Pilot study of sole conformal peroperative interstitial brachyradiotherapy of early stage breast carcinoma using high-dose rate afterloading*

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In this study of high-dose-rate brachyradiotherapy to the lumpectomy site as the sole radiation are documented a three-dimensional treatment planning and preliminary results of accelerated partial-breast irradiation. From March 2002 to July 2004 25 patients were prospectively included in this study. Six patients were excluded becuase of definitive histology of lobular carcinoma or positive margin. The median age was 63.2 years (range: 44–77 years). Median follow-up of all patients is 11 months (range: 3–25 months) with a minimum follow-up of 3 months. Radiation was delivered using the high-dose-rate remote afterloader VariSource with ^{192}Ir source. The patients received radiation twice a day at least 6 hours apart for a total of 10 fractions over five days with a single dose of 3.4 Gy. The total dose was 34.0 Gy prescribed as a minimum peripheral dose to match or minimally exceed the volume defined by the surgical clips as seen on CT scans. Freehand technique allows conformal placement of the catheters to the shape of the lumpectomy cavity. We use the method of geometric optimalisation which allows the calculations of dose distribution in relation to target. At a median follow-up of 11 months none of patients developed in-field breast recurrences, one patient had out-of-field recurrences. There were no regional nodal recurrences. At each patient, there was calculated target volume size in cm^3 (median 91.3 cm^3) dose volume histogram (DVH), dose homogenity index (DHI). Median DHI was 0.42. Median volume of breast tissue getting 100% of the prescription dose, V_{100}, is 87%; and V_{150} 48.5%. We have noticed two treatment complications: hematoma and abscess in the place of tumorous bed after exstirpation. At last follow-up, patients rated the overall cosmetic outcome excellent.

This method is suitable just for patients with histologically confirmed small tumors (<3 cm in diameter) without negative prognostic factors for local recurrence (age at least 40 years, negative surgical margins, nodal involvement – maximum three positive nodes without extracapsular extension).

Key words: breast cancer, radiotherapy, peroperative radiation, interstitial brachytherapy

Breast conserving surgery is an attractive alternative to mastectomy for patients with Stage I a II breast cancer and it is now considered to be an equivalent therapy to mastectomy. The current standard of care for breast-conserving therapy includes a postlumpectomy course of whole-breast external beam radiotherapy (EBRT), which typically requires 5–7 weeks to complete. The purpose of radiotherapy (RT) is to prevent recurrence by eliminating residual foci of cancer that might remain in the surrouding breast tissue. This conservative approach still has the same radical intent as the destructive surgery first done by William Halstead over 100 years ago. The main obstacle for a wider acceptance of breast-conserving surgery is the of 6–7 duration weeks of postoperative radiotherapy, which has several disadvatages: the long course of treatment and very often distant abode of patients from a department of radiotherapy [1, 14]. It has been estimated from patterns of care study by the American College of Surgeons that only 50% of women in the United States who are eligible for breast-conserving surgery receive this form of treatment. Equally problematic, that 15% of women who should receive radiation after conservative treatment do not receive seems it [8].

Accelerated partial-breast irradiation (APBI) may be defined as any scheme that delivers radiotherapy to the tumor site and some surrouding tissue over a short overall period (5–8 days). Among the approaches described to date using

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brachyradiotherapy to accomplish this are following: low-dose rate (LDR) or high-dose rate (HDR) interstitial implantation or a baloon catheter (MammoSite) and single-fraction intraoperative irradiation using 50 kV orthovoltage radiation (Intrabeam) or electrons 4–12 MeV (Mobetron, Novac-7) [13, 14]. Irradiation of the tumor bed only is being investigated in several clinical trials. The number of studies with median follow-up times about 6 years using mainly interstitial high-dose rate APBI, 8–10 fractions, and total doses of 32 to 34 Gy have found low rates of breast recurrence and good cosmetic outcome. However, many centers do not have significant brachyradiotherapy experience [2, 3, 5, 11, 15].

Presented are preliminary data concerning the use of three-dimensional conformal planning of peroperative interstitial brachyradiotherapy of early stage breast carcinoma. This pilot study ranks among methods of accelerated partial-breast irradiation using high-dose rate (HDR) interstitial multicatheter brachyradiotherapy (^{192}Ir).

Patients and methods

Sole conformal peroperative interstitial brachytherapy was delivered to patients with early stage breast carcinoma. From March 2002 to July 2004 25 patients were prospectively included in this study which was approved by the Ethics Committee of Masaryk Memorial Cancer Institute. All patients gave informed consent. Six patients were excluded becuase of definitive histology of lobular carcinoma or positive margin. The median age of the 19 women in this pilot study was 63.2 years (range: 44–77 years). Median follow-up of all patients is 11 months (range: 3–25 months) with a minimum follow-up of 3 months.

Study objectives. The objective was to establish the methodics of peroperative brachytherapy for the clinical practice, evaluation of treatment complications, cosmetic effect and local control of the illness.

Eligibility criteria and diagnostic work-up. Patients with invasive lobular histology were excluded. Initially all patients were axillary node negative (only 3 patients had 1 to 3 axillary nodes positive). Eligibility criteria included histology of adenocarcinoma; clinical stage T1–T2 (tumor size <3 cm) and axillary node-negative breast cancer with mikroscopic negative resection margins. Pretreatment work-up included clinical examination, mammography and breast ultrasonography and axillary with biopsy of breast tumor, chest X-ray, liver ultrasonography, gynecologic examination and bone scintigraphy, pretreatment CT of breast, serum CEA and Ca15-3 levels, and blood tests. This method is suitable just for patients with histologically confirmed small tumors (<3 cm in diameter) without negative prognostic factors for local recurrence (age at least 40 years, negative surgical margins, nodal involvement – maximum 3 positive nodes without extracapsular extension).

Patients population, follow-up. The patients' characteristics are summarized in Table 1. The follow-up schedule included breast examination every 3 months. Mammography was done at 6 months postradiation and then once a year with ultrasonography. Cosmetic result was assessed every 3 months.

Table 1. Patients' characteristics, planning treatment volume (PTV) and dose homogenity index (DHI) characteristics

Number of patients	Age of patients	Mamma	Follow up (months)	Number of fractions	Number of levels puncture	Dose / fraction (Gy)	PTV (cm^3)	DHI (dose homogenity index)
1	74	sin	16	10	2	3.4	71.2	0.419
2	54	sin	25	9	2	3.4	137.6	0.647
3	73	dx	11	10	2	3.4	100.9	0.576
4	44	sin	21	10	1	3.4	56.0	0.463
5	73	sin	14	8	2	4.0	103.5	0.326
6	75	sin	7	10	2	3.4	123.4	0.325
7	67	dx	8	10	1	3.4	100.2	0.473
8	64	sin	10	10	2	3.4	46.9	0.393
9	49	sin	11	10	2	3.4	76.3	0.378
10	52	sin	18	10	1	3.4	40.1	0.6
11	51	sin	23	10	2	3.4	76.8	0.424
12	64	dx	8	10	2	3.4	304.4	0.393
13	77	dx	17	10	1	3.4	160.1	0.559
14	63	dx	18	10	1	3.4	91.3	0.451
15	51	sin	16	8	2	4.0	69.0	0.419
16	50	sin	6	10	2	3.4	107.2	0.361
17	60	dx	3	8	2	4.0	144.0	0.419
18	69	sin	4	10	2	3.4	76.2	0.425
19	67	dx	3	10	2	3.4	77.4	0.462
median	63.2		11				91.3	0.424

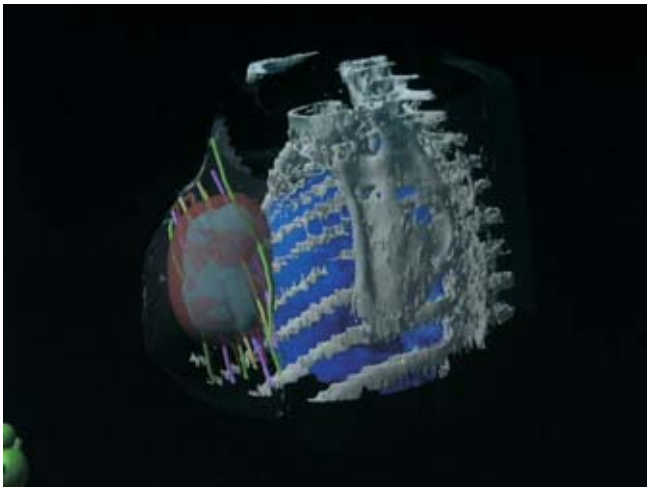

Figure 1. 3D reconstruction of target volume with applicators.

Surgery and brachyradiotherapy. In this trial the patients underwent standard lumpectomy. During the surgery the needles were inserted into the tumor bed and nylon catheters were threaded through the needles. The margins of cavity was marked by clips. The very important, maybe the most important thing, is the right and accurate definition of the target volume. That's why we use a combination of preoperative (preimplant) CT scans of 2–5 mm intervals and 2 mm thickness to identify the tummor with postoperative (postimplant) CT scans with the clips location and with the applicators.

Radiation was delivered using the high-dose rate remote afterloader VariSource with ^{192}Ir source and peroperative interstitial application of multicatheters. The patients received radiation twice a day at least 6 hours apart for a total of 10 fractions over five days with a single dose of 3.4 Gy. The total dose was 34.0 Gy prescribed as a minimum peripheral dose to match or minimal exceed the volume defined by the surgical clips as seen on CT scans. We used the method of geometric optimalisation which allows the calculation of dose distribution in relation to target. During brachytherapy, antibiotics were used as a prophylaxis. After finishing brachyradiotherapy (usually within 10 days since the resection) the catheters were painlessly removed. The patients are regularly observed.

Before surgery, CT examination was done in the quadrant with tumorous infiltrate. After total extirpation of tumor plastic tubules for interstitial brachytherapy and x-ray contrast clips indicating cavity walls were peroperatively placed into the tumor bed. Placing of the indicators was done using needles with free-hand technique. The number and dislocation of conductors depends on the target volume. There was used one- or more-level puncture. With the interval of 3 to 5 days after surgery, CT planning examination was done. The shots weree replaced to the planning system BrachyVision. The system enables construction and spatial view of all the important tissues and structures, especially skin, lungs and ribs. In every section there is also charted position of the applicators. The target volume (tumor bed with security border) in every cut was determined on the base of preoperative CT examination, placing of x-ray contrast clips and position of apllicators. Planning system enables three-dimensional view of the shape of target volume and placing of conductors. Then, in the planning modulus, there is done the optimalization of dose distribution and setting of "dwell time" – irradiating times in every position of the source. Using so called local shift of referential isodosis and adjusting the times in every position of the source we can adapt the shape of referential isodosis to the target volume (conformal "inverse" planning). The radiotherapy is started within 5 days from the operation after definitive histology. Except local control of the illness, the cosmetic effect of this curative method is also carefully evaluated.

Results

Nineteen patients were evaluated in presented study. None have died and None developed in-field breast recurrences, one patient had out-of-field recurrences. There were no regional nodal recurrences.

The median volume encompassed by the 34.0 Gy isodose shel was 91.3 cm^3 (range: 40.1–304.4 cm^3). The dose of the skin was lower than 50% of applied doses. From patients point of view the final cosmetic results is not the least important thing, in fact for some of them it is a matter of great importance. Using this technique of irradiation we achieved some really good cosmetic results. At each woman, there was calculated target volume size in cm^3 (median 91.3 cm^3) dose volume histogram (DVH), dose homogenity index (DHI). Median DHI was 0.42 (Tab. 1). Median volume of breast tissue getting 100% of the prescription dose, V_{100} is 87%, and V_{150} 48.5%.

At all patients, the dose on skin did not exceed 50% of the applied dose on the referential isodosis. We have noticed two treatment complications: hematoma and abscess in the place of tumorous bed after exstirpation. Data on the cosmetic outcome from treatment continues to be favorable. At last follow-up, patients rated the overall cosmetic outcome excellent (EORTC, grade 0–1). No case of teleangiectasia have been reffered.

Discussion

The expression "conformal radiotherapy" is used mostly for external radiotherapy. Its objective is to adapt the irradiated volume to an irregular shape of target volume. The definition of a target volume at brachyradiotherapy was traditionally based on orthogonal (two vertical) skiagrams which enabled the imagine of placing the applicator with x-ray contrast markers. However, they did not enable spatial (3D) view of critical organs and structures. Plannig of brachytherapy then fell behind plannig of external radiotherapy which was

based on spatial reconstruction on the strength of CT scans. Planning systems developed for brachytherapy during last years enable 3D reconstruction and precise planning of optimal dose distribution in target volume also in critical organs (Tab. 1).

In randomized clinical trials of conservative breast surgery with or without whole-breast radiation the percentages of recurrences in the lumpectomy site ranged from 5–12% for women who had radiation and from 25–35% for women who did not have radiation [3, 5, 6, 15].

At 57 months' median follow-up, POLGAR et al [12] described two local recurrences to be "remote" from the implanted volume among 45 patients treated with HDR brachyradiotherapy (30.3 Gy or 36.4 Gy in 7 fractions over 5 days with 2 cm margins).

PERERA et al [10] reports a small (39 patients), single-institution, pilot study of HDR brachyradiotherapy (37.2 Gy in 10 fractions over one week) as a sole modality of adjuvant radiotherapy after breast-conserving surgery. The recurrence rate after surgery in their series was 16.2% (6 patients) at 5 years. Only 2 patients (5.1%) had in-field recurrences. All ipsilateral breast recurrences were salvaged by mastectomy (4 patients) or repeat lumpectomy (2 patients) and whole-breast radiation. The 5-year overall survival was 86%.

DAS et al [4] treated 50 patients with postoperative accelerated partial-breast irradiation with interstitial brachyradiotherapy underwent CT-guided 3D treatment planning; patient selection criteria included: tumors <3 cm, fewer than three positive nodes without extracapsular extension, negative surgical margins, negative postlumpectomy mammogram, surgical clips or seroma for target volume delineation. The target volume is defined as the volume encompassed by a 2 cm margin outside the lumpectomy cavity in all dimensions. Free-hand needles were then placed in regions not covered by the template for optimal target volume coverage. Geometric optimization for volume implant was done and basal dose points on the central plane were generated with the help of the treatment planning software; prescription of 3.4 Gy for 10 fractions. The volume of breast tissue getting 100% of the prescription dose, V100, ranged from 89 cm^3 to 560 cm^3, with an average volume of 226 cm^3. The median dose homogenity index (DHI) is reported 0.70.

OTT et al [9] reports only one of 69 patients (1.4%) in the study with interstitial multicatheter brachyradiotherapy implants developed a bacterial infection of the implant. No other perioperative complications (bleeding, hematoma) were observed.

MAJOR et al [7] definet planning treatment volume (PTV) for using HDR brachyradiotherapy for partial breast irradiation as a lumpectomy cavity and 1 cm margin (the average volume of PTV was 54.5 cm^3). The median value V_{100} (dose point were optimized with conformal system) 0.86.

In conclusion, sole peroperative brachyradiotherapy via HDR afterloading has a number of positives. It shortens the adjuvant therapy, helps prevent delay in application of other therapeutic modalities (chemotherapy and/or further radiotherapy) and improves the treatment sequencing, all of which reduced hospitalization time and treatment costs. Advantages of 3D conformal planning of interstitial brachytherapy are: exact imaging of target volume and its relation to other critical structures (skin, ribs, lung). Accurate also optimalization, imaging and evaluation of dose distribution. This free-hand technique allows conformal placement of the catheters to the shape of the lumpectomy cavity. It also decreases frequency of late postradiotherapy changes and improves even the cosmetic effect of the treatment. This method is suitable just for patients with histologically confirmed small tumors (<3 cm in diameter) without negative prognostic factors for local recurrence (age at least 40 years, negative surgical margins, nodal involvement – maximum three positive nodes without extracapsular extension). However, local disease control comparable with results achieved with standard adjuvant radiotherapy has to be verified in a randomized clinical study.

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