Accelerated partial breast irradiation: state of the art

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Accelerated partial breast irradiation can be applied by means of different techniques. It offers an opportunity for reducing the treatment duration considerably and harbours the potential for less exposure of healthy tissue to higher radiation doses. However, evidence issued from randomized trials is limited. European and American experts call our attention to the potential dangers of widespread implementation of these techniques without any long-term data on outcome and ask for complete information of patients on the potential hazards and risks if accelerated partial breast irradiation is used instead of whole breast irradiation.

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Introduction

Breast conservative surgery (BCS) is a reasonable treatment alternative to mastectomy as shown by randomized trials provided adjuvant radiotherapy is performed. This adjuvant radiotherapy results in a significant reduction of the risk of ipsilateral breast tumour recurrence (IBTR) (below 1% per year of follow-up). The standard of care for this adjuvant radiotherapy is whole breast irradiation (WBI). Recently, interest has been shown in accelerated partial breast irradiation (APBI), especially because this technique allows reducing the burden of treatment on patients by reducing the total number of fractions. We intend to review the current status briefly and to discuss available techniques and evidence concerning accelerated partial breast irradiation.

Techniques for APBI

Various techniques have been described in order to offer APBI as a therapeutic option after BCS. This ranges from the use of interstitial BT techniques to highly conformal external irradiation.

BT consists of the implantation of a source guide allowing after-loading with a radioactive source and hence intense and focalised dose administration. It is a highly conformal treatment, but as the dose is much more intense in the immediate vicinity of the radio-active source, the homogeneity of the administered radiation dose within the target is suboptimal. The heterogeneity, which can be reduced by careful source guide placement and treatment planning, has the potential to yield subsequent late complications, especially fibrosis. The MammoSite® and other derived similar techniques represent an alternative, but in essence these techniques can be considered as a BT approach.[1]

More recently, electronic BT has been developed and promoted.[2] Two systems are currently available and administer low energy electronically generated radia-

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tion: the Axxent Electronic Brachytherapy System by Xoft, Inc (Fremont, CA) and the Intrabeam Photon Radiosurgery Device by Carl Zeiss Surgical (Oberkochen, Germany). The Xoft system consists of a miniature electronic X-ray source in a flexible probe combined with a balloon applicator. The Zeiss system consists of a mobile photon radiosurgery system where electrons are generated in the main unit and via an electron beam drift tube reach a conical applicator positioned in the surgical bed. These systems are used within the operating room and therefore both constitute an intraoperative approach. An alternative for intraoperative radiotherapy (IORT), but with more constraints as far as radiation protection is concerned, is the use of an intraoperative electron beam such as the one proposed by the IntraOp Mobetron® (IntraOp Medical Corporation, Sunnyvale, CA), a self-shielding electron linear accelerator designed and developed in 1993. The American Society for Therapeutic Radiology and Oncology (ASTRO) has recently highlighted the risk in the United States of utilisation of all these devices with personnel of limited expertise in the field of radiation treatment of cancer, BT and dose administration principles, radiation safety and biology, or normal tissue tolerances.[2]

APBI can also be applied with external radiotherapy techniques aiming at obtaining a highly conformal and uniform dose distribution in a well-circumscribed target area. The adequate definition of target boundaries in a postoperative setting is clearly a pitfall; nevertheless, even without congruity between observers on the exact localisation and extent of this target area, the randomized trials are favouring the application of a supplementary dose within this given area (boost versus no boost trial conducted by the EORTC and the Lyon trial are both positive in outcome).[3,4] However, this is fundamentally different from an approach where WBI is not applied and dose administration is merely concentrated on the area considered as being at the highest risk of recurrence. In the latter approach one aims at a relative sharp dose fall-off outside the target to spare the surrounding healthy tissue as much as possible. This obviously raises the question on how the boundaries are defined.

To obtain a shortening of the total treatment duration and hence a reduction of the number of fractions (hypo-fractionated treatment), nowadays, several techniques are used in the field of external radiotherapy, such as intensity-modulated radiation therapy (IMRT), tomotherapy and even stereotactic body radiotherapy (SBRT) with adapted linear accelerators or tracking systems such as the one developed by Accuray (CyberKnife®). The main disadvantage of using external radiotherapy for APBI is the integral dose to the body: a significant proportion of normal tissue receives a low dose because of the multiplicity of the number of incident beams.[5] There has been some concern in the literature about the increase of carcinogenic effects of these low doses on larger volumes which could potentially translate into a higher incidence of treatment induced secondary cancer. The latter can only be evaluated after a long-term follow-up.

What about clinical evidence?

Not many data are available from randomized controlled trials, whatever the technique used, on the effect of APBI on outcome (i.e. local control, cosmetic outcome, late radiation-induced normal tissue effects and survival). In the early days of APBI, small trials have been conducted. The general message of these early phase II/III trials is that strict selection criteria should be applied to APBI.

There is only one randomized trial which has been published and recently updated on the use of BT for APBI. The Hungarian single institution randomized trial on APBI reported on 258 patients randomized between WBI (50 Gy) versus HDR multi-catheter BT (36.4 Gy in 7 fractions of 5.42 Gy each) or limited field electron beam irradiation (EB; 50Gy in 25 fractions).[6] The series has been updated in 2008, and with a median follow-up of 6.2 years there was still no significant difference in 7-year rates of local recurrence (LR), disease-free survival (DFS) or cancer-specific survival (CSS). There has also been a long-term evaluation reported at 12 years, based on a subpopulation of 45 prospectively selected patients with T1N0-N1mi, non-lobular breast cancer without the presence of an extensive intraductal component (EIC) and with negative surgical margins. The authors conclude that HDR multi-catheter with Ir^{192} interstitial implant yields excellent long-term local control, survival and cosmetic results.

Other series, such as the one from the William Beaumont Hospital, report on long-term effects of

Table 1. Overview of patient and tumour characteristics in TARGIT-A trial. Adapted from Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomized, non-inferiority phase 3 trial. Lancet 2010;376:91-102.[9]

	Targeted intraoperative radiotherapy	External beam radiotherapy
Age <54	21%	16%
Tumour size <2 cm	86%	86%
Invasive ductal carcinoma	95%	94%
DCIS present	50%	51%
Grade <3	85%	85%
No lymphovascular invasion	86%	87%
No lymph nodes involved	82%	84%
Receptor status		
estrogen receptor-positive	90%	93%
HER2-negative	87%	87%
Adjuvant therapy		
hormone therapy	65%	67%
chemotherapy	10%	13%
Margins (at first excision)		
free	90.5%	90.2%

low-dose rate BT but since these effects are presented in the context of a non-randomized matched controlled study, they obviously do not yield the same level of evidence.[7]

Techniques such as MammoSite® or even intra-operative approaches require a word of caution: these techniques do not really allow conforming the treatment to the geometry of the operative bed. Moreover, during surgery a therapeutic decision has to be taken without having the final pathological report. Finally, some of these techniques harbour an increased risk of infection (up to 10% with the MammoSite®).

Recently, the TARGIT-A trial has been presented at the annual meeting of the American Society of Clinical Oncology (ASCO) and published this year.[8,9] This trial has been designed as a prospective non-inferiority phase III trial comparing standard adjuvant conventional external irradiation to targeted intraoperative radiotherapy using the Intrabeam® device (point-source of low energy X-rays). The patients randomized in the experimental arm have been treated with a 20 Gy surface dose attenuating to 5-7 Gy at 1 cm depth. Patients were eligible if older than 45 years, and if they were presented with invasive unifocal ductal carcinoma suitable for wide local excision. No other selection criteria were defined. However, participating centres were allowed to restrict inclusion criteria beyond the core protocol. The predefined non-inferiority was an absolute difference of 2.5% in the primary endpoint i.e. local recurrence. Fourteen percent of the patients allocated to the Intrabeam® procedure received additional external beam radiotherapy based on pathological findings. The Kaplan-Meier estimates of local recurrence in the conserved breast at 4 years are 1.2% (95% CI 0.53-2.71) and 0.95 (95% CI 0.39-2.31) for the targeted intra-operative approach and external beam radiotherapy group, respectively. However, it is noteworthy that less than 20% of patients have a follow-up beyond 4 years. The authors urge for caution, firstly because of the short follow-up and secondly because these results are only valid for patients with similar clinicopathological features (summarized in *Table 1*).

Recently, the Groupe Européen de Curiethérapie - European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) published guidelines on the use of BT as a technique for APBI.[10] These recommendations aim at presenting clinical guidelines with regard to the use of APBI with BT outside the context of a clinical trial. There is a three-level classification: a low-risk group where APBI with BT is an acceptable option, an intermediate-risk group where APBI is considered acceptable provided it is a part of a prospective clinical trial and a high-risk group

Key messages for clinical practice

1. Whole breast irradiation (WBI) is the standard approach after breast conservative surgery.
2. Accelerated partial breast irradiation (APBI) can be considered as an alternative for WBI in a selected minority of patients, but long-term data on outcome are lacking.
3. Patients should be informed on the potential hazards risks of APBI and commit themselves to regular and long-term follow-up.
4. Patients as well as clinicians should be encouraged to participate in prospective trials.

where it is clearly contraindicated. The only situation where APBI with BT is considered a possible alternative to the more classical WBI plus or minus boost is the one where the patients "ageing at least 50 years with unicentric, unifocal, pT1-T2 (<30mm), pN0, non-lobular invasive breast cancer without the presence of an EIC and lymphovascular invasion and with negative surgical margins of at least 2 mm". This statement is further balanced by the fact that the authors insist "on the necessity that the patient is fully informed that WBI is an established treatment that has documented long-term efficacy with low-risk of early and late side-effects" and that "the patients should be familiar with the possible risks and benefits of APBI taking into account the lack of long-term results (beyond 10 years)". Taken together these statements plead the case for application of strict selection criteria and informed consent.

The ASTRO established guidance for patients and physicians through a screening of the published literature on APBI and expert opinion.[11,12] As for the GEC-ESTRO, they defined different levels: a 'suitable' group for whom the concept is acceptable outside the context of a clinical trial, a 'cautionary' group where they raised concerns about the possible application of these techniques outside a clinical trial, and an 'unsuitable' group where these modalities are not recommended. They also stress the importance of informing patients completely that the actual standard of care is WBI. The patients considered suitable for APBI are those with BCS, accepting to be committed to long-term follow-up in order to evaluate local efficacy and toxicity. In essence, patients should be older than 60, without BRCA I/II mutations. Patients should be presented with unicentric and clinically unifocal lesions with a total size lower or equal to 2 centimeters.

The pathological characteristics of the tumour should be the following: $\leq$2 cm (T1), infiltrating ductal carcinoma (excluding lobular and pure ductal carcinoma in situ), negative margins (minimal distance from the resection margin to the tumour rim should be at least 2 mm), any grade. Presence of lymphovascular invasion is a contra-indication. There should be no nodes involved based on sentinel node biopsy or axillary lymph node dissection. If neoadjuvant chemotherapy has been applied and downsizing and down-staging is observed, nevertheless WBI should be proposed to these patients. The authors of the ASTRO guidelines insist, just as their European colleagues do, on the necessity of informing patients on the lack of long-term outcome data. Patients should be aware that compared to WBI, there is a potential increased risk of ipsilateral breast tumour recurrence which may lead to a more aggressive surgical treatment (mastectomy) and systemic treatment and could be associated with an increased risk of distant metastases and death and long-term radiation induced toxicity. Even if some of the devices used in the intraoperative approach for APBI are currently available in Belgium, one should not omit to inform the patient comprehensively on the lack of long-term data on local control and toxicity.

Conclusions

Interest within the medical community for APBI seems to be growing as it offers the option for a rapid treatment, yielding the opportunity to reduce exposure of a large amount of normal tissue to higher radiation doses and at the end reducing the burden of a daily fractionation on the patient. However, the European and American guidelines are very strict and only a minority of patients is eligible for APBI. Moreover, patients should be informed that, even if they are considered suitable for this technique, long-term outcome data on survival, local control and toxicity are not yet available. Therefore, patients as well as clinicians should be encouraged to participate in prospective clinical trials raising the question on the efficacy and toxicity of APBI as compared to WBI.

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