Review article

Brachytherapy in breast cancer

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Abstract

Breast conserving surgery (BCS) with postoperative radiotherapy has been a standard treatment of early stage breast cancer for the last 30 years. Interstitial brachytherapy has been used as a boost therapy after whole breast external beam radiotherapy (EBRT), and recently, it's been investigated in selected patients as a possible technique of a single radiotherapy modality (partial breast irradiation, PBI) after tumorectomy. Further clinical studies are required to define the most appropriate candidates for breast brachytherapy as a sole modality treatment and to determine the best delivery method of brachytherapy (multicatheter interstitial implant vs. balloon brachytherapy) in such patients.

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Key words: breast cancer, interstitial brachytherapy, PBI, boost.

Purpose

Breast conserving surgery (BCS) with postoperative radiotherapy has been a standard treatment of early stage breast cancer for the last 30 years. Interstitial brachytherapy has been used as a boost therapy after whole breast external beam radiotherapy (EBRT), and recently, it's been investigated in selected patients as a possible technique of a single radiotherapy modality (partial breast irradiation, PBI) after tumorectomy. The aim of the study is to discuss some aspects of current status of breast cancer brachytherapy.

Technique of breast implantation

The major concern in performing a breast implant is the adequate coverage of the tumor bed. It depends mainly on a good outline of the surgical cavity. Preplanning of the implant can provide an important information about the target geometry and required placement of the source guides. It is essential in achieving acceptable target coverage, dose uniformity throughout the irradiated volume and critical structure avoidance. Whenever possible, the placement of interstitial brachytherapy needles should be assisted by ultrasonography. With this technique the lumpectomy cavity can be outlined in all dimensions. Skin marks should be placed for reference at time of implantation. These dimensions can be compared to clinical estimate of the location of the lumpectomy cavity, the presurgical mammograms, and the position of the scar. In the intraoperative setting, the dimensions of the lumpectomy cavity can be directly obtained, and the placement of the deep plane of interstitial needle should be verified by ultrasound [1, 2].

A variety of modalities have been used for identification of the target volume in preparation for the implant. These include the use of surgical clips, ultrasound, CT, MRI, and intraoperative visualization of excision cavity geometry. RTOG 95-17 protocol requires at least six radiopaque clips to be left within the cavity at the time of surgery to define the maximal extent of the cavity in three dimensions. Visualization of the clips under fluoroscopy allows the determination of an optimal direction of approach for the source guides in order to achieve the most conformal coverage of the target volume with the minimum number of source ribbons or wires. Skin marks should be placed to guide the needle insertions.

A number of various techniques of breast implantation are described by different authors. In some centers, dedicated templates are used to control the spacing of the guide needles. Some authors used only one point of entrance for the guide needles to improve the cosmetic results [3]. Intraoperative procedure can be an option with placing four or five plastic tubes, 2 cm apart, in each of two planes separated by 2 cm at the time of the breast tumor excision [4]. The position of the dummy sources should be determined by radiographs localization. Within 6 hours of surgery, plastic tubes should be loaded with the active sources.

Brachytherapy boost

The beneficial effect of radiation therapy boost to the tumor bed after BCS and whole breast irradiation have been largely demonstrated in numerous papers. In a group of 113 patients after BCS who received external beam whole breast irradiation (median 50 Gy) plus a boost dose to the tumor bed delivered by PDR brachytherapy

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(PDR-BT) the boost dose has been chosen in accordance to the pathologic tumor characteristics: 20 to 25 Gy after incomplete resection or vascular invasion or close margins, 15 Gy in T2-G3 stage [5]. The overall local failure rate after a median follow-up of 61 months was 4.4%. The actuarial 5- and 8-year local recurrence-free survival rates were 95% and 93%, respectively. An excellent or good cosmetic outcome was noted in 90% of the patients. A boost dose of 25 Gy resulted in significantly higher rate of late toxicity. In the EORTC "boost versus no boost" randomized trial 22881/10882, 2661 patients enrolled in the boost arm were analyzed [6]. All patients received 50 Gy whole breast irradiation and a boost dose of 16 Gy to the primary tumor bed after microscopically complete tumorectomy. Sixty-three percent of patients received a boost dose with electrons, 28% with photons beams, and 9% with interstitial BT. At 5 years of follow-up, local recurrences were seen in 4.8% of patients who received an electron boost, in 4% of cases with a photon boost received, and in 2.5% of patients who underwent BT. No differences were noted in terms of late toxicities.

For LDR breast brachytherapy used as a boost following 45 to 50 Gy of EBRT, the American Brachytherapy Society has recommended a total dose of 10 to 20 Gy at a rate of 0.3 to 0.7 Gy per hour. In source positioning the maximum skin dose should be no higher than the prescription dose. A typical maximum skin doses for boost implants are approximately 50% of the prescription dose.

In a French study after external beam irradiation (45 Gy in 25 fractions), a boost to the primary tumor was prescribed at 85% basal dose rate according to Paris system [7]. Intersource spacing varied from 1.5 to 2 cm. Linear activity ranged from 1.3 to 1.8 mCi/cm. Mean dose rates were 0.53 Gy per hour for patients with local recurrence and 0.56 Gy per hour for recurrence-free patients. Local recurrence rates were 10% for T1 (2/20), 15% for T2a (21/138), 23% for T2b (30/129), and 25% for T3 (13/53). The local tumor-control rates at 15 years were 76% for T1 and T2a and 70% for T2b and T3 lesions. Local tumor control correlated with dose rate and tumor size. Similar observations were reported by other authors [8]. The local failure rate was increased significantly with implant dose rates < 0.3 Gy per hour. The incidence of late normal tissue complications and poor cosmetic outcome was significantly higher in the patients treated with implant dose rates > 1 Gy per hour. It has been postulated that the implant dose rate should be maintained between 0.3 and 0.7 Gy per hour to maximize local tumor control and reduce late normal tissue injury.

The available data regarding using HDR as a boost is limited [9-12]. In Hungarian study 207 women with stage I or II breast cancer treated with BCS and whole breast radiotherapy (WBRT) and subsequently randomized to either radiation boost to the tumor bed or no further therapy [11]. The radiation boost consisted of 16 Gy of electron irradiation or 12 to 14.5 Gy fractionated HDR brachytherapy (HDR-BT). In 52 patients treated with HDR-BT the 5-year local tumor control rate was 91.4%. Excellent to good cosmetics result was reported in 88.5% of patients. Similar results were noted in the group of patients receiving an electron irradiation boost. The brachytherapy boost can be applied before or after EBRT, usually with 1 or 2 week break between EBRT and brachytherapy. The ABS recommends a dose fractionation scheme that yields early and the late effects are approximately equivalent to those of 10 to 20 Gy LDR following 45 to 50 Gy EBRT [13]. Controlled clinical studies are required in order to additionally define the most appropriate doses to be used for boost treatment.

Partial breast irradiation

Adjuvant whole breast radiotherapy (WBRT) is a standard procedure and world-wide accepted modality after BCS. Its main role is to sterilize areas of possible residual microscopic disease after tumor excision, but it is also recommended because of frequent multifocality and/or multicentricity of breast cancer. Postoperative radiation therapy can reduce the incidence of local recurrence from 20-30% to < 10% [14-16]. It has been proved that the local recurrence has a negative impact on survival [17]. The vast majority of local recurrences occur in close proximity to the tumor bed and it has been suggested that a good local control could be achieved by irradiating just the tumor bed and the surrounding tissues [14, 18-21]. The local recurrence rate outside the tumor bed is about 15%, and is no different from the incidence of a contralateral breast cancer [22]. The beneficial effect of WBRT on the risk of local recurrence is reduced by the possible long-term development. A partial breast irradiation with the use of brachytherapy could reduce the incidence of long-term vascular side effects by reducing irradiated volume of chest wall, heart and a lung. Taking into account clinical reasons, patients comfort and economical aspects, BT partial breast approach, can shorten considerably the overall treatment time from the 5 to 6 weeks to less than 10 days with a significant reduction of the delay for the other planned adjuvant therapies [23-26].

The first clinical data of using LDR, followed by HDR-BT comes from the experiences acquired nearly 20 years ago. In Italian study, LDR-BRT the total dose of 50 to 60 Gy has been delivered to the involved quadrant of 115 patients with T1-2 N0-1 tumors after quadrantectomy and axillary dissection. Patients with axillary node involvement received chemotherapy or tamoxifen. Fifteen percent of patients had a positive or unknown margins after surgery and 20% – invasive lobular carcinoma. The 5-year local recurrence, disease-free survival and overall survival were 6%, 83%, and 96%, respectively [27]. In another two studies patients were assigned to receive LDR implant (45 Gy over 3.5 to 6 days) or HDR implant (32 Gy in 8 fractions twice a day) [23, 28]. Treated volume included 2 cm of breast tissue surrounding the tumor bed. All patients had tumors smaller than 4 cm with negative margins. Patients with one to three positive axillary nodes were admitted. At a median follow-up of 75 months one breast recurrence (2%) and three nodal recurrences (6%) were reported. In an update of this study, 150 patients were included with a mean follow-up

of 46 months [29]. Authors reported 1% of breast failure and 3% of regional node failure. Cosmetic outcomes were good or excellent in 75% of patients. In a British study a MDR remote-controlled afterloading system employing ^{137}Cs was used to deliver total dose of 45 Gy in four fractions over 4 days. At a median follow-up of 6.3 years, 18% of the eligible patients developed a breast relapse. Only one local recurrence (4%) occurred among patients with tumors smaller than 2 cm. The rate of incidence had grown to 35% among patients with tumors of 2 cm or larger [30]. In one of the largest single institution that experiences a group of 199 patients older than 40 years, with infiltrating ductal carcinomas < 3 cm in diameter, with negative surgical margins and pathologically negative axillary nodes received accelerated partial breast irradiation (APBI) after breast-conserving surgery [31, 32]. APBI consisted of LDR implant that delivered 50 Gy over 96 hours at dose rate of 0.52 Gy per hour in 120 patients. An HDR implant delivered 32 Gy in eight fractions (71 patients) or 34 Gy in 10 fractions (8 patients). The treated volume encompassed the surgical margin plus 2 cm surrounding margin. Seventy percent of the patients received adjuvant chemo- or hormonal therapy. The reported 5-year actuarial ipsilateral recurrence rate was 1%. Cosmetic results were considered to be good or excellent in 99% of cases in patients who had been followed-up for ≥ 5 years. These results were compared with a matched group of 199 patients treated with conventional WBRT at the same institution. There were no statistical differences between the two groups in terms of local failure, regional local failure, distant metastases, disease-free survival, overall survival, and cause-specific rates. The Radiation Therapy Oncology Group (RTOG) promoted a prospective phase I and II trial (RTOG 95-17) of APBI alone after lumpectomy [12]. The inclusion criteria included invasive nonlobular tumors ≤ 3 cm after lumpectomy with negative surgical margins and axillary dissection with zero to three positive axillary nodes without extra capsular extension. In this study the number of 100 patients received LDR (1/3 of patients) implant delivering 45 Gy in 3.5 to 5 days or HDR implants (2/3 of patients) delivering 34 Gy in 10 fractions in 5 days (twice a day). At a median follow-up of 2.7 years, 3% of the HDR patients experienced 3 or 4 stage of acute toxicity. In the LDR subgroup the rate of 3 or 4 toxicity was 9%. No patients experienced late grade 4 complications, however the grade 3 late toxicity occurred in 18% of the LDR group and 4% of the HDR group. In the German-Austrian trial, the amount of 274 patients were included. Selection criteria were: age older than 35 years, ECOG performance status of two or more, a maximum tumor diameter of 3 cm, negative margins, tumors with positive hormones receptors, negative axillary nodes or presence of a single micrometastasis with at least nine nodes removed [33]. A PDR technique (0.60 median dose per pulse each hour until a prescribed median total dose of 49.8 Gy) or HDR technique (32 Gy in eight twice-daily fractions) were performed. At a median follow-up of 12 months, no patients developed ipsilateral recurrence. Regarding acute toxicity, only 5% of patients experienced mild radiodermatitis and 1% experienced moderate radiodermatitis. Regarding late toxicity, 7% of patients experienced mild pain in the irradiated area and 1% developed intermittent pain. Mild or moderate fibrosis was palpable in 18% of cases, mild to moderate telangiectasia were found in 8% of patients. On the whole, the cosmetic outcome was judged good or excellent in 93% of patients. The Breast Cancer Working Group of the Groupe Europeen de Curietherapie/European Society for Therapeutic Radiology and Oncology activated a phase III trial in which patients are randomized to receive APBI (HDR/PDR implant) or whole breast irradiation (50 to 50.4 Gy plus 10 Gy electron boost).

The American Brachytherapy Society recommends total dose of 34 Gy in 10 fractions to the CTV when HDR-BT is used as the sole modality [13]. It is proposed to provide 3.4 Gy at two fractions per day separated by at least 6 hours. This was also the dose used in a phase II RTOG trial [18]. In March 2005 the RTOG in association with the National Surgical Adjuvant Breast and Bowel Project (NSABP), activated a phase III randomized study (NSABP B-39) investigating standard whole breast radiotherapy versus partial breast radiotherapy after lumpectomy for women with early stage breast cancer.

Further clinical studies are required to define the most appropriate candidates for breast brachytherapy as a sole modality treatment and to determine the best delivery method of brachytherapy (multicatheter interstitial implant vs. balloon brachytherapy) in such patients.

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