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Technical note

Apples and oranges: comparing partial breast irradiation techniques

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A few decades ago, breast conserving therapy (BCT), consisting of breast conserving surgery followed by radiation therapy (RT), was found to be equivalent to mastectomy in terms of overall survival.[1] Since then, recurrence rates have one down sharply, opening the doors to further treatment de-escalation for low-risk breast cancer patients. As such, partial breast irradiation (PBI) is an RT approach able to decrease the treatment burden for patients by reducing both treated volumes and treatment duration.

Several techniques for PBI (and tumour bed boost irradiation) are available. Hereby, we emphasize important key-points regarding the clinical and technical aspects of the most prevalent ones. These techniques can be divided into three main groups: brachytherapy, intra-operative RT (IORT), and external beam RT (EBRT). External beam and brachytherapy are widely available and accepted techniques.[2,3] Conversely, controversy exists about the two different IORT techniques, one electron-based (IOeRT) and one using 50 kV X-rays. Recently, the ESTRO IORT Task Force has provided a comprehensive overview of IOeRT, and long-term results of a subgroup of the TARGIT-A trial, using a 50 kV X-ray device, have been published.[4,5]

However, the conclusion that several types of PBI are equivalent to whole breast RT requires a critical appraisal as physical RT properties are different for each PBI technique, influencing significantly dose distribution, irradiated volumes, dose homogeneity and skin doses, all of which may result in significant differences in clinical outcomes. Moreover, the timing of PBI in relation to primary surgery is different, which can be significant for patient selection, further management and outcomes. Hence, as radiation and surgical oncology professionals, we know that it is not possible to extrapolate the results from one PBI technique to another: this is like comparing "*apples and oranges*".

There are two basic principles behind PBI: i) to select low-risk breast cancer patients characterized by low postoperative ipsilateral breast tumour recurrence rates (IBTR); ii) to apply an accurate tumoricidal RT dose to the target volume. If these two concepts are both respected, then outcomes after PBI will not be inferior to whole breast RT, whatever PBI technique used. Therefore, our critical appraisal addresses these key principles.

1) The **low-risk IBTR group** is constituted of female patients aged more than 50 years, pT1, unifocal, grade 1-2, non-lobular/non-DCIS, negative surgical margins, luminal-like and uninvolved lymph nodes. Of these, patients aged more than 70 can be considered a **very-low-risk IBTR group,** who are also candidates for PBI and might even be treated with endocrine therapy alone, for example in the case of limited life-expectancy due to comorbidity. Importantly, for patients with dense breasts on mammography, a preoperative breast MRI should be considered if planned for PBI to assure unifocal disease.[6,7]

2) Concerning the **target volume**, we know from Holland et al. that the risk for residual cancer cells decreases with the distance from the edge of the primary tumour.[8] Additionally, we also learned that the local recurrence risk depends on biological tumour factors. Taken together, for PBI which should be restricted for low-risk patients, a margin of 2 cm around the primary tumour site (i.e., the site of the highest likelihood of harbouring residual tumour foci) constitutes the clinical target volume (CTV).[8,9] After tumour resection, which is rarely concentric, this margin can be reduced by the tumour-free margin excised around the primary tumour, ideally measured in the major 6 directions, leading to variable margins,

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Table 1
Main partial breast irradiation techniques.

	EBRT	Interstitial Brachytherapy PDR, HDR, LDR	Endocavitary balloon[a]	IORT	IOeRT
Type of treatment	Non-invasive	Invasive	Invasive	Invasive	Invasive
Time of RT	Postoperative	Intraoperative/ postoperative	Postoperative	Intraoperative/ postoperative	Intraoperative
Specialized device/specialized centre	No	yes	yes	yes	yes
Type of RT	High-energy photons	Nuclide, mostly ^{192}Ir	Nuclide, mostly ^{192}Ir	50-kV photons	High-energy electrons
Coverage of clinical target volume	Best	Good	Fair to poor	Poor	Good
RT volume prescription	~ Tumour bed+20 mm to CTV; +5 mm to PTV	~ Tumour bed+20 mm	Dose prescribed 10 mm from applicator surface	Dose prescribed 1 mm from applicator surface	Tumour bed+20 mm determined at time of surgery
Number of treatment days	Different protocols: 5-15	Different protocols: 1-10	5	one	one
Dose homogeneity	Best	Fair	Poor	Poor	Good
Sparing of normal tissue excluding skin	Least	Good	Good	Good	Good
Skin dose	Low	Low	Variable	Variable	Lowest
Technical feasibility for various size/shape/location	Best	Good	Poor	Poor	Good
Draw backs	Dose to normal tissues; Variability in determining tumour bed especially after oncoplastic surgery	Specialized centres; dependent on tumour location within breast; invasive	Low dose at >10 mm from applicator surface; Specialized centres; dependent on tumour location within breast; invasive	Very low dose at >5 mm from applicator surface; Time added to surgery; No final histology available; Specialized centres; dependent on tumour location within breast; invasive	Time added to surgery; No final histology available; Specialized centres; dependent on tumour location within breast; invasive

IORT – intraoperative radiation using 50 kV X-ray device.
EBRT – external beam radiation therapy; PDR- pulse dose rate; HDR-high dose rate; LDR-low dose rate; IOeRT- intraoperative electron radiation therapy.
[a] Example: MammoSite (Hologic, Marlborough, MA).

varying between 0 and 2 cm. The resulting CTV is not only irregular but also not at all coincident with the surgical cavity, which is much too often used as the basis for a target volume shaped around it. This makes any "endo-cavitary" approach highly unlikely to be successful in covering the correct CTV.[10] For postoperative approaches, tissue replacement and displacement during oncoplastic surgery highly complicates the identification of the initial tumour site and, thereby, the CTV, even when using guidelines.[9] Thus, these patients are often not suitable candidates for PBI, unless RT is given before the oncoplastic tissue rearrangement, as is feasible especially with IOeRT.[4]

Table 1 shows the variation in the ability to deliver the prescribed tumouricidal dose with an appropriate dose distribution to the entire anatomically defined target volume. The decision which PBI-technique is most appropriate should be based on knowledge of the pros and cons of these modalities combined with appropriate expertise, and knowledge of the various RT schedules for PBI (e.g., 5-fractions EBRT-regimen of the Florence trial).[11]

Importantly, the different PBI techniques require different skills. Mobile IORT technology led to growing use of IORT-PBI, mostly 50 kV low-energy X-rays (e.g., TARGIT-A trial) and IOeRT (e.g., ELIOT trial).[5,12] However, these techniques are not identical, with large differences concerning dose distributions, dose homogeneity and skin doses. The 50 kV spherical applicator that is positioned within the lumpectomy cavity provides a surface dose around the applicator (one can only adjust the size of the applicator), with a steep dose gradient and leading to only 25% of the prescribed dose at 1 cm distance (Fig. 1A). Moreover, in case of bleeding in the lumpectomy cavity during the procedure it can lead to even more ineffective dose delivery while an applicator-skin distance

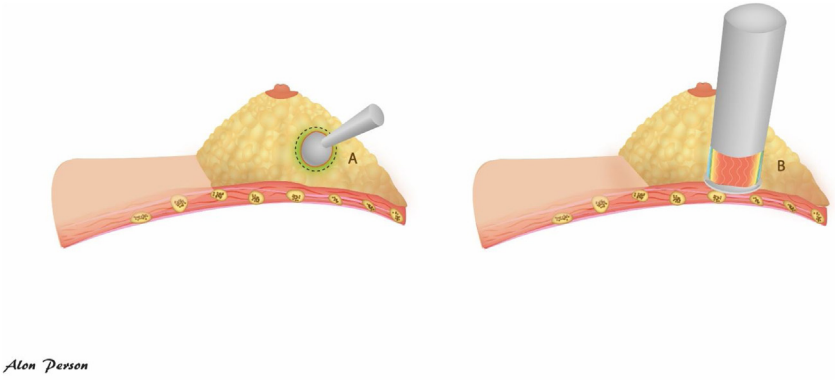

Fig. 1. Intraoperative radiation techniques. A: A 50 kV spherical applicator positioned within the lumpectomy cavity. The therapeutic prescribed dose is at the surface around the applicator, with a steep dose gradient and leading to only 25% of the prescribed dose at 1 cm distance. B: Intraoperative electron radiation applicator. During surgery the irradiated volume to be irradiated can be fully determined and adjusted.

less than 1 cm can lead to significant skin doses and complications. Conversely, for IOeRT the irradiated volume can be determined and fully adjusted at the time of surgery according to the size of the primary tumour and the local anatomy, while the skin is retracted (Fig. 1B). Therefore, an improved dose coverage and lower RT-related skin complications rates can be obtained as compared to 50 kV X-rays.

While mobile IORT techniques require some specific expertise, and interstitial brachytherapy-PBI is more demanding and mainly done at specialized centres, EBRT-PBI can be applied in every radiation oncology department. Contrary to IORT, brachytherapy- and EBRT-PBI can be done after recovery from the surgery and, most importantly, knowing final pathology results. This is important, as illustrated by Tallet et al. including IORT patients selected based on the GEC-ESTRO and ASTRO criteria for PBI, with one-third of the patients needing additional whole-breast-irradiation mainly due to the presence of lymph node involvement and/or an extensive intraductal component.[6,7,13] This combination was associated with increased grade 3 toxicity (the IORT dose used for definitive treatment is 21 Gy, significantly higher than the 10 Gy that is mostly used if an IORT boost is planned with whole breast EBRT).[4,13]

For our patients, the main treatment outcomes of interest include both disease-related outcomes and RT-related toxicity. Efficacy of PBI is closely related to adequate patient selection and adequate dose delivery to the CTV. Adverse events and cosmetic results are strongly influenced by the adopted RT schedule, the irradiated volume (and ratio with the volume of the non-target ipsilateral breast), and the technique. As we indicated above and, in the table, the best results will be obtained when respecting the inseparability of all those parameters.

Conflict of interest

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