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Partial breast irradiation: Targeting volume or breast molecular subtypes?

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A B S T R A C T

The eligibility criteria for partial breast irradiation (APBI) are mainly based on histopathological factors, which not always explain the clinical behaviour of breast cancers. International guidelines represent useful platform to collect data for continued refinement of patient selection, but the clinical applicability to APBI series showed some limitations, particularly among the intermediate and high-risk groups. The heterogeneity of APBI techniques, along with the heterogeneity of breast cancer, generates clinical results, where the predictive value of the histopathological factors can assume different weight. There is a need of further refinement and implementation of risk factors. Currently, the impact of breast cancer subtype on local control is matter of investigation, and treatment decision about radiotherapy is generally made without regard to the breast cancer subtype. However, receptor status information is easily available and some histopathological factors have not a definite role, there is no uniform interpretation. As molecular classification becomes more feasible in the clinical practice, it will provide added value to conventional clinical tumour characteristics in predicting local recurrence in breast cancer and may play an important role as predictor of eventual patient outcomes.

The strength and the attractiveness of APBI (accelerated partial breast irradiation) techniques lie in reducing the volume treated, with potential decrease of normal tissue toxicity, and in shortening the treatment time, with a favourable impact on treatment costs and patients' convenience. APBI came into the limelight at the turn of the century thanks to the availability of more sophisticated radiotherapy tools, after having been for years a niche treatment for brachytherapy experts [1]. Its use has been spreading very fast and clinical practice has often overtaken results from randomized trials. A pattern of care analysis of 4172 patients treated with MammoSite in the period 2002–2007 revealed that most patients treated outside clinical trials did not belong to the so-called low-risk group [2]. As a consequence of this dramatic increase in APBI use, a higher incidence of subsequent mastectomy has been reported in patients treated with APBI than whole breast irradiation (WBI) (4% vs. 2.2%, $p < 0.001$) [3]. The only meta-analysis available confirmed the increased risk for both local ($p < 0.001$) and regional recurrence ($p < 0.001$) caused by APBI, not translating in a survival difference ($p < 0.55$), so far [4].

It is a matter of fact that the proper patient selection is critical to the success of any kind of treatment: in APBI setting, the paucity of phase III data and the shortness of follow-up make the decision making even more challenging.

The rationale for APBI stem from the observation that up to 85% of local recurrence (LR) occurred in the original tumour bed (true recurrence, TLR) [5,6]. Conversely, the rationale for leaving the remaining breast untreated in the early-stage of BC (breast cancer) came from the observation that without radiotherapy (RT) the incidence of other quadrant in breast recurrence (elsewhere recurrence, ELR) was the same as contralateral breast cancer (CLBC) [7]. However, many other studies showed a protective effect of whole breast irradiation (WBI) against any ipsilateral breast reappearances whose rate is lower compared to the rate of CLBC [8].

The rationale of WBI is fundamentally based on the expected multifocality/multicentricity of BC. Another interesting theory supports that LR is caused by loss of heterozygosity in morphologically normal cells close to the tumour [9], or by self-seeding of circulating tumour cancer cells rather than residual disease [10]. RT is effective because it affects the microenvironment, causing the

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inhibition of the growth of genetically unstable morphologically normal cells [11]. The unfavourable events reported in 1822 patients treated with ELIOT off protocol were in keeping with these expectations: TLR were almost twice the number of ELR (2.3% vs. 1.3%) and the ELR rate was similar to that of CLBC [12].

There is a general agreement that the most suitable patients for the delivery of APBI are those at low risk of harbouring microscopic disease beyond the tumour site. However, assuming that multicentricity/multifocality is relatively common in patients with clinically unifocal tumours, the best candidates could be those whose distant occult disease remains permanently dormant by the effect of systemic therapies and/or by indolent nature. In fact, several pathologic studies showed a relatively high incidence of occult foci of carcinoma remote from the index tumour, but their biologic significance remains uncertain.

Even considering small sized tumours ($\leq$2 cm), malignant foci were detected in more than 40% and 10% of cases at distances >2 and >4 cm, respectively, from the primary tumour [13,14]. Other studies found a more limited extension of microscopic disease, supporting the use of APBI in selected cases. Vicini et al. [15] pointed out that, although residual disease was present in 38% of patients re-excised after initial lumpectomy with negative margins, it was limited within 10 mm from the edge of the primary excision in >90% of cases. The extension of the peri-tumoral tissue to be irradiated raises the issue of the optimal target volume for APBI. The common definition of clinical target volume (CTV) includes the tumour excision cavity or the surgical breech in case of full-thickness closure with a 1–2 cm margin. According to different APBI techniques, the planning target volume (PTV) of different sizes is created [16]. This heterogeneity of treatment volume could generate difficulty of interpretation of outcomes in the near future, but later on, it can open the possibility to choose the best APBI modality according to the patient category of risk.

Once the treatment volume extension is settled, radiation oncologists have to face the challenge of the tumour bed definition, as methods based on preoperative imaging, surgical reports, postoperative clinical breast evaluation, leave a great deal of uncertainty. Besides, the tumour bed is changing over time. The seroma volume shrinkages [17], surgical clips could migrate [18], the 3D reconstruction of the CTV on CT scans is subject to the interobserver variability [19]. Finally, the observation that the treatment volume is certainly correlated with the volume of excised breast tissue, but not necessarily with the maximal tumour size represents another potential pitfall [20].

Published consensus guidelines for APBI have been published in the attempt to identify ideal patients, but the whole picture is still too limited, as recognized by the Panelists, as well [21,22]. Both guidelines are based on risk factors known as prognostic for LR, such as tumour margins, size, grade, receptor status, histology, extensive intraductal component, lymph node status and age.

The application of APBI guidelines provided conflicting results. Patients included in the MammoSite Registry Trial grouped according to ASTRO categories showed no difference regarding LR at 5 years (suitable, cautionary and unsuitable group reported 2.6%, 5.4% and 5.3%, respectively, $p < 0.19$), but many histological factors requested by Panelists were not known [23]. Patients treated with intraoperative electrons (ELIOT) off protocol showed significant difference regarding outcomes throughout all the 3 groups when categorized according to ASTRO guidelines [24], but did not when categorized according to ESTRO recommendations [25]. Among ELIOT patients, most of the risk factors included in the guidelines, such as age <50 years, large tumour size, grading, number of involved lymph nodes, and negative hormone receptors, the presence of peritumoral vascular invasion, an elevated proliferative index (Ki-67), proved to be predictive for LR [12].

Other parameters, such as HER2 amplification, proliferation index, biological subtype and systemic treatment are not part of these guidelines. Their added value to conventional risk factors in predicting outcome is under investigation. High Ki-67 level, which is a nuclear marker of cell proliferation, is associated with worse survival, but it is also a risk factor for local recurrence [26,27]. Other markers, such as p53, bcl-2, and cyclin D1, appear to be promising as predictive factors for local recurrence and survival in breast cancer, but so far results have been inconsistent [28].

In addition, the role of some histopathologic factors in APBI setting appears to be inconsistent. This is the case of extensive intraductal component (EIC), which several studies considered a negative factor for LR [29,30]. EIC failed to predict for an increased risk of LR in ELIOT population, probably because a large amount of EIC is removed by the quadrantectomy [24,25]. Other studies confirmed that EIC loses its predictive value for local recurrence once completely removed with negative tumour margins [31,32]. More concordant results are achieved with oestrogen receptor (ER) status. The presence of an ER negative (ER−) tumour had a significant adverse effect on outcome after APBI [33,34].

Negative oestrogen receptor status was the only variable associated with LR among patients with invasive breast cancer in two different series from the MammoSite Registry Trial, categorized according to ASTRO groups [35].

More complete information regarding high-risk patients (younger than 50 years of age with DCIS or invasive BC with any receptor status and either N0 or N1) will come from mature results of the NSABP B-39/RTOG 0413 trial.

Making a decision to apply APBI on the basis of pathologic tumour features represents an issue for some techniques. The full view of surgical specimen is not yet available at a time of delivering intraoperatory forms of APBI and therefore, the treatment decision must rely on the information obtained from preoperative biopsy and from intraoperative frozen-section analysis. However, not all the tumour characteristics can be reliably established from biopsies. This aspect was considered by Targit investigators, who allowed performing WBI in case of high-risk tumour features in the final reporting [36]. Besides, the accuracy of pathological reporting is crucial. A programme of QA including synoptic pathology reporting could reduce the interobserver disagreement which mainly concerns lymphovascular invasion, extensive in situ carcinoma and the size of resection margin [37].

Age remains one of the most important prognostic factors among women with BC and it is certainly the most immediate criterion of evaluation [38]. The most reasonable cut-off seems to be 50 years of age. In a group of patients treated with high dose rate BRT considered cautionary according to ASTRO guidelines, the 5-year LR rate was 0% in patients entered this category only because of age vs. 13% in patients considered cautionary for other pathological features ($p < 0.02$) [39].

Among ELIOT off protocol patients, young age, <50 years, is a major independent risk factor for LR; at median follow-up of 36 months, the TLR and the ELR rates were 4.35% and 2.72%, respectively, in women aged <50, compared to 1.65% and 0.03% in those who were >60 years [12].

The negative effect of young age also seems to be independent of BC subtypes [40].

An exception could be made for triple negative tumours (TN) in the young. Kim et al. demonstrated that an age of under 35 was not a poor prognostic factor for recurrence and cancer-specific survival in TN subtype unlike other subtypes ($p < 0.001$) [41]. In addition, BC occurring in the young appear to be enriched with specific genes conferring a more aggressive behaviour compared to BC in older women [42,43] found that the lack of expression of CK19 in young

women with TN BC causes a higher probability of locoregional and distant relapse than in older patients.

More recently, gene expression profiling studies using DNA microarrays have identified prognostic gene expression sets to predict outcome in breast cancer patients. These gene-expression signatures proved to be superior to clinicopathologic assessment in predicting distant metastases and overall survival [44]. Recent data suggests that biologic subtypes also have an impact on locoregional recurrence (LRR) outcomes [42,45,46].

There are 4 major molecular subtypes of breast cancer identified by gene expression studies. In the clinical setting, these subtypes can be more conveniently approximated by immunohistochemical (IHC) staining pattern for oestrogen receptor-positive (ER+), progesterone receptor-positive (PR+), and human epidermal growth factor receptor 2-positive (HER-2+) expression. It implies that fenotype-based subtypes, although reliable surrogates, could not strictly correspond to the underlying genotype-based.

The subtypes are luminal A (ER+ or PR+ and HER-2-negative), luminal B (ER+ or PR+ and HER-2+), HER-2 enriched (ER− and PR− and HER-2+) and basal like (ER− and PR− and HER-2) [47]. HER-2 and basal-like subtypes have poor prognosis [48]. Luminal B tumours, which express higher level of proliferation genes, have poorer outcomes than luminal A tumours [49].

The association of the molecular subtypes with rates of local recurrence has been the object of several studies.

Nguyen et al. [42] report the 5-year local recurrence rate in a population of 793 patients. The overall rate was 1.8%, ranging from 0.8% for luminal A and 1.5% for luminal B to 8.4% for HER-2 and 7.1% for basal subtypes. HER-2 and basal subtypes were more frequently high grade and of larger size, and occurred in younger patients than the luminal subtypes. On multivariate analysis (MVA) with the luminal A group as the baseline, both the HER-2 subtype (adjusted hazard ratio [AHR] 9.2; 95% CI, 1.6 to 51, $p < 0.012$) and the basal subtype (AHR 7.1; 95% CI, 1.6 to 31, $p < 0.009$) were associated with an increased risk of local recurrence.

In a study by Voduc et al. [46], where 2985 patients were analyzed with a median follow-up of 12 years, HER-2 and basal subtypes showed a significantly high risk of locoregional relapse after breast conserving therapy (BCT). This aggressive behaviour is also seen with T1a–T1b N0 stages [50]. It could raise some concerns about the use of APBI for small tumours expressing HER-2 and basal subtypes. However, the fact that adjuvant trastuzumab was not administered in these studies could have influenced the local recurrence rate. Basal-like tumours, and in particular the immunophenotype corresponding to TN profile, show some contrasting behaviours which make challenging the management of local therapies. Some studies have shown that the basal or TN subtype BC are associated with an increased risk of both LR and distant metastases [42,51] with a shorter median time to recurrence [52] However, if only early stage TN BC is considered, these outcomes, locoregional and distant recurrence, were not different from other breast molecular subtype after BCT [53]. In a dedicated analysis of pattern of failure in TN BC, Wilkson et al. [54] did not show any difference in clinical outcome between TN and ER+ patients treated with APBI, both of them reporting an excellent local control and survival.

The lack of relationship between TNM staging system and the outcome of TN BC observed in a retrospective analysis by Park et al. [55] might explain these conflicting results. While the relapse-free survival (RFS) of patients with HR+ and HER-2 steadily decreased as the stage becomes more advanced, the RFS of TN patients are not influenced by stage. In fact, the early and the initially advanced stages (1–3A) shared the same outcome, which worsened only in very advanced stages (3B–3C).

Regarding the impact of molecular subtypes on the pattern of local failure in the breast in patients receiving BCT, a study by Hattangadi-Gluth et al. [56] found that basal and HER-2 subtypes are significantly associated with higher rates of TR. At 5 years, basal (4.4%) and HER-2 (9%) tumours had a significantly higher incidence of TLR than luminal B (1.2%) and luminal A (0.2%) subtypes ($p < 0.0001$). This biologic aggressiveness might imply a mechanism of radioresistance, but it is worth mentioning that none of patients was given trastuzumab. In this series the majority of ELR were luminal A tumours. Other reports pointed out that patients with ER+ tumours are more likely to develop ELR rather than TLR [57,58]. This observation stresses the importance of the accurate selection of patients at low-risk of distant occult breast disease and demonstrate the effective local control of APBI in ER+ tumours. In addition, Hattangadi-Gluth et al. [56] found that younger age was significantly associated with both TLR and ELR, once again confirming the importance of the age to select patients suitable for APBI.

In the ELIOT off protocol patients, compared to Luminal A, which had a very low risk of TLR and ELR (0.15 and 0.20/100-year, respectively), local failure in HER-2 tumours occurred solely as TLR [12]. If this pattern of failure is caused by inadequacy of APBI or by intrinsic radioresistance is unknown. The basal-like tumours presented a higher risk of both TLR and ELR compared to ER+ tumours. In this analysis, Luminal B carcinoma showed a higher incidence of TLR (0.96/100-year) as well as of ELR (0.55/100-year). At multivariate analysis, unfavourable molecular subtypes were independent predictor of local relapse.

Currently, integrating the biomolecular, histopathological and clinical information is not straightforward and the complexity of the whole scenario can lead to conflicting results. There is a growing evidence in literature that molecular subtypes can have a great impact also in locoregional management of breast cancer, but they need to be validated in datasets and confirmed in randomized trials.

Conflict of interest statement

All the authors declare no conflict of interest.

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