limited number of patients. By 41 breast cancer, SUVmax was positively correlated with Ki-67 (P<0.0004) and triple negative breast cancer (P=0.004) (28).

Considering these sequences, Fusco *et al*. evaluated if dynamic contrast enhanced (DCE)-MRI with DW-MRI in 31 suspicious breast lesions (15 malignant and 16 benign proved by histological examination) could increase the diagnostic power. The combination of DCE and DW-MRI did not improve the sensitivity and specificity observed if DCE and DW-MRI were considered separately (29).

In a meta-analysis of 19 studies on the diagnostic performance of proton MRI spectroscopy for the differentiation between malignant and benign breast lesions, the pooled overall sensitivity and specificity were 73% and 88%, respectively (30). Spectroscopy seems to be highly specific for identifying tumours diameter, multifocal and multicentric disease and in situ breast cancer, however further systematic researches are necessary to verify its diagnostic value.

Of potential interest is also the application of the integrated positron emission tomography (PET)/MRI. Kong *et al*. analyzed a sample of 42 [18F]-Fluorodeoxyglucose (18F-FDG)-PET/MRI studies and achieved a sensibility of 87.5% in detecting breast cancer lesion compared to a PET imaging that achieved a sensibility of 79%. The limit of this approach is the low number of centre equipped with this diagnostic tool (31).

The use of these imaging modalities other than conventional MRI, when validated by solid clinical studies, could add useful information and could represent in the future an alternative to the use of conventional MRI.

Current studies and future perspectives

In the study by Tallet *et al*. (12), MRI was part of the preoperative staging in the 79% of patients considered for PBI with IORT. On the other hand, the randomized trials on IORT PBI did not include MRI as a part of standard staging mainly because their study design was made before more recent knowledges. Only in the TARGIT trial, MRI was performed in 5.6% of the patients.

To our knowledge, most of the ongoing randomized

or single arm clinical trials on PBI do not systematically includes MRI for the patient staging.

The prospective single arm ongoing TARGIT-Elderly trial (NCT01299987) is performing IORT in verified early invasive cancer for patients aged >70 years, and does not require breast MRI for staging (32). In such a setting, it could be considered appropriate the only use of a standard staging because breast density has a less impact in elderly patients. The single arm ongoing TARGIT-C (consolidation) study should confirm the efficacy of a single dose of IORT in a well selected group of patients older than 50 years with small breast cancer and absence of risk factors; also in this trial, MRI is not considering an inclusion criterion (33).

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/Radiation Therapy Oncology Group (RTOG) 0413 study is a randomized phase III trial comparing conventional breast RT and PBI with different techniques for women older than 50 years with stage 0, I, or II breast cancer. Also in this trial, MRI is not considered as a staging procedure (34).

Other ongoing studies on PBI include preoperative MRI for patient selection. A pilot study of the Chicago University (35) aiming at determining if PBI following lumpectomy in patients screened with MRI provides similar rates of local failure, limited acute skin toxicity, late complications and cosmetic outcome when compared to historical rates of toxicity of patients treated with standard whole breast RT.

Another study (36) currently recruiting, on the use of CyberKnife for PBI, includes breast MRI when there is a suspicion of multicentric disease. The additional suspicious areas will require a positive biopsy before changing treatment approach.

In a quite different setting, a phase II RTOG study of repeat breast preserving surgery and 3D-conformal partial breast re-irradiation for local recurrent breast carcinoma (37) performs a bilateral breast mammogram and bilateral breast MRI within 120 days prior to study entry.

In conclusion, literature data including the Tallet's study show that MRI is able to detect lesions outside the target volume of RT in about 4% of the patients' candidates to IORT. Other literature data support the use of MRI for the PBI selection criteria (24) although the GEC-ESTRO and ASTRO guidelines do not recommend the routinely use of MRI to select patients for PBI.

The magnitude of the gain by MRI in the setting of PBI is a worthy issue deserving further investigation, preferably in the setting of prospective clinical trials. The most conclusive approach would be a study randomizing patients who undergo or not MRI before PBI.

Until more long-term and solid data looking at cost-effectiveness and clinical outcomes will be available, the use of preoperative MRI in PBI candidates may be performed in patients with mammographically dense breasts or with discrepancies between mammography and ultrasound and second look with ultrasound, as proposed by Tallet *et al.* (12). Moreover, clinical and biological factors as well could help to identify patients with high risk of multicentric lesions who could benefit the most from MRI.

Upon these considerations, MRI can be a very powerful and useful tool to optimize patient selection for PBI but its use outside clinical trials should be discussed in multidisciplinary setting in order to balance costs and benefits for each single patient.

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Footnote

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References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707-16.
2. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early

breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013;14:1086-94.
3. Bonet M, Godoy P, Cambra MJ, et al. Are breast cancer patients treated with radiotherapy younger now than ten years ago? Rep Pract Oncol Radiother 2014;20:22-6.
4. Deantonio L, Cozzi S, Tunesi S, et al. Hypofractionated radiation therapy for breast cancer: long-term results in a series of 85 patients. Tumori 2016;102:398-403.
5. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol 2013;14:1269-77.
6. Polgár C, Fodor J, Major T, et al. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. Radiother Oncol 2013;108:197-202.
7. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2014;383:603-13.
8. Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. Ann Oncol 2001;12:997-1003.
9. Clark RM, McCulloch PB, Levine MN, et al. Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. J Natl Cancer Inst 1992;84:683-9.
10. Polgár C, Van Limbergen E, Pötter R, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). Radiother Oncol 2010;94:264-73.
11. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys 2009;74:987-1001.
12. Tallet A, Rua S, Jalaguier A, et al. Impact of preoperative magnetic resonance imaging in breast cancer patients candidates for an intraoperative partial breast irradiation. Transl Cancer Res 2015;4:148-154.
13. Schnall MD, Blume J, Bluemke DA, et al. MRI detection of distinct incidental cancer in women with primary breast cancer studied in IBMC 6883. J Surg Oncol 2005;92:32-8.
14. Sardanelli F, Giuseppetti GM, Panizza P, et al. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in Fatty and dense breasts using the whole-breast pathologic examination as a gold standard. AJR Am J Roentgenol 2004;183:1149-57.
15. Sardanelli F, Giuseppetti GM, Panizza P, et al. Sensitivity of MRI Versus Mammography for Detecting Foci of Multifocal, Multicentric Breast Cancer in Fatty and Dense Breasts Using the Whole-Breast Pathologic Examination as a Gold Standard. AJR Am J Roentgenol 2004;183:1149–57.
16. Lord SJ, Lei W, Craft P, et al. A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer. Eur J Cancer 2007;43:1905-17.
17. Boné B, Aspelin P, Bronge L, et al. Sensitivity and specificity of MR mammography with histopathological correlation in 250 breasts. Acta Radiol 1996;37:208-13.
18. Al-Hallaq HA, Mell LK, Bradley JA, et al. Magnetic resonance imaging identifies multifocal and multicentric disease in breast cancer patients who are eligible for partial breast irradiation. Cancer 2008;113:2408-14.
19. Godinez J, Gombos EC, Chikarmane SA, et al. Breast MRI in the evaluation of eligibility for accelerated partial breast irradiation. AJR Am J Roentgenol 2008;191:272-7.
20. Tendulkar RD, Chellman-Jeffers M, Rybicki LA, et al. Preoperative breast magnetic resonance imaging in early breast cancer: implications for partial breast irradiation. Cancer 2009;115:1621-30.
21. Kühr M, Wolfgarten M, Stölzle M, et al. Potential impact of preoperative magnetic resonance imaging of the breast on patient selection for accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys 2011;81:e541-6.
22. Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 2008;26:3248-58.
23. Fischer U, Zachariae O, Baum F, et al. The influence of preoperative MRI of the breasts on recurrence rate in patients with breast cancer. Eur Radiol 2004;14:1725-31.
24. Sardanelli F, Boetes C, Borisch B, et al. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer 2010;46:1296-316.
25. Di Leo G, Trimboli RM, Benedek A, et al. MR Imaging for Selection of Patients for Partial Breast Irradiation: A Systematic Review and Meta-Analysis. Radiology 2015;277:716-26.

26. Karan B, Pourbagher A, Torun N. Diffusion-weighted imaging and (18) F-fluorodeoxyglucose positron emission tomography/computed tomography in breast cancer: Correlation of the apparent diffusion coefficient and maximum standardized uptake values with prognostic factors. J Magn Reson Imaging 2016;43:1434-44.
27. Molinari C, Clauser P, Girometti R, et al. MR mammography using diffusion-weighted imaging in evaluating breast cancer: a correlation with proliferation index. Radiol Med 2015;120:911-8.
28. Soussan M, Orlhac F, Boubaya M, et al. Relationship between tumor heterogeneity measured on FDG-PET/CT and pathological prognostic factors in invasive breast cancer. PLoS One 2014;9:e94017.
29. Fusco R, Sansone M, Filice S, et al. Integration of DCE-MRI and DW-MRI Quantitative Parameters for Breast Lesion Classification. Biomed Res Int 2015;2015:237863.
30. Baltzer PA, Dietzel M. Breast lesions: diagnosis by using proton MR spectroscopy at 1.5 and 3.0 T--systematic review and meta-analysis. Radiology 2013;267:735-46.
31. Kong E, Chun KA, Bae YK, et al. Integrated PET/MR mammography for quantitative analysis and correlation to prognostic factors of invasive ductal carcinoma. Q J Nucl Med Mol Imaging 2016. [Epub ahead of print].
32. Neumaier C, Elena S, Grit W, et al. TARGIT-E(lderly)--prospective phase II study of intraoperative radiotherapy (IORT) in elderly patients with small breast cancer. BMC Cancer 2012;12:171.
33. TARGIT-C(Consolidation) Prospective Phase IV Study of IORT in Patients With Small Breast Cancer (TARGIT-C). ClinicalTrials.gov Identifier: NCT02290782. Available online: https://clinicaltrials.gov/ct2/show/NCT02290782?term=targit+c&rank=1
34. Radiation Therapy (WBI Versus PBI) in Treating Women Who Have Undergone Surgery For Ductal Carcinoma In Situ or Stage I or Stage II Breast Cancer. ClinicalTrials.gov Identifier: NCT00103181. Available online: https://clinicaltrials.gov/ct2/show/NCT00103181?term=NSABP+B-39%2FRTOG+0413&rank=2
35. Partial Breast Irradiation in a Low-risk Population Screened With MRI. ClinicalTrials.gov Identifier: NCT01255553. Available online: https://clinicaltrials.gov/ct2/show/NCT01255553?term=NCT01255553&rank=1
36. CyberKnife Stereotactic Accelerated Partial Breast Irradiation (SAPBI) (CK-SAPBI). ClinicalTrials.gov Identifier: NCT02365714. Available online: https://clinicaltrials.gov/ct2/show/NCT02365714?term=NCT02365714&rank=1
37. Radiation Therapy in Treating Women With Locally Recurrent Breast Cancer Previously Treated With Repeat Breast-Preserving Surgery. ClinicalTrials.gov Identifier: NCT01082211. Available online: https://clinicaltrials.gov/ct2/show/NCT01082211?term=RTOG+1014&rank=1

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