



## Special commentary

## Has partial breast irradiation by IORT or brachytherapy been prematurely introduced into the clinic?

Harry Bartelink<sup>a,\*</sup>, Celine Bourcier<sup>b</sup>, Paula Elkhuizen<sup>a</sup><sup>a</sup> Netherlands Cancer Institute, The Netherlands; <sup>b</sup> Institut Gustave Roussy, France

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## ABSTRACT

In contrast to most new oncology treatments, wide clinical introduction of partial breast irradiation (PBI) is not based on level A trial evidence. Despite promising phase I/II data, new reports based upon large cohorts of patients mention more recurrences and/or complications from PBI compared with whole breast irradiation (WBI), necessitating more careful selection of patients for PBI while awaiting long term results of major clinical trials. In an attempt to improve this we give preoperative PBI within a prospective trial.

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During the last decade partial breast irradiation (PBI) has rapidly entered clinical practice on a wide scale. It is claimed by several authors to be a safe procedure with good cosmetic results and due to the shorter treatment time, allowing more women living far away from a radiotherapy center to have access to breast conserving therapy (BCT). Several approaches have already been introduced into the clinic: intra-operative irradiation with electrons from a linear accelerator or a 50 KeV source in the operation room, implantation of a balloon with a radioactive source in the surgical cavity, or an interstitial implant with several needles filled later on with a radioactive source. More recently, PBI with external irradiation with IMRT has also been applied in the clinic.

**Evidence based medicine – local control after APBI?**

Accelerated partial breast irradiation is currently gaining increased interest in early breast cancer management despite the fact that level A evidence is still lacking. No publication of large randomized clinical trials with sufficient follow up is available. Only one small trial with 5 year follow-up (median = 66 months) has been published, showing equal local control after either whole breast irradiation (WBI) or brachytherapy partial breast irradiation (brachy PBI), but this trial has limited numbers ( $n = 130$  patients per treatment arm) and is therefore underpowered to demonstrate a non-inferiority treatment [1]. A larger phase III clinical trial with sufficient patient numbers ( $n = 2232$ ) recently reported an equal local control after WBI or IORT [2] but this publication has been

heavily criticized, due to a short median follow up of 2 years, limited depth penetration of the radiation beam and inclusion of low risk patients receiving also adjuvant chemo- and/or hormonal therapy [3].

Even though level A evidence for APBI use has not yet been reached, the brachy PBI (especially mammosite use) has increased in the USA from virtually 0% in 2000 to 13% in 2007 [4] and has since then been rapidly increasing. In order to attempt a careful introduction of PBI into the clinic, guidelines for selection of patients for PBI have been published (GEC-ESTRO and ASTRO), mainly based on low risk factors for local recurrence, although these guidelines could not be based upon the required level A evidence.

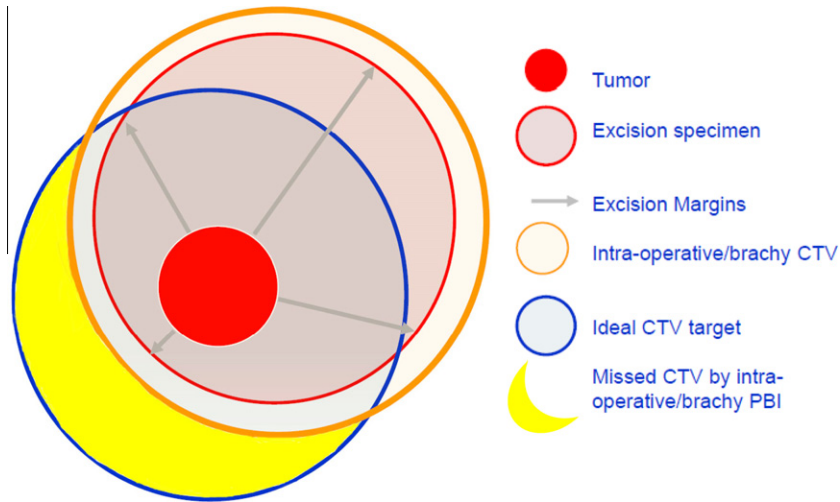
One of the main limitations of the use of brachy PBI or IORT is the absence of pathology information during intra-operative procedures. On the other hand, one of the most important advantages of 3D-conformal or IMRT post-operative PBI is its ability to evaluate all pathologic data before radiation treatment to better identify those breast cancer patients who would benefit from APBI, either in ongoing clinical trials or outside clinical trials according to GEC-ESTRO and/or ASTRO recommendations. Fortunately several ongoing phase III randomized clinical trials with thousands of patients are now nearing completion worldwide (NSABP B39, RAPID, ELIOT trials) [5]. These trials will finally provide an answer to guide clinicians in selecting patients for PBI.

**Evidence based medicine – APBI target volumes?**

Apart from a shorter treatment time, authors defend the more precise irradiation of the tumor bed by using brachy PBI or IORT as such techniques are performed during the lumpectomy

\* Corresponding author.

E-mail address: [h.bartelink@nki.nl](mailto:h.bartelink@nki.nl) (H. Bartelink).



**Fig. 1.** Breast tumors are often eccentric located with highest risk of residual tumor in the region of the narrowest resection margin, therefore CTV by brachy or IORT is not covered.

procedure. One wonders if this is indeed the case, as f.e. in a major review of surgical specimens there appeared to be no relationship between the size of the specimen and the tumor size [6–8]. Another striking phenomenon is the neighborhood the tumor at the margin of the surgical specimen [7–9]. This means that precise irradiation with for example 1 cm margin around the original tumor will be overtreatment at the side with a large margin in the surgical specimen; however undertreatment will occur on the other side with a minimal margin in (see Fig. 1). Hence, the use of 3D-conformal or IMRT/IGRT post-operative PBI probably better covers the target volume rather than intra-operative procedures.

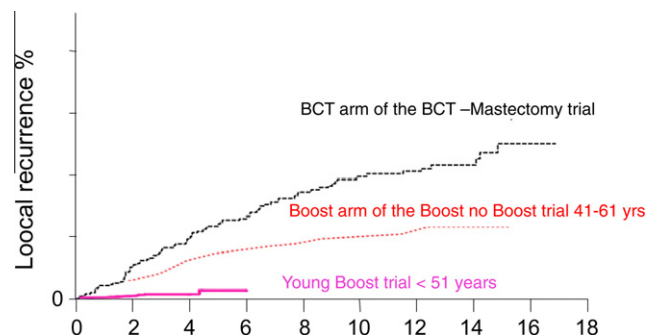
### Increased complication rate?

In BCT it is well known that surgical complications such as hematoma, infection and abscess lead to poorer cosmetic outcome [10]. Extending the operation time, particularly by performing extra procedures such as inserting needles, is most likely to produce more complications, and thus a worse cosmetic outcome. In a recent analysis using the USA Medicare billing system, 85,783 patients receiving BCT followed by WBI were compared with 6952 patients treated with brachy PBI [11]. All patients were above the age of 67. Among a cohort of older women with breast cancer, brachy PBI was associated with worse long-term breast preservation and increased complications but no difference in survival. Indeed, significantly more post-operative complications were observed (i.e. mastitis, abscess, wound healing, fistula, hematoma etc.). In addition, a higher rate of late radiation complications was seen in the PBI patient cohort (i.e. rib fracture, breast pain and fat necrosis). Only a limited increase in radiation pneumonitis was observed in the WBI patient cohort. Although this study has several limitations: i.e. no information on pathology, only mastectomy rate but no local recurrence rate, mostly use of single catheter with a balloon etc., it really reflects the outcome on a large number of patients treated, and it contains therefore an important message that PBI should be carefully introduced into the clinic. This makes the long term results from ongoing major clinical trials even more interesting, as the Smith et al. paper analyzed only patients older than 67 years of age, a population that according to the CALGB trial may be adequately treated with lumpectomy and adjuvant hormonal therapy if they have positive estrogen receptor [12]. One may even argue that a large part of this older patient population is exposed to an avoidable toxic treatment with PBI. Another

aspect is the fact that PBI is nowadays also widely used for patients younger than 67; one wonders what the amount of subsequent mastectomies/local recurrences will be in the younger population, as it is well known that younger patients have a higher risk after BCT [13].

### More breast recurrences?

Recently encouraging results have been reported from phase II/III trials, particularly after 3D-conformal APBI in which no excess of local relapses was observed [14,15]. However, R. Orecchia presented the results of the ELIOT trial comparing WBI to IORT (electrons) at the EBCC meeting in Vienna and at the ESTRO meeting in Barcelona. The median follow up was 5 years with a very low local recurrence of 0.7% rate in the WBI arm, while the ipsi-lateral breast recurrence rate was 7-fold higher in the PBI arm at 5 years. An unexpected observation was also that the annual recurrence rate in the PBI arm increased with follow up, suggesting that with longer follow up more recurrences will be seen in the PBI arm. It has to be mentioned here that less recurrences were seen in patients suitable for PBI according to the GEC-ESTRO and ASTRO criteria. As mentioned above, one still has to wait a number of years for the long term results of the Targit A and other large phase III trials. This finding of a higher breast recurrence rate in the IORT arm of the ELIOT trial is in line with Smith's paper revealing a 2-fold higher mastectomy rate after PBI, if compared with WBI patients. The excellent low local recurrence rate of the WBI arm of the ELIOT trial is nowadays more often observed even in high risk young patients



**Fig. 2.** Local breast recurrence rate in three consecutive WBI trials from 1980 till 2012 (modified from Ref. [34]).

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