The Role of Brachytherapy in the Treatment of Breast Cancer

Daniela Kauer-Dorner · Daniel Berger

Department of Radiotherapy, Medical University of Vienna, Vienna, Austria

Keywords

Breast cancer · Brachytherapy · Partial breast irradiation · Boost therapy

Summary

Radiotherapy plays an important part in the management of breast cancer. Especially after breast-conserving surgery, external whole breast irradiation, occasionally with an additional local boost, is an integral part of breast conservation. Besides external radiation techniques, brachytherapy (BT) has long been among the treatment options, especially with regard to local boost application. With the emerging implementation of accelerated partial breast irradiation (APBI), BT in general and interstitial multi-catheter BT in particular, are gaining an increasing role in the management of a selected group of early breast cancer patients. APBI is an approach to reduce the irradiated area to the former tumor bed rather than treating the whole breast tissue in patients with a low baseline local recurrence risk. After a variety of phase I–III clinical studies, it is clearly evident that APBI will play a role in the treatment of this selected patient group. In this review, we focus on the clinical development and different available techniques of breast BT and provide a preview of prospects for its use.

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Introduction

With an estimated 1,676,600 new cases and 521,900 deaths, breast cancer is the most frequent malignant tumor in women worldwide [1]. Breast-conserving surgery (BCS) followed by external whole breast irradiation (WBI), frequently including a local

boost therapy, is accepted as standard therapy in the breast-conserving management of early breast cancer (stage 0–II) [2]. Since the late 1990s, a new approach of fractionation has been established in the postoperative treatment. Hypofractionation with a reduced total dose of 39–42.6 Gy in 13–16 fractions administered within 3 weeks is now widely accepted as a standard method for WBI [3, 4]. Besides external beam irradiation, brachytherapy (BT) represents an important radiotherapeutic modality in breast cancer treatment. In the beginning, breast BT was mainly used for local boost therapy. However, in trying to de-escalate treatment time and treatment volume while maintaining the local control rates of WBI, accelerated partial breast irradiation (APBI) has quickly evolved as an attractive new approach. From the beginning of APBI, BT has played a role as the oldest and best investigated technique of delivering radiation doses to the breast. In this review, we focus on the role of BT in modern breast cancer treatment and on the different techniques, and provide an overview of outcomes and future trends.

Brachytherapy

BT is a type of radiotherapy in which tiny amounts of radioactive material sealed in catheters, wires, needles, or seeds are placed directly into the tumor tissue or the former tumor bed if used as postoperative treatment. Because of the precise positioning of the radiation sources into the tumor or the tumor bed, high doses can be applied to small areas. Furthermore, due to Newton's inverse-square law, which applies to ionizing radiation, the dose accordingly decreases with the distance to the center of the source, and high doses can be applied to target areas while avoiding high dose levels at nearby organs at risk (OAR). BT is commonly used in the treatment of cervical, prostate, and breast cancer as monotherapy or as a boost therapy in addition to external beam therapy. However, it may also be used as part of the treatment procedures in several other tumors, such as carcinoma of the head and neck region, respiratory tract, digestive tract, and soft tissue sarcoma [5].

BT can be delivered as intracavitary, intraluminal, or multicatheter interstitial BT (MIB) as a temporary application or as a permanent seed application.

Concerning the treatment of breast cancer, MIB has been investigated for a long time with extensive follow-up [6, 7]. For this technique, between 14 and 20 flexible, afterloading catheters are placed in the breast closely around the lumpectomy cavity. Application is free-hand or template-guided, mostly under general anesthesia. The change from 2-dimensional (2D) reconstruction of the implant geometry and treatment planning based on X-ray reconstructions to computed tomography(CT)-based 3D planning has significantly improved implant quality. In modern BT, a computer program (treatment planning system) is used to calculate the exact dose delivered by a radioactive sealed source (usually Ir-192) inside the breast area requiring treatment. A small radiation source, motor-controlled and dwelling within the applicators (needles or tubes), is used to deliver the treatment using a so-called afterloader device: Radiation is delivered via applicators for the shortest possible time while the patient remains in a shielded room. This ensures maximal radiation protection of the personnel. A major part of the planning process is the applicator reconstruction where the implant geometry is digitized onto 3D images on which the target volume can be defined. Inserted catheters are numbered, positioned, and placed relative to the surrounding tissue and other catheters. As mentioned above, if 2D treatment planning is employed, applicators are visualized by using radiographs and then projected onto CT simulation scans (fig. 1). The assessment of accurate implant geometry [8] for individualized treatment planning has always been an essential part of quality assurance in the planning process in order to limit the irradiated volume as much as possible and to limit the dose to adjacent OAR like skin, lungs, and heart [9]. To avoid any necrosis in the implanted tissue from radiation, the dose nonuniformity ratio (DNR) is monitored and kept below 35%. The DNR is the ratio of the target which receives a dose equal to or higher than 150% of the reference dose to the target which receives a dose equal to or higher than the reference dose [10]. Before the year 2000, implant geometry was thus mainly defined on radiographs, while after that period, CT-based simulation emerged in BT planning where the implant is directly visualized as located in the target tissue. This technological progress has resulted in better reconstruction accuracy (<1 mm spatial resolution) and a significant reduction in the treated volume by 30–40% in breast BT over the last 10 years at the Medical University of Vienna (unpublished).

Using MIB, the dose can be delivered using low dose rate (LDR), pulsed dose rate (PDR), or high dose rate (HDR) techniques, depending on the length of time the radioactive source remains in place [11]. In LDR BT, radiation sources deliver doses continuously with dose rates between 0.4 and 2 Gy/h over a few days. LDR regimens were mainly used in early APBI trials where doses of up to 45 Gy in 4.5 days were used [12]. While radiobiologically advantageous, LDR cannot be delivered in an afterloading setup. In HDR BT, a single radiation source delivers the dose to the application site using the above described afterloading setup. Doses are delivered at a rate of 12 Gy/h or higher to the so-called dwell

Fig. 1. Development from **a** X-ray-based catheter visualization to **b** computed tomography-based brachytherapy planning and **c** dose distribution in an APBI (accelerated partial breast irradiation) patient.

positions so that large doses can be administered within a few minutes. PDR BT, which is also administered using an afterloading setup, uses dose rates of up to about 3 Gy/h, and the dose needed is administered (pulsed) every hour, 24 h per day. In this way, it combines the physical and radioprotection advantages of HDR with the radiobiological advantages of LDR [13].

Role of Brachytherapy in Local Boost Therapy

The treatment intention of adjuvant breast irradiation is to minimize the risk of local recurrence after BCS. It is well known that especially the tissue immediately surrounding the primary tumor (bed) is at highest risk of giving rise to recurrence. Clinical and pathological findings have clearly documented high rates of failure patterns in the closest vicinity of the primary index lesion [14–17]. This strongly supports dose escalation to the tumor bed after WBI. Several randomized studies have already demonstrated an evident benefit of local boost therapy with reduced 5-year local recurrence rates from 7.3–13.3% in the non-boost groups to 3.6–6.3% in the boost groups [18–22]. The randomized boost versus non-boost EORTC 22881-10882 trial is the landmark study proving the significant benefit of a local boost after WBI in terms of local control rates, however, without any measurable effect on long-term overall

survival. After 20 years of follow-up, the actuarial overall rate of ipsilateral breast tumor recurrence (IBTR) was 16.4% in the no-boost group versus 12% in the boost group [23]. Interstitial BT is one of the oldest and time-tested techniques of boost application and has been used by several institutions participating in the EORTC 22881-10882 trial. Besides interstitial BT, there are other methods of administering local boost therapy, in particular, external beam irradiation and intraoperative radiotherapy. Limited data are available comparing advantages and disadvantages of brachy boost therapy and the other techniques [24, 25]. Until now, no significant difference could be identified in terms of local control and side effects like fibrosis between BT and other modalities. All show excellent or good cosmetic outcome; however, prospective head-to-head comparisons are not available. Arguably, treatment volumes are always lower with BT, giving BT an advantage over external beam or intraoperative electron therapy. Besides local control and cosmetic outcome, the dose to OAR has been intensively investigated as it is the surrogate parameter of treatment toxicity. Terheyden et al. [26] could demonstrate a significant dose reduction with HDR BT to the investigated OAR such as lung, ribs, skin, and heart for right-sided breast cancer compared to external beam radiotherapy, while left-sided irradiation did not show a difference in the maximum dose to the heart. Regarding the dose to the lung, it is well established that the pneumonitis risk due to radiation is proportional to the mean dose to the lung, and the long-term risk of secondary malignancy induction seems to be related to the lung dose [27–29]. A brachy boost delivers a lower dose to the lung compared to external techniques, but further studies are needed to confirm any advantage translating into favorable long-term clinical outcome.

Role of Brachytherapy in Accelerated Partial Breast Irradiation

Looking at local control after BCS followed by WBI, several prospective trials demonstrated that a very large percentage of local recurrences (69–90%) arises in the very close vicinity of the initial tumor area [30–32]. Therefore, concentrating the required total dose to the area of highest risk of an ipsilateral in-breast recurrence, a lot of normal breast tissue at greater distance from the index tumor and OAR like lung, heart, and skin could be spared from acute and chronic side effects, which also could eventually favorably influence cosmetic outcome. The biological model of the linear quadratic equation, on which the estimation of radiation effects is based, formed the basis of the fractionation scheduling of accelerated delivery in partial breast irradiation. Based on the concept of radiobiological equivalence, shortening a treatment course requires decreasing the total dose, and the reduction in treated volume permits an increase in the dose per fraction to achieve the same clinical outcome as with a longer treatment course. BT, which has been in use for boost radiation after WBI as described above, provides an excellent technique to deposit a high radiation dose into the small area of the former tumor bed with a rapid dose falloff around the target volume. At the beginning of the APBI trials, the only form of

BT was MIB using multiple catheters to deliver radiation to the lumpectomy cavity [33–36]. One of the earliest trials using MIB for APBI was started in the late 1980s by Guy's Hospital using LDR MIB for monotherapy in 27 non-randomized patients, followed by the Ontario trial performed at the London Regional Cancer Center with 39 patients. Both studies included patients with unfavorable risk factors like positive resection margins, large tumors, and node-positive disease, resulting in high ipsilateral in-breast recurrence rates (37%/16.2%) These discouraging results triggered the discussion of proper selection criteria for patients suitable for APBI, establishing risk factors for local recurrence like young age, tumor size, node-positive disease, positive or unknown resection margins, high nuclear grade, lymphovascular invasion, and extensive intraductal component. Furthermore, the development of image-based catheter implantation, implant reconstruction, and dose planning replaced 2D orthogonal-based treatment planning and resulted in a marked improvement in tumor dose coverage. All these efforts promoted the initiation of several prospective trials of modern MIB with strict patient selection criteria [37–41]. The key study to establish MIB APBI as a single treatment option after BCS is a randomized, non-inferiority phase III trial including 1,184 patients from multiple centers in Europe, which was recently published by the GEC-ESTRO Breast Cancer Working Group [42]. 5-year local control, disease-free survival, and overall survival were similar for MIB APBI and external WBI after BCS in early breast cancer patients with comparable early toxicity and patient compliance [43], and the trial proved non-inferiority of the de-escalation of treated volume, total dose, and overall treatment duration with MIB APBI compared to WBI. Patients included in the largest randomized trial of APBI versus WBI, NSABP B39/RTOG 0431, including MBI are still in follow-up and results are pending.

Another development in the use of MBI in primary breast-conserving treatment is the further shortening of the treatment duration from about 10–8 fractions given over 4–5 days to single-dose irradiation. Hannoun-Lévi et al. [44] recently reported a phase I/II trial of single-dose irradiation with 16 Gy in elderly women with promising outcome in terms of local control and acceptable acute toxicity and cosmetic outcome. Besides this study, more trials are focusing on the benefit of MIB post BCS as a treatment option in elderly breast cancer patients. Treatment decisions in elderly cancer patients need to focus not only on local control and overall survival but primarily on quality of life. Sumodhee et al. [45] and Genebes et al. [46] demonstrated in their studies that MIB can perfectly apply sufficient local irradiation with maximum preservation of OAR in a very short treatment period with excellent local control and low acute and chronic side effects. This could be an ideal alternative for elderly breast cancer patients, representing a compromise between omitting radiotherapy and a whole course of WBI.

Besides the primary treatment of early breast cancer patients, APBI using MIB is gaining increasing importance in the local treatment of IBTR after a second course of BCS. Radical mastectomy is still regarded as the gold standard treatment for IBTR. However, there is an increasing philosophy for a second course of breast-conserving local treatment for IBTR including radiation

after BCS to minimize the risk of a second local recurrence. MIB is the most commonly used technique of second-course local irradiation with promising results on local control with well accepted acute and chronic side effects and a high percentage of excellent to good cosmetic results [47–49].

In the early days of APBI, MIB was the only technique to deliver APBI with promising clinical results; however, MIB is highly dependent on the operator and the center's expertise. Since 2002, balloon-based BT devices and hybrid applicators including MammoSite® (Hologic, Marlborough, MA, USA), Contura® (Hologic), and Savi® (Cianna Medical, Aliso Viejo, CA, USA) have been introduced. The 5-year analysis of treatment efficacy, cosmetic outcome, and toxicity of MammoSite breast BT from the American Society of Breast Surgeons showed excellent results comparable to other forms of APBI [50]. However, using the single-channel MammoSite carries a certain risk of dosimetric limitation resulting in limited ability to shape the radiation dose to the target volume and OAR, which may in turn result in a greater risk of healthy tissue damage. The development of multi-luminal hybrid BT devices like Contura and Savi has combined the user-friendly application of MammoSite with the dosimetric advantages of MIB [51]. These new devices provide adequate targeting of the tumor bed and better control over the radiation dose to critical structures. Further research will be needed to define the potential of these devices as well as advantages and disadvantages in terms of clinical outcome in comparison to classical MIB.

Conclusion

Radiotherapy plays an essential part in breast-conserving treatment, and external beam irradiation is the most widely used modality. However, BT can deliver radiation doses to the target volume in a highly conformal way, thereby minimizing exposure of normal surrounding structures and OAR. The use of modern imaging technologies like CT, or even ultrasound and MRI, together

with highly sophisticated treatment planning software, have further improved the accuracy of individualized treatment planning. However, there are still unanswered questions concerning the use of breast BT as a boost therapy or for APBI in primary or recurrent breast cancer: There is a variety of options for delivery with external and internal techniques for boost application and partial breast irradiation, but data are not sufficient to clearly favor any particular technique. Further research is required firstly to determine the optimal technique with regard to long-term local control and side effects, and secondly to define the best approach for individual patients. Patients with small breasts and planned eventual oncoplastic surgery might be the best candidates for external or intraoperative electron radiotherapy [52] as a boost or partial breast irradiation, while women with larger breasts might benefit more from different invasive techniques like MIB or balloon-based BT. Long-term follow-up data of BT, especially periods exceeding 10 years, are not currently available but are needed to support the efficacy of breast BT given the high survival rate of these patients. Finally, consensus guidelines on suitable patient selection criteria are available from national and international societies like ESTRO, ASTRO, and DEGRO but should be harmonized between countries and even different techniques. Proper patient selection criteria suitable for APBI and harmonized biologically equivalent dose schedules will simplify the comparison of data from different trials. A potential barrier to the wide adoption of MIB for APBI might be the complex and difficult handling of interstitial BT. MIB is technically demanding and operator- and center-dependent, and therefore it may be a less popular technique compared to other BT modalities. A lot of effort has already been put into giving general recommendations for performing MIB for APBI and boost therapy, but more clinical research is needed.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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