New radiation therapy technique for breast cancer: should the IOERT boost be a standard technique?

"Various methods for accelerated partial breast irradiation are under investigation, but long-term results are not available."

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The standard treatment for early breast cancer comprises wide local excision, sentinel lymph node biopsy or axillary lymph node dissection and whole-breast radiotherapy (WBRT), including boost radiation if indicated, and adjuvant medical treatment. Multiple randomized clinical trials and meta-analyses demonstrated the effectiveness and safety of WBRT, and revealed that local control plays a crucial role in overall survival [1,2]. The European Organisation for Research and Treatment of Cancer (EORTC) boost versus no boost trial demonstrated that the additional dose escalation to the tumor bed, the tumor bed boost, further improved local control rates [3]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG [Oxford, UK]) overview suggested that differences in local treatment that substantially affect local recurrence rates would avoid approximately one breast cancer death over the next 15 years for every four local recurrences avoided and should reduce 15-year overall mortality [2]. The local recurrence rate is estimated for 1% per year, and varies according the literature between 4 and 7% after 5 years and up to 10–20% in the long-term follow-up [1,4–6]. The majority of patients who develop local recurrences do so within 2–5 years [1,7]. Patients with local recurrences have an increased risk of distant metastases, and local recurrence seems to be an independent predictor of distant metastasis [7–15]. Patients who develop recurrences in the short term have a worse prognosis than patients who develop recurrences in the long term [1,7]. Based on these data the reduction of local recurrence rates should be one of our treatment goals. Many factors contribute to the reduction of local recurrence rates, such as improved diagnostic tools, modern surgical techniques, the extensive pathologic evaluation of specimen and margins, the increasing use of adjuvant systemic therapies and the extensive use of radiation therapy.

Standard radiation therapy comprises 50–55 Gy in daily fractionations for 5–6 weeks. The additional application of an external boost radiation of 10–16 Gy to the tumor bed can reduce the local failure rate by 40% [3,16–19]. With this therapy an excellent local tumor control can be achieved.

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On the basis of these low local recurrence rates the concept of whole-breast irradiation comes up for discussion and accelerated partial breast irradiation (APBI) is increasingly under consideration. Various methods for APBI are under investigation, but long-term results are not available. APBI may be delivered during surgery as a single dose or after surgery in various fractionations. Intraoperative radiotherapy (IORT) is delivered as a single dose during surgery as APBI, or can be applied as an anticipated boost irradiation during surgery combined with additional WBRT after surgery.

The Salzburg concept combines intraoperative electron radiotherapy (IOERT) in boost modality, delivered by a linear accelerator, with WBRT after surgery, and argues for the further reduction of local failure rates. We published our results on IOERT boost plus WBRT versus WBRT plus postoperative electron boost and calculated 5-year actuarial rates of ipsilateral breast tumor recurrence (IBTR) of 0.0 and 4.3%, respectively [20–23]. The 10-year results with actuarial 10-year IBTR rates of 2.7% in the IOERT boost plus WBRT group are submitted for publication [Reitsamer R, Kopp M, Menzel C *et al.*: 10-year results of IOERT boost and whole breast radiotherapy in breast cancer patients. Manuscript submitted]. With our study, we could demonstrate that immediate IORT boost yields excellent local control, and a further reduction of local failure rates is possible compared with standard radiation schemes. The advantages of IOERT in boost modality are the precise boost application directly to the tumor bed without the risk

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of a topographic miss. The complete skin sparing avoids irradiation of the skin, and therefore the development of teleangiectasies. The target volume is smaller for the IOERT boost than for conventional postoperative boost techniques. Dose distribution is very homogeneous for electrons, and a dose of 9 Gy to the 90% reference isodose is biologically equivalent to 17 Gy for the tumor effect and to 26 Gy for the late effect on the normal tissue. These factors result in excellent cosmesis. Furthermore, the postoperative WBRT can be reduced for 7–10 days.

Lemanski *et al.* from the French group, using IORT in boost modality plus postoperative WBRT also reported very promising results with local recurrences in the long-term follow-up (10-year local recurrence rate of 4%) [24].

However, the huge advantage of APBI, the very short radiation period, or the inclusion of the complete radiation into the surgical procedure, convinces at a first glance. The promising short-term results of those studies must not negate the potential increase in local recurrence rates with the risk of reduction in overall survival rates.

In the Electrons Intraoperative Therapy (ELIOT) trial, the Milan group delivers electrons directly to the tumor bed in the operating room immediately after excision of the tumor [25–30]. A single dose of 21 Gy with energies up to 9 MeV, is applied from a mobile linear accelerator to the tumor bed, while shielding the thoracic wall with a lead plate. The question of increased late normal tissue toxicity arises as consequence of the application of a high single dose of 21 Gy. Long-term cosmetic results and local control rates are eagerly awaited. Dose homogeneity and full coverage of the target volume are advantages, as well as the single-shot modality.

Long-term results for partial breast irradiation are available for interstitial brachytherapy [31–34]. The results are excellent, but patient comfort is very low and the effort is high. High-dose-rate (HDR) brachytherapy can be performed in an outpatient procedure, but the risk of skin retractions after iridium implants is high, especially after narrow distance of needles to the skin surface, with poor cosmesis. Antonucci *et al.* recently published data on APBI with brachytherapy and reported 10-year IBTR rates of 5% for APBI brachytherapy and 4% for WBRT, concluding APBI to be comparable to WBRT in selected low-risk patients [35].

The MammoSite™ technique is the further development of HDR brachytherapy [36–41]. The device consists of an inflatable balloon with a catheter, which is placed inside the lumpectomy site. An Ir-192 source can be placed into the centre of the balloon through the catheter twice a day for 5 days, prescribing 34 Gy in 1 cm distance of the balloon. The dose-limiting factor for MammoSite is the dose to the overlying skin and the dose to the thoracic organs, such as the heart and lung. The spreading of the wound bed by the balloon will probably worsen the cosmetic outcome in the long-term follow-up, although good cosmesis is reported in the short-term follow-up. One problem is that only 20–25% of patients with breast-conserving surgery are eligible for the MammoSite procedure [42,43]. Teleangiectasies appear in 30% of patients if the balloon-skin distance is less than 7 mm. The dose inhomogeneity with only one seed in the middle of the balloon cannot equal dose distribution obtained with multicatheter brachytherapy. Furthermore, 34 Gy at 10 mm may be insufficient, especially in young patients.

The intraoperative targeted radiotherapy (TARGIT) uses a miniature electron-beam-driven x-ray source called Intrabeam™, which emits x-rays with 50 kV from the point source [44.45]. Spherical applicators with various sizes are used to keep the irradiated tissue at a distance from the x-ray source. This device is inserted intraoperatively into the tumor bed after excision of the tumor, and emits x-rays from within the breast. The irradiation time is 20–25 min, and the system applies 20 Gy at the surface and 5 Gy at 10 mm from the surface of the applicator, which possibly could be insufficient for tumor control.

Three German Oncology Societies, the German Society of Radiation Oncology, the German Society of Senology, and the Working Group for Gynecological Oncology of the German Cancer Society, discourage the routine use of APBI outside clinical trials, independent of the method (interstitial brachytherapy with multicatheter technique, IOERT, the Intrabeam system or the balloon catheter technique MammoSite) [46]. They state that WBRT remains the gold standard in the treatment of early breast cancer until definite results show that APBI neither impairs therapeutic outcome nor cosmetic results.

The American Society for Radiation Oncology (ASTRO [VA, USA]) released a consensus statement on APBI recently, and proposed three patient groups for APBI, a 'suitable' group, a 'cautionary' group and an 'unsuitable' group [47]. The authors define a 'suitable' group for APBI with very low risk for recurrence including all of the following criteria: patients with invasive ductal, lymph node

negative, hormone responsive breast cancer up to 2 cm (T1) and negative margins by at least 2 mm, and older than 60 years. All patients younger than 50 years or patients with nodal involvement are 'unsuitable' for APBI. In other words, according to these criteria approximately 75% of patients would not be suitable for APBI in our patient population. The authors of the consensus statement recognize that APBI is unlikely to replace WBRT for all or even most patients treated with breast-conserving surgery.

However, the authors report in this consensus statement that approximately 32,000 women in the USA have been treated with the MammoSite brachytherapy catheter. Even if many of those patients have been treated within a clinical trial, most of those patients have been treated with the MammoSite system outside a clinical trial. Although the MammoSite is US FDA-approved, we are still lacking long-term results.

Future perspective

The incidence of breast cancer decreased in recent years in Europe and the USA probably due to the decrease of hormone-replacement therapy, but will be stable or increase again due to lifestyle, diet and lack of physical activity in many countries. Detection of early-stage breast cancers due to screening programs and breast cancer awareness of patients will further increase in the future. However APBI will be an option only for a small subset of patients with low risk of recurrence, especially for the older patients with small node-negative, endocrine-responsive tumors. The majority of patients will still need WBRT. For those patients the intraoperative electron boost combined with postoperative WBRT will possibly be the standard of care. The results from the prospective randomized trials ELIOT and TARGIT, as well as from the NSABP B-39/RTOG 0413 trial, comparing whole breast irradiation followed by optional boost with three different partial breast irradiation techniques (multicatheter brachytherapy, MammoSite balloon catheter, 3D conformal external beam radiation), which is still open to accrual, can be awaited in several years.

> *"The authors of the consensus statement recognize that APBI is unlikely to replace WBRT for all or even most patients treated with breast-conserving surgery."*

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