Original paper

High-dose-rate interstitial brachytherapy for accelerated partial breast irradiation – trial results of Azerbaijan National Center of Oncology

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Abstract

Purpose: To describe early results of two cohorts of patients with low and intermediate risk of early breast cancer treated with accelerated partial breast irradiation (APBI) using different schedules of multicatheter brachytherapy.

Material and methods: Patients with early stage breast cancer after breast conserving surgery were enrolled for a prospective analysis. The APBI, using multicatheter brachytherapy, was delivered either eight times 4 Gy in five days with a planned total dose of 32 Gy, or seven times 5 Gy in four days with a planned total dose of 35 Gy. Primary endpoints were side effects.

Results: Forty-eight patients were enrolled between 2012 and 2014. Patients characteristics were as follow: median age of patients was 55 years, early breast cancer was defined according GEC-ESTRO recommendations. With a median follow-up period of 37 months, no significant differences regarding late side effects and cosmesis between two cohorts of patients were documented. In total, cosmesis was excellent in 13/48 (27.1%) patients, good in 34/48 (70.8%) patients, and moderate in 1/48 patient (2.1%).

Conclusions: Accelerated partial breast irradiation using multicatheter brachytherapy with 32 Gy/8 fractions and 35 Gy/7 fractions for early breast cancer seems to be similar in terms of late side effects. According to our findings, APBI was also feasible for intermediate-risk of early breast cancer patients.

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Key words: APBI, breast cancer, intermediate risk, interstitial brachytherapy.

Purpose

Recently, partial breast irradiation has become a standard adjuvant treatment modality for early stage breast cancer [1,2,3,4,5,6,7]. It could be done by different radiotherapy techniques like photon beams, electron beams, and brachytherapy [7,8,9,10,11,12]. In our view, accelerated partial breast irradiation (APBI) with interstitial multicatheter brachytherapy (BT) has the major advantages like more conformal and flexible dose distribution pattern, limitation of very high dose (particularly close around to applicators) in small volume (i.e., tumor bed), excellent protection of organs at risk (heart, skin, lung), advantageous cosmetic results, and very short treatment time [2,13,14,15]. In case of use of external beam radiotherapy (EBRT), some of above mentioned issues also could be overcome, but only due to rather complicated treatment techniques: respiratory gating (i.e., deep inspiration breath hold), breast immobilization, treatment in prone position *etc.*, while others could not, even by implementation of the latest EBRT achievements [16,17,18]. Therefore, today interstitial multicatheter brachytherapy based APBI is probably the most appropriate method corresponding to requirements for partial breast radiotherapy [2,19,20,21].

There is a number of publications available about high-dose-rate interstitial APBI, but in the majority of them, different dose fractionation was used: from 10 to 7 fractions by 3.4 Gy to 5.2 Gy [19,21,22,23,24]. We started APBI as treatment option for early breast cancer in 2012, after institutional review board approved treatment protocol.

The primary objective of presented trial was to compare early results of patients received APBI with different schedules of multicatheter brachytherapy.

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Material and methods

Eligibility

We analyzed treatment results of 48 patients with early stage breast cancer who received adjuvant multicatheter interstitial APBI after breast conserving surgery at the National Center of Oncology, Baku from January 2012 to December 2014. Inclusion criteria, according to the Groupe Européen de Curiethérapie and the European Society for Radiotherapy & Oncology (GEC-ESTRO) recommendations on patient selection for APBI of low and intermediate risk groups were as follows: age ≥ 40 years, tumor size by final pathology ≤ 3 cm, negative axillary lymph nodes (sentinel or dissection), microscopically negative or close (≤ 2 mm) surgical margins, invasive ductal or lobular carcinoma, unicentric/unifocal tumors. Exclusion criteria consisted of younger age, tumors more than 3 cm in size, positive margins (presence of tumor tissue on surgical margins), axillary lymph nodes' metastasis, presence of extensive intraductal component, multicentric/multifocal tumors [24,25,26,27,28]. All patients have signed informed consent before the treatment. Patient and tumor characteristics are given in Table 1.

Brachytherapy technique

Implantations usually were done 3-5 weeks after breast conserving surgery under general anesthesia [29,30]. We used plastic tube applicators of specialized interstitial breast catheter kits (Varian Medical Systems, Inc., Palo Alto, CA, USA). At the beginning, to keep both parallel orientation and equal distance between inserted needles, an advanced breast template system applicator (Varian Medical Systems, Inc., Palo Alto, CA, USA) was applied. Since 2015, we have practiced free hand needle insertion technique.

Tumor bed was defined based on pre-surgery mammograms, ultrasonography (US), and magnetic resonance imaging (MRI) investigations, and pre-implantation 2 mm slice thickness computed tomography (CT) scan without contrasting, which allowed visualization of scar, seroma, fibrosis area, clips, and projection of these structures on the skin. Additionally, the relation of needles to the clips was checked by X-rays (C-arm) during implantation procedure.

Needles were introduced in triangular setting with 15 mm distance, in amount sufficient enough to cover previously defined tumor bed with 1.5-2.0 cm margin. Seven to eighteen (median, 11) plastic catheters were used for adequate covering of the clinical target volume (CTV). The high-dose-rate brachytherapy (HDR-BT) was applied on an out-patient basis, two times daily with 4 to 6 hours interval. Twenty one patients received 8 fractions by 4 Gy (arm one), and 27 – 7 fractions by 5 Gy HDR-BT (arm two). Total treatment time including the day of implantation was four and five days, respectively. For skin care and infection prophylaxis, we used an aseptic bandages with povidone-iodine or octenidine applied to the areas of applicators enter-exit. Patients were advised against taking a shower for the duration of treatment. Routine administration of antibiotics was not done. Immediately after the last fraction, catheters were removed and patients were discharged.

Table 1. Patients and tumor characteristics

Characteristic	Number (n = 48)
Age	
Median age (years)	55 (40-68, SD: 7.4)
40-49	14 (29.2%)
50-59	23 (47.9%)
≥ 60	11 (22.9%)
Menopausal status	
Pre-menopausal	14 (29.2%)
Post-menopausal	34 (70.8%)
Tumor size (mm)	
Mean	16.5 (SD: 6.3)
Range	5-29
5-10	9 (18.8%)
11-20	23 (47.9%)
21-30	16 (33.3%)
Histologic type	
Invasive ductal carcinoma	46 (95.8%)
Invasive lobular carcinoma	2 (4.2%)
Histologic grade	
Grade I	4 (8.3%)
Grade II	25 (52.1%)
Grade III	16 (33.3%)
Unknown	3 (6.3%)
Surgical margins	
Close (≤ 2 mm)	6 (12.5%)
Negative (> 2 mm)	42 (87.5%)
Lymph node assessment	
Sentinel	21 (43.8%)
Lymph node dissection	27 (56.2%)
Lympho-vascular invasion (LVI)	
LVI positive	4 (8.3%)
LVI negative	44 (91.7%)
Estrogen receptor (ER) status	
ER positive	41 (85.4%)
ER negative	7 (14.6%)
Progesterone receptor (PR) status	
PR positive	38 (79.2%)
PR negative	10 (20.8%)
HER2 receptor status	
Positive	11 (22.9%)
Negative	35 (72.9%)
Unknown	2 (4.2%)

SD – standard deviation, LVI – Lympho-vascular invasion

Planning and treatment

High-dose-rate brachytherapy was done using ^{192}Ir source of 370 GBq initial activity with GammaMed HDR Plus afterloading machine (Varian Medical Systems, Inc., Palo Alto, CA, USA). Target definition and delineation was done according GEC-ESTRO Breast Cancer Working Group recommendations [26]. Post implantation CT images were transferred to BrachyVision treatment planning system (Varian Medical Systems, Inc., Palo Alto, CA, USA), on which the target volume segmentation and planning was performed. After the tumor bed was identified, a margin of 1.5 cm was uniformly expanded while keeping a minimum distance of 5 mm from the skin surface to create a CTV. Posteriorly, the CTV did not expand to the chest wall muscles. Planning target volume (PTV) was the same as CTV. After catheters' reconstruction, a geometrical optimization with subsequent manual modification of the dwell times and positions was done to achieve homogenous dose distribution among the CTV. The aimed dose constraints for the plan were: V_{100} for CTV > 90%, dose non-homogeneity ratio (DNR, relation of volume received 150% of prescribed dose to the volume received 100% of prescribed dose, $V_{150}/V_{100\%}$) was ≤ 0,33, and the dose to the skin surface and chest wall ≤ 70% of prescribed dose. Twenty two patients received 8 times 4 Gy, and twenty six patients 7 times 5 Gy fractions.

Table 2. Adjuvant systemic treatment of 48 early stage breast cancer patients

Treatment	Number (%)
Chemotherapy only	5 (10.4)
Chemotherapy followed by endocrine therapy	24 (50)
Endocrine therapy only	17 (35.4)
No adjuvant systemic therapy	2 (4.2)

Table 3. Dosimetric characteristics of brachytherapy planning

Characteristic	Number
Volume of CTV	
Mean	101.7 cc (SD: 47.2)
Range	56.6-220.3 cc
Volume of 100% of prescribed dose ($V_{100\%}$)	
Mean	111.5 cc (SD: 52.1)
Range	59-244 cc
Volume of 150% of prescribed dose ($V_{150\%}$)	
Mean	37.8 cc (SD: 17.6)
Range	17.4-87.7 cc
Volume of 200% of prescribed dose ($V_{150\%}$)	
Mean	10.4 cc (SD: 4.2)
Range	4.4-20.4 cc
Dose non-homogeneity ratio (DNR)	
Mean	0.35 cc (SD: 0.05)
Range	0.29-0.45 cc
Number of channels	
Median	11
Range	7-18
Dose/fractionation	
4 Gy/8 fractions	21 (43.8%) patients
5 Gy/7 fractions	27 (56.2%) patients

SD – standard deviation, CTV – clinical target volume

Adjuvant systemic therapy

Adjuvant chemotherapy and endocrine therapy were done after APBI according to National Comprehensive Cancer Network (NCCN) guidelines: 29 (60.4%) patients received chemotherapy, and 41 (85.4%), endocrine therapy (see Table 2) [31].

Results

The mean DNR was 0.35 (SD: 0.05; range, 0.29-0.45). The mean for maximum skin surface dose per fraction was 2.1 Gy (range 1.8-3 Gy) in 8 fraction, and 2.6 Gy (range 2.1-3.7 Gy) in 7 fraction brachytherapy regimens. There were no significant differences in the main treatment indexes between two arms (Table 3). Analysis of dose distribution within the CTV by use of different partial breast irradiation techniques shows different pattern of dose delivery. Thus, the total dose of EBRT to tumor bed is 50-60 Gy (both for early and late effects), given by 2 Gy fractions, while the total dose of APBI in our study is 37.3 Gy and 44.8 Gy in arm one (8 APBI fraction), and 43.8 Gy and 56.0 Gy in arm two (7 APBI fraction) for early (α/β = 10 Gy) and late (α/β = 3 Gy) effects, respectively. As it can be seen from the above calculations, the tumor dose of APBI is significantly less than one's of EBRT (37.3 Gy and 43.8 Gy dose equivalent to 2 Gy fractionation [EQD_2] vs. 50-60 Gy). But these doses are the minimum doses at the periphery of CTV, and we should take into consideration that the dose distribution of interstitial APBI is highly non-homogenous in comparison with EBRT. The mean volume of CTV in our patients was 101.7 cc, while mean $V_{150\%}$ was 37.8 cc. Therefore averagely, 37.2% of CTV (highest risk CTV, according to needle placement within the tumor bed) received 64 Gy (arm one) and 76.6 Gy (arm two), and higher EQD_2 dose. On the other hand, APBI by multicatheter interstitial brachytherapy allows significant decrease of radiation exposure of organs at risk in comparison to whole breast EBRT three to four fold [32,33,35].

All patients were followed-up every three months during the first two years after treatment, and then every six month. Examination included mammography, ultrasound of breast and regional lymph nodes bilaterally, abdomen and pelvis, chest X-rays, blood test, echocardiography, gynecological examination. Mammograms were obtained every 12 months, or if any suspicion arise.

In case of abnormal findings during mammography and ultrasound analysis, additional breast MRI and, if necessary, core-needle biopsy were performed to exclude local recurrence. The median follow-up was 37 months for all patients, 41 months for eight fractions APBI patients (arm one), and 33 months for seven fractions APBI patients (arm two). No loco-regional nor distant relapses were found during this period.

Cosmetic effects were evaluated using four grade score as excellent, good, moderate, and poor, according to Harvard criteria of Harris *et al.* E_0: excellent aesthetic result, at first sight no visible therapy related sequalae, both breasts have a similar appearance; E_1: good, minimal changes in pigmentation, a visible scar, localized telangiectasia; E_2: moderate, marked sequalae with a clear deformation of the breast contour, nipple displacement, or marked skin changes, but yet "acceptable"; E_3: bad, severe retraction or fibrosis, severe telangiectasia; E_4: complications: skin necrosis [32,33]. Fat necrosis was evaluated according to Lovey *et al*. scoring system: grade 0 – no fat necrosis; grade 1 − asymptomatic fat necrosis (painless palpable mass, radiologic or cytological findings); grade 2 − symptomatic fat necrosis requiring non-narcotic analgesics; grade 3 − symptomatic fat necrosis requiring narcotic analgesics for more than 2 weeks; grade 4 − symptomatic fat necrosis requiring surgical intervention [33,34]. There were no significant differences according to cosmetic results between two arms of patients. Cosmetic results were excellent in 13 (27.1%) patients, good – in 34 (70.8%) patients, moderate in one patient (2.1%). Forty-three (89.6%) of 48 patients were free of fat necrosis during follow-up period. In total, five patients developed fat necrosis, of which four (8.3%) had grade 1 fat necrosis revealed as painless mass by palpation and proven by mammography. Only one patient developed grade 2 symptomatic fat necrosis with painful palpable breast mass requiring core-needle biopsy. She was treated by two week course of analgesic and steroid with good cosmetic result.

Discussion

There are several dose/fractionation regimens of interstitial multicatheter APBI have been reported in literature: from 10 times 3.4 Gy to 7 times 5.2 Gy [22]. Polgar *et al*. found although non-significant trend for higher local recurrence rate for those patients treated with a lower tumor bed dose (10-year local relapse rate with 30.3 and 36.4 Gy tumor bed dose: 28.6% vs. 5.6%; $p = 0.073$) [21]. In our study, we compared late side effects of two different APBI regimens after median follow-up of 3 years and did not find any significant differences between them. The rationale to change fractionation schedule were both logistical reasons and patients' compliance. Lesser amount of radiotherapy fractions is more convenient for patients, particularly for those who travel for a long distance from radiotherapy center. Also, earlier removing of interstitial catheters could lead to decrease of secondary infection probability. On the other hand, shorter treatment time is more usable for department staff: less load of medical personnel (less treatment procedures, dressings etc.) and brachytherapy devices.

Increase of fraction size did not lead to higher probability of fat necrosis in our observation, but we still need longer follow-up for final conclusion. Thus, Budrukkar *et al*. investigating fat necrosis at 171 patients after interstitial APBI for early stage breast cancer with median follow up time 48 months revealed that median time to develop of a event was 24 months (range, 4-62 months; SD, 20), and the only significant factor impacting adversely on fat necrosis probability was volume of surgical excision [34]. In another study, Lövey *et al.* [36] found increased dependence of fat necrosis incidence from $V_{150\%}$ of more than 70 cc and $V_{200\%}$ of 20 cc, which could be avoided due to proper needle placement and dose optimization by 3D CT based planning (in our patients mean $V_{150\%}$ was 37.8 cc and mean $V_{200\%}$ was 10.4 cc). Therefore, according to recent data, there is no evidence of connection between the most frequent late complication as fat necrosis and APBI fraction size.

Conclusions

After 3 years follow-up, we did not find any differences between 32 Gy/8 fractions and 35 Gy/7 fractions APBI regimens in terms of disease free survival and early and late toxicity of the treatment. According to our findings, APBI was also feasible for intermediate-risk early breast cancer patients. Further researches with inclusion of low and intermediate risk group patients could substantiate new, shorter, and equally effective APBI regimens, which would be more convenient for patients, especially for those who travel long distances (taking into consideration that APBI technique is mostly available in dedicated radiotherapy centers). Shorter (2-3 days) APBI regimens also could improve radiotherapy workflow.

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Disclosure

Authors report no conflict of interest.

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