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Original Article

Intraoperative radiation therapy: is it a standard now?

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SUMMARY

The question whether and for whom the gold standard of whole breast radiotherapy (WBRT) may be replaced by accelerated partial breast irradiation (APBI) is one of the most controversial issue in the adjuvant breast cancer setting. Among different APBI techniques, intraoperative radiation therapy (IORT) is particularly appealing to patients and physicians, because the procedure is fast, convenient, normal structures sparing and able to solve some clinical problems, like the integration with chemotherapy. Early findings from phase II and randomized phase III trials show the approach of APBI in selected patients at low risk for local recurrence is safe and well tolerated, but short follow-up creates some reservations. Since recurrences of breast cancer can occur after a considerably time delay, final assessment of APBI will only be valid after sufficient follow-up from prospective randomized trials with large patients number. Until then APBI should be considered experimental. Furthermore, many questions regarding the appropriate patient selection criteria, treatment volume and dose fractionation still exist. In the context of risk-adapted RT, the key to success is the proper selection of the patients. Both the American and European Society of Radiology and Oncology provided a consensus statement regarding patient selection criteria based on tumour and patient-related features. The 5-year results of the non-randomized ELIOT study from Milan, using 21 Gy-full dose, identified a group of patients who may be good candidates for the treatment. The stratification of patients according to clinical phenotype or by molecular class and a widespread use of preoperative breast magnetic resonance imaging might be better identify patients eligible for APBI.

Introduction

Breast conserving surgery (BCS) in combination with whole breast irradiation (WBRT) has been widely accepted as a standard of care in the management of early breast cancer (BC), since multiple large randomized trials have demonstrated equivalent local survival outcome when compared to mastectomy.[1,2] The recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview[3] showed that WBRT provides a 19% absolute reduction in the 5-year risk of local recurrence (LR) and a 5% absolute reduction in the 15-year risk of death from breast cancer. As a consequence, it is said that one death from BC would be avoided for every four local recurrences prevented. This is a very strong statement to face, carrying important implications. Currently the most commonly used schedule for WBI after BCS is 45 to 50 Gy delivered over 5–6 weeks with 1.8–2 Gy daily fractions, followed by an additional boost to the tumour bed of 10–16 Gy over 1–2 weeks. Any change in daily fractionation, total dose and target volume must be in the first place safe for the patients, guaranteeing rate of local control, toxicity and cosmetic outcome similar to traditional regimens. As a matter of fact, radiotherapy (RT) has got through relevant technological advances during the last 20 years and the availability of more sophisticated tools for delivering high-precision RT and for calculating dose distribution inside and outside the target volume, has sped up the interest in shortened treatment courses. In BC adjuvant setting, the good outcome of the majority of early stage tumours has led to consider as of priority importance some other aspects beyond the local control, mainly related to a general concept of quality of life (QoL). Any difficulties related to convenience, access, cost are felt like a burden for old or active working women. BC therapy has become more and more risk-adapted onto the patients over the last years and the trend is towards a reduction in intensity and in extension. While in the surgical scenario, mastectomy and axillary dissection have been replaced by BCS and sentinel node biopsy, the reduction of RT remains a controversial issue, since many uncertainties over proper patient selection, optimal treatment, outcomes still exist.

Intraoperative radiation therapy

The strength and the attractiveness of accelerated partial breast irradiation (APBI) techniques are those of reducing the volume

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treated, with potential decrease of normal tissue toxicity, and reducing the treatment time, with a favourable impact on RT waiting times and treatment costs.

Among the different methods, intraoperative RT (IORT) offers the advantage of a very precise delineation of tumour bed, which is identified under visual control, solving the problem of potential geographic miss. Furthermore, an immediate oncoplastic surgery can be performed straightaway, with excellent cosmetic results. Not of minor importance, IORT allows high sparing of normal tissue, as the critical structures can be easily shielded or moved away from the radiation field: that might solve the problem of cardiac and lung exposure and the correlated risk of late sequelae. Since the skin and the subcutaneous tissue are not irradiated, any change in breast appearance are not expected, leading to a better cosmesis.[4] Compared to other APBI techniques, IORT with electrons (ELIOT) offers the most homogeneous dose distribution, with an average dose inside the target volume closest to the prescribed dose.[5] IORT with one single fraction has the advantage of a one-shot procedure that includes surgery and RT at the same time. Extending the operation of few minutes avoid long WBRT and solve the practical question of travelling back and forth from RT centre, which in some countries or in some circumstances might be an obstacle. In addition, the all-in-one approach avoids any delay in of both local and systemic treatments. Frozen section analysis is clearly the most limiting aspect of intraoperative technique, as the definitive pathology findings may reveal some aggressive tumour features for whom a limited radiation field is contraindicated, on the basis of current acknowledge.

A main concern is the biological equivalent dose (BED) for IORT. The tool most commonly used for determining isoeffective doses is the linear–quadratic (LQ) model. The question is whether the LQ model used for comparison of fractionation schedules is applicable for single fractions >10 Gy,[6] although Brenner speculated that it could be reasonably used up to about 18 Gy per fraction.[7] Within the limit of this radiobiological model, the single dose of 21 Gy is equivalent to a fractionated dose of 65 Gy, while BEDs for other ABPI regimens are lower than those for standard fractionation regimens of 60–66 Gy Another point of concern is a single shot dose does not allow for the potentially beneficial radiobiological effects of reoxygenation and redistribution on enhancing radiosensitivity.[8]

The TARGIT-A trial

The recent publication on the preliminary results of TARGIT-A trial,[9] a prospective randomised non inferiority phase III study comparing IORT using low-energy X-rays of 50 kV with WBRT, has invigorated the debate. The prescribed dosed is 20 Gy in one fraction to the applicator surface, which corresponds to 5–7 Gy at 1 cm from the applicator. Within the limits of the currently available radiobiological models, it is assumed that a dose of 20 Gy at the applicator surface is equivalent to a fractionated dose of 70 Gy, while a dose of 5 Gy at 1 cm is equivalent to a fractionated dose of 18 Gy. The main concern is whether this dose is sufficient to sterilise microscopic residual disease and whether the irradiated volume is large enough to ensure an adequate coverage of the areas at risk. The pattern of tumour foci distribution around the primary tumour may be spatially distributed beyond the area of effective dose coverage, according to pathologic data.[10] By contrary, ELIOT procedure involves a larger volume with a higher and more homogeneously delivered dose. In addition, unlike the TARGIT trial, ELIOT is performed over a more extended surgery, since quadrantectomy is mandatory.

Although, among the eligibility criteria, TARGIT-A included age ≥45 years old, T2-T3 tumour, N0-N1 nodal status, the majority of patient were at relatively low-risk. In fact, median age was 63 years, tumour size was smaller than 2 cm in 86% of cases, 90% of cases were estrogen-positive, and 82% of the nodes were not involved.

While 854 patients (86%) receive APBI alone, 142 patients (14%) had APBI + WBRT, due to adverse prognostic factors emerged in postoperative pathologic report. It was technically feasible because of the small portion of the target volume irradiated to full dose, limited to the tumour bed surface. Using ELIOT, the extension of target volume becomes a critical point for acute and late tolerance, as 2–3 cm around the excision site receive full dose of prescription. Being analysed in the experimental arm, these latter patients may have contributed to the APBI better outcome. The Kaplan–Meier estimate of local recurrences (LR) at 4 years was 1.2% in the IORT arm and 0.95% in WBRT group (p NS), The frequency of any complications was similar between the two groups.

Veronesi presented results of a clinical trial including 1822 patients treated off protocol.[11] At 4 years, the actuarial rate of LR is 4.84% (annual rate of 1.21%), 2/3 of which were at the same quadrant of the primary tumours, while 1/3 occurred in other quadrants. Side effects were mild (1.8% of fibrosis and 4.2% of liponecrosis). Although in both studies patients were at relatively low-risk, the ELIOT study presented a slight worse profile due to the inclusion of patients who did not fully satisfied the stricter eligibility criteria of the randomized phase III trial (unicentricity, ≤2.5 cm tumour size, clinically negative axilla and age ≥48 years).

The main criticism is that both in TARGIT trial and ELIOT study, follow-up is too short (median 24 and 36 months, respectively) to consider APBI as alternative to WBRT for selected patients and mature data on late toxicity are lacking. In the TARGIT trial, the most LR occurred at 2–3 years, while in ELIOT study the median time of appearance was 29.2 months. The literature shows that ipsilateral recurrences distant from the original tumour site (called new primary, NP) have a longer mean time to relapse than LR around the original tumour bed (called true recurrence, TR) (7.3 years vs. 3.7 years, $p < 0.0001$). Both TR and NP develop at similar rates until about 8 years after treatment, when TR rates stabilize, but NP rates continue to rise.[12] Furthermore in the TARGIT trial, out of 2232 patients, only 420 (19%) completed 4-year follow-up (212 in the APBI group).

Consensus statements

In response to the increasing use of APBI off clinical trial several consensus statements from different panels have been published regarding the appropriate use of APBI. The Biedenkopf expert panel[13] and the DEGRO expert panel[14] assert that APBI is not a standard option, due to the lack of long-term follow-up data, and explicitly points out that "PBI should be performed only as part of a prospective trial". The 11th St Gallen expert consensus meeting[15] considered that APBI is an acceptable option for patients aged ≥60 with h favourable tumour patterns, but it should be still considered experimental On the other side, the NCCN guidelines published in 2011[16] open the possibility to patients to be given APBI according to criteria identified by ASTRO consensus for the "suitable" group.[17] In the same time, the NCCN guidelines 2011 allow that breast irradiation may be omitted in patients who meet most of the characteristics described in the American Society for Radiation Oncology (ASTRO) suitable group, like 70 years of age or older with T1, N0, estrogen –receptor positive (ER) tumours, creating a double-face decision-making.

ASTRO and GEC-ESTRO recommendations

The American Society for Radiation Oncology (ASTRO) and the Groupe Européen de Curiethérapy-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) provided a consensus regarding patient selection criteria and best practices for the use

of APBI outside the context of a clinical trial. Both guidelines are based on the results of a systematic literature review of ABPI data and are supported by the opinions of breast cancer experts. The ASTRO Task force defines "suitable" for APBI patients having over age 60, pathologically negative nodes, unicentric T1 cancer, positive ER status, absence of lymphovascular space invasion (LVI) and widely negative margins (>2mm). Most of phase I/II studies included this category of patients. On the other hand, "unsuitable" patients are these with any following criteria: tumour size >3 cm, positive margins, any positive lymph nodes, no axillary surgery, extensive LVI, multicentricity, DCIS >3 cm, BRCA1 or 2 mutation, neoadjuvant systemic therapy.

The GEC-ESTRO Breast Cancer Working Group[18] recommends 3 categories as well, with some minor differences regarding the range of age, the tumour size and the axillary status. Being based essentially on specimen analysis, these recommendations are not supposed to be applied to ELIOT patients to a full extent. ASTRO Task Force clearly stated that "the groups proposed are not intended to apply to patients who receive intraoperative radiotherapy for whom complete pathologic assessment cannot be performed before treatment". This is without no doubt one of the greatest issues, because the definitive pathologic report can show histologic or biomolecular features for which WBRT would be the best choice. TARGIT-A included the possibility to complete the treatment by adding WBRT, in case of critical pathological findings, but this aspect has not been considered in ELIOT full dose of 21 Gy. To better define patients candidates to intraoperative procedure, some efforts to improve the pre-irradiation pathologic tumour evaluation can be done. Being able to rely on a good quality standard of preoperative and intraoperative pathologic assessment, many of the tumour features requested by ASTRO and GEC-ESTRO consensus panel might be satisfied.

Interestingly, ASTRO categories, when were applied to patients treated with MammoSite procedures, failed to differentiate patients for whom APBI could be appropriate treatment or not.[19] In univariate analysis performed in the ELIOT study,[11] tumour size, number of positive lymph nodes, proliferative index (Ki-67), young age, LVI, overexpression of HER2 and ER negative status, increased the risk of LR. In multivariate analysis age<50 years, tumour size>2 cm, remained independent predictors of local relapse. This finding is in line with the literature data.[20] Although EORTC trial[20] reported high-grade (G3) carcinoma as one of the most important risk factors for LR, neither ASTRO nor GEC-ESTRO guidelines considered it as relevant for patient selection. In ELIOT study,[11] G3 tumours showed a significant higher incidence of local failure compared with G1 tumours (7.19% vs. 0.86%).

Elderly patients: better less than nothing?

The question whether APBI technique can adapt to a subgroup of patients with low risk of recurrences, is highly relevant for elderly patients for whom standard of care is more likely omitted than for younger patients. The use of breast irradiation decreases substantially with age, although over half of cases of BC occur in women aged ≥65 years. Current data suggest that the risk of LR after BCS and endocrine therapy may decline with age, while competing risks of death, particularly vascular, increase.[21] The updated results of the CALGB trial[22] showed that for elderly patients with (ER) positive stage I tumours, Tamoxifen (TAM) alone might be sufficient, yielding a LR rate of 8% at 10.5 years. However, the association with WBRT resulted in an absolute reduction of 6% in LR when compared to TAM alone. As also shown in the EBCTCG overview,[3] the absolute effect of WBRT on LR was greater in younger than in older women, but still significant (5-year risk reductions of 22%, 16%, 12% and 11% for those aged <50, 50–59, 60–69, and ≥70 years, respectively, 2p = 0.00002). Nevertheless, WBRT may not represent the optimal standard of care for these patients. The effects of omission of WBRT in women with low-risk BC treated by BCS and endocrine therapy were tested in the PRIME randomised trial, assessing the QoL in irradiated and non-irradiated old patients.[23] Although there were no global differences in QoL scores between the patients treated with or without RT, WBRT was found associated with increased breast symptoms, which persisted, and in some cases worsened, for up to 5 years after treatment. Even after several years, patients from both groups were still expressing concern about the recurrence of BC. For these category, APBI might be a better alternative than WBRT or no irradiation at all. Lemanski and colleagues[24] started in 2004 a phase II study to investigate the role of ELIOT as the sole modality in elderly patients, aged 65 or older, with T1N0 unifocal ductal carcinoma. The prescribed dose was 21 Gy at the 90% isodose. At a median follow-up of 30 months, only 2 patients (0.42%) experienced local relapse (1 in the same quadrant and elsewhere). All the questionnaires of QoL indicated excellent scores, with no change from baseline. In the ELIOT study,[11] 43.3% of the patients were older than 60 years (789 out of 1822). In this group, although with less strict selection than that used for the Montpellier study, local relapse was 2.28% at 3 years median follow-up. With about 0.8% annual recurrence rate this group was in line with the results expected from APBI technique. In many respects, APBI might be already considered as a standard for elderly patients with early stage breast cancer.

Towards a better patient selection

Molecular markers

Recent DNA microarray profiling of BC has identified distinct subtypes of BC with different clinical and biological behaviour, from the relatively good prognosis of patients with Luminal A tumours to the worst prognosis of those with basal like and HER2 tumours.[25] Although, Wilder[26] reported similar 3-year ipsilateral breast local control rate for Luminal A, HER2 and triple negative patients treated with APBI, this issue is controversial. Some authors hardly consider even WBRT as appropriate for triple negative patients, due to high risk of LR.[27] In the ELIOT study,[11] compared to Luminal A, which has a very low risk of true local recurrence (0.15/100-year), the cases with Luminal B carcinoma showed a higher incidence of true local recurrence rate (0.96/100-year, respectively), and even higher when considering basal like and HER2 positive carcinoma (1.19 and 3.88/100-year, respectively. At multivariate analysis, unfavourable molecular subtypes were independent predictor of local relapse. The rate of second ipsilateral tumours, as well, increased when moving from Luminal A to Luminal B, to basal-like carcinoma. In a parallel way, Gabos and colleagues[28] found that ER negative/HER2 positive and TN subtypes are independent prognostic factors associated with higher rate of LRR (14.7% and 11%, respectively) compared with ER positive/HER2 negative subtype (3.4%). Molecular markers should be incorporated into risk-adapted RT to help proper patient selection.

Preoperative breast magnetic resonance imaging

Although the ASTRO Task Force[17] does not support routine use of Magnetic Resonance Imaging (MRI) in APBI setting, its utility in finding abnormalities not detected by mammograms or ultrasound is noteworthy (up to 34%)[29] and might be clinically relevant. Several studies have examined the potential of MRI to improve patient selection for APBI. Al-Hallaq and colleagues[30] found abnormalities outside the probable radiation field in 8.1% of 110 patients meeting the eligibility for NSAPB/RTOG protocol. In 4.5% of cases the disease was multicentric and in 3.6% it was unifocal. In a study of 260 patients with a median age of 57 years, MRI identified

additional cancer foci in the ipsilateral breast in 4.2%.[31] The synchronous lesions occurred at a median distance of 3.0 cm of intervening tissue between lesions on MRI. By univariate analysis lobular histology, pathologic T2 and AJCC stage II were significantly associated with additional ipsilateral disease. In the study performed by Goldinez[32] MRI identified additional foci of tumour in 38% of cases believed to be eligible for APBI on the basis of conventional radiological workup. Of these, 10% had an additional cancer in a different quadrant from the index tumour.

As in patients treated with APBI, it is mandatory no mammographically occult breast cancer is missed, MRI should be strongly considered for a proper selection, even if routine use is not considered in the current phase II and III studies.

Is intraoperative radiation therapy a standard?

After BCS, the rationale for treating the whole breast is to destroy any residual microscopic tumour cells or additional occult foci anywhere in the ipsilateral breast. This treatment effect in quadrants of the breast other than the index tumour is lost with APBI. A metanalysis of 3 randomized trials,[33] whose two are considered outdated according to current standard of care, comparing APBI vs. WBRT with pooled total of 1,140 patients showed that locoregional control could be an issue, although APBI does not seem to jeopardize survival. In applying this modality of risk-adapted RT, the key to success is grounded on selecting patients at low risk of harbouring occult microscopic disease at distance from tumour bed, in order to ensure an annual rate of LR lower than 1%. To increase the challenge, different methods of APBI treat different volume of residual breast tissue and use different biological effective radiation doses. Age proved to be one of the most important predictive parameter for LR.[34] In ELIOT study,[11] in the 368 patients who were <50 years, the LR was 4.35% and the rate of secondary cancers 2.72%. In the German/Austria APBI phase II trial,[35] given the significant difference in local control according to age, the authors concluded that patient younger than 50 years ought to be excluded from APBI protocols. The NSABP B-39/RTOG 0143,[36] which randomises women between conventional WBRT versus three APBI techniques, closed the accrual to low-risk group in 2007, and now is enrolling patients defined at high-risk (age >50, 1–3 nodes positive, ER negative). This trial is bound to be very important to define the role of APBI in high-risk BC. A few preliminary information regarding the efficacy of APBI in the "unsuitable" group are available. At 5 years, Patel[37] observed no significant difference in local control or overall survival between high and low-risk patients treated with APBI.

Another point of concern full-dose IORT has a tumour control BED (using an alfa/beta of 4) and a late-response BED (using an alfa/beta of 2) higher than those of a conventional schedule of 60 Gy in 30 fractions.[8] Given that, we should expect an increased incidence of severe fibrosis. Nevertheless, clinical experiences reported to date do not support this hypothesis.[11]

The replacement of WBRT by APBI for low-risk patients based on the recent results appears to be logical, but requires further confirmations. Overall clinical appropriateness criteria for APBI need to be determined by ongoing trials or by mature data from the closed phase III ones. Until then, a reasonable attitude is to follow the ASTRO/GEC-ESTRO recommendations in case of APBI outside clinical studies.

Conflict of interest statement

The authors have no conflict of interest to declare.

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