Sole conformal perioperative interstitial brachytherapy of early stage breast carcinoma using high-dose rate afterloading: longer-term results and toxicity

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SUMMARY

AIMS AND BACKGROUND: This study of high-dose-rate brachytherapy to the lumpectomy site as the sole radiation presents longer-term results and toxicity of accelerated partial-breast irradiation, using three-dimensional treatment planning.

MATERIALS AND METHODS: From March 2002 to July 2004, 25 patients were prospectively included in this study. Six patients were excluded because of definitive histology of lobular carcinoma or positive margin. The median age at the time of treatment was 63.2 years (range 44–77 years). Median follow-up of all patients was 44 months (range 30–53 months) with a minimum follow-up of 30 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 computed-tomography (CT) scans. Free-hand technique allows conformal placement of the catheters to the shape of the lumpectomy cavity. Side-effects and toxicity were scored using the EORTC/RTOG scale.

RESULTS: At a median follow-up of 44 months none of the women had developed in-field breast recurrences, one patient had out-of-field recurrences and one patient presented distant metastases. There were no regional nodal recurrences. In each woman, target volume size in cm3 (median 91.3 cm3), dose volume histogram (DVH), and dose homogeneity index (DHI) were calculated. Median DHI was 0.42. Median volume of breast tissue receiving 100% of the prescription dose, V_{100}, was 87%; and V_{150} 48.5%. We noticed two treatment complications: haematoma and abscess in the place of the tumour bed after extirpation. At last follow-up, all patients rated the overall cosmetic outcome as excellent or good.

CONCLUSIONS: This method is suitable only for patients with histologically confirmed small tumours (<3 cm in diameter) without negative prognostic factors for local recurrence. We observed low treatment-related morbidity and mild long-term toxicity with good treatment results.

KEY WORDS: breast cancer, radiotherapy, interstitial brachytherapy

BACKGROUND

Breast conserving therapy is an attractive alternative to mastectomy for patients with Stage I and 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 post-lumpectomy 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 surrounding 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 to wider acceptance of breast-conserving surgery is the dogma of 6-7 weeks of postoperative radiotherapy, which has several disadvantages: the long course of treatment and very often distant abode of patients from a department of radiotherapy are a substantial burden on women [1, 2]. 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, 15% of women who should receive radiation after conservative treatment do not [3].

Accelerated partial-breast irradiation (APBI) may be defined as any scheme that delivers radiotherapy to the tumour site and some surrounding tissue over a short overall period (5-8 days). Among the approaches described to date using brachytherapy to accomplish this are the following: low-dose rate (LDR) or high-dose rate (HDR) brachytherapy using interstitial implantation or a balloon catheter (MammoSite), and single-fraction intraoperative irradiation using 50 kV orthovoltage radiation (Intrabeam) or electrons 4–12 MeV (Mobetron, Novac-7) [2, 4]. Irradiation of the tumour bed only is being investigated in several clinical trials. The number of studies with median follow-up times of 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 centres do not have significant brachytherapy experience [5, 6, 7, 8, 9].

Long-term results of the use of three-dimensional conformal planning of perioperative interstitial sole brachytherapy of early stage breast carcinoma including late effects and morbidity are presented.

MATERIALS AND METHODS

Sole conformal perioperative 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 because of definitive histology of lobular carcinoma or positive margin. The median age at the time of treatment of the 19 women in this pilot study was 63.2 years (range: 44–77 years). Median follow-up of all patients was 44 months (range: 30-53 months).

Study objectives. The objective is to establish methods of perioperative brachytherapy in clinical practice, and evaluate treatment complications, cosmetic effect and local control. 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 (tumour size <3 cm), and axillary node-negative breast cancer with microscopic resection margins negative for ductal carcinoma. Pretreatment work-up included clinical examination, mammography and breast and axillary ultrasonography with biopsy of breast tumour, chest X-ray, liver ultrasonography, gynaecological examination and bone scintigraphy, pretreatment CT of breast, serum CEA and Ca15-3 levels, and blood tests.

Patient population, follow-up. Patient characteristics are summarized in Table 1. The follow-up schedule included breast examination every 3 months. Mammography was done at 6 months after brachytherapy and then once a year together with ultrasonography. Cosmetic effect was assessed every 3 months.

Surgery and brachytherapy. In this group the patients underwent standard lumpectomy. During the surgery the needles were inserted into the tumour bed and nylon catheters were threaded through the needles (free-hand technique). The margins of the cavity were marked by clips. A very important, maybe the most important, aspect was the correct and accurate definition of the target volume. For this reason we used a combination of preoperative (preimplant) CT scans of 2–5 mm intervals and 2 mm thickness to identify the tumour with postoperative (postimplant) CT scans with the location of clips and applicators. Radiation was delivered using the high-dose rate remote afterloader VariSource with ^{192}Ir source and perioperative 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

Table 1. Overall characteristics of patients (N = 19)

Characteristics	Value 1	
Age (years)	65	(48; 80)
Follow-up (months)	44	(30; 53)
Region		
m. dx	N = 8	(42.1 %)
m. sin	N = 11	(57.9 %)
Parameters of radiotherapy		
Two levels of catheters	N = 16	(84.2 %)
Number of catheters (mean)	9	(5; 14)
Dose (Gy)/Fraction	3.4	(3.0; 4.0)
Number of fractions	10	(8; 10)
PTV (cm^3)	95.7	(40.1; 304.4)
$Dose_{min}$ (Gy)	60.0	(32.0; 77.6)
$Dose_{max}$ (Gy)	1029.6	(574.1; 2084.6)
Mean (Gy)	165.8	(129.6; 198.7)
Modal (Gy)	118.4	(95.3; 177.5)
Median (Gy)	147.0	(115.2; 175.4)
STD	2.46	(0.67; 3.54)
V_{85} (%)	96.3	(82.0; 99.0)
V_{100} (%)	88.0	(65.0; 95.5)
V_{150} (%)	48.0	(24.0; 65.0)
DHI	0.43	(0.31; 0.65)
Chronic changes	N = 12	(63.1 %)
Fibrosis (degree 1)	N = 8	(42.1 %)
Fibrosis (degree 2)	N = 2	(10.5 %)
Skin changes (degree 1)	N = 3	(15.7 %)
Skin changes (degree 2)	N = 1	(5.3 %)

[1] Continuous variables are expressed as median with MIN/MAX values (in parentheses). Binary variables are summarized as N and % of given category.
[1] No. of cells is expressed in log scale as arithmetic mean and standard error of transformed values ($X_{transformed} = \ln[X]$)

minimally exceed the volume defined by the surgical clips as seen on CT scans. We used the method of geometric optimisation which allows the calculation of dose distribution in relation to the target. During brachytherapy, antibiotics were used as a prophylaxis. After finishing brachytherapy (usually within 10 days after the surgery) the catheters were removed. The patients were regularly observed.

Before the operation, CT examination was done in the quadrant with tumourous infiltrate. After total tumour extirpation plastic tubules for interstitial brachytherapy and X-ray contrast clips indicating cavity walls were preoperatively placed into the tumour bed. Placing of the indicators was done using needles with free-hand technique. The number and dislocation of conductors depends on the target volume. One or more level puncture was used. With an interval of 3 to 5 days after the operation, CT planning examination was done. The scans were transferred to the planning system BrachyVision. The system enabled construction and spatial view of all the important tissues and structures, especially the skin, lungs and ribs. In every section there was also the charted position of the applicators. The target volume (tumour bed with security border) in every cut was determined on the basis of preoperative CT examination, placing of X-ray contrast clips and position of applicators. The planning system enabled a three-dimensional view of the shape of the target volume and placing of conductors. Then, in the planning mode, optimisation of dose distribution and setting of "dwell times" was carried out. Using so-called local shift of reference isodoses and adjusting the times in every position of the source, we could adapt the shape of reference isodoses to the target volume (conformal "inverse" planning). Radiotherapy was started within 5 days after the operation after definitive histology. Except for local control of the illness, the cosmetic effect of this curative method was also carefully evaluated.

Statistical methodology. Standard summary statistics were used to express values of measured parameters (median supplied with MIN/MAX values, mean with standard error and frequency analysis). Differences between two groups of patients with and without chronic changes were tested using standard t-test for two independent samples.

RESULTS

In the study 19 patients were evaluated. None of the women has died. None of the women developed in-field breast recurrences; one patient had out-of-field recurrences. Distant metastases were found in one patient. There were no regional nodal recurrences.

The median volume encompassed by the 34.0 Gy isodose shell was 91.3 cm^3 (range 40.1-304.4 cm^3). In each woman, target volume size in cm^3 (median 91.3 cm^3), dose volume histogram (DVH), and dose homogeneity index (DHI) were calculated. Median DHI was 0.42 (Table 1). Median volume of breast tissue receiving 100% of the prescription dose, V_{100}, was 87%; and V_{150} 48.5%.

In all the women, the dose on the skin did not exceed 50% of the applied dose on the reference isodose. We noticed two treatment complications: haematoma and abscess in the region of the tumourous bed after extirpation (2 of 19 pts, 10.5 %). Data on the cosmetic outcome from treatment continues to be favourable. At at least 30 months of follow-up, all patients rated the overall cosmetic outcome as excellent or good (EORTC, grade 0-2). No G3 or G4 acute or late toxicity were observed.

Late chronic changes were observed in 63.1% (12 patients): fibrosis G1 (EORTC/RTOG scale) was seen in 42.1% (8 pts), fibrosis G2 in 10.5% (2 pts). Skin changes were observed in 15.7% (3 pts): G2 toxicity (mild teleangiectasia) was seen in 5.3% (1 pt) (Table 1). Fat necrosis was not observed.

Therapy-related features were analyzed for their relationship to cosmetic outcome and toxicity rating. The analysis was done only for fibrosis due to the low number of patients presenting with late skin toxicity. Therapy-related features analyzed were number of fractions, number of catheter levels, number of applicators, PTV volume, dose parameters, standard deviation (STD), dose-homogeneity index (DHI), V_{85}, V_{100} and V_{150} (Table 2).

Fibrosis was significantly associated with STD and inversely associated with number of applicators, single dose per fraction and modal dose applied. No association was found with other parameters.

DISCUSSION

Adjuvant radiotherapy after conservative breast surgery remains a question which has not been answered yet and its indication and volume are the topics of a variety of studies. Ways are being sought to shorten the total duration of the therapy, to reduce the toxicity, to improve the comfort of patients and to reduce the treatment costs, while safety and effectiveness of the treatment must be preserved.

One of the possibilities for some of the patients is to dose the radiation only to the bed of the tumour – without the necessity of irradiating the whole breast – either intraoperative ir-

Table 2. Characteristics of patients with and without fibrosis

Characteristics	Patients without fibrosis (n = 9)		Patients with fibrosis (n = 10)	
Age (years)	66	(3)	64	(2)
Region m. sin	N = 6	(66.7 %)	N = 4	(40 %)
Parameters of radiotherapy				
Two levels of catheters	N = 10	(100 %)	N = 6	(60 %)
Number of catheters (mean)	9.6	(0.4)*	8.2	(0.7)*
Dose (Gy)/Fraction	3.6	(0.1)*	3.3	(0.1)*
Number of fractions	8.7	(0.6)	7.4	(0.8)
Number of fractions (=10)	N = 5	(55.6 %)	N = 6	(50 %)
PTV (cm^3)	95.8	(8.0)	112.5	(18.9)
$Dose_{min}$ (Gy)	58.2	(3.3)	60.7	(2.3)
$Dose_{max}$ (Gy)	1027.2	(124.5)	1183.4	(101.3)
Mean (Gy)	166.5	(5.4)	164.6	(4.1)
Modal (Gy)	134.7	(7.3)*	116.4	(4.9)*
Median (Gy)	151.2	(4.5)	145.5	(4.3)
STD	2.1	(0.2)*	2.7	(0.2)*
V_{85} (%)	95.2	(1.4)	93.9	(1.3)
V_{100} (%)	87.6	(2.3)	84.5	(2.3)
V_{150} (%)	50.0	(3.3)	46.3	(2.8)
DHI	0.43	(0.03)	0.46	(0.02)

[1] Continuous variables are expressed as arithmetic mean with standard error (in parentheses). Binary variables are summarized as N and % of given category.
* Mark for statistical significance between patients with and without fibrosis (t-test, $p < 0.05$)
[1] No. of cells is expressed in log scale as arithmetic mean and standard error of transformed values (Xtransformed = ln[X])
[2] Test of significance of differences between two compared methods (t-test)

radiation or interstitial brachytherapy, which is a more frequently used method.

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 to 12% for women who had radiation and from 25 to 35% for women who did not have radiation [6, 7, 9, 10].

At 57 months' median follow-up, Polgar et al. [11] described two local recurrences as "remote" from the implanted volume among 45 patients treated with HDR brachytherapy (30.3 Gy or 36.4 Gy in 7 fractions over 5 days with 2 cm margins).

Perera et al. [12] reported a small (39 patients), single-institution, pilot study of HDR brachytherapy (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%.

Major et al. [13] defined planning treatment volume (PTV) for using HDR brachytherapy for partial breast irradiation as the lumpectomy cavity and 1 cm margin (the average volume of PTV was 54.5 cm^3). The median value of V_{100} (dose points were optimized with conformal system) was 0.86.

Ott et al. [14] reported that only one of 69 patients (1.4%) in the study with interstitial multicatheter brachytherapy implants developed a bacterial infection of the implant. No other perioperative complications (bleeding, haematoma) were observed.

Ott et al. [15] reported the perioperative morbidity, acute and late toxicity and cosmetic outcomes in 3-year results of the German-Austrian phase II trial of partial breast irradiation. In 274 patients they observed perioperative complications in 5.5% and 3-year local control in 99.3%. Acute toxicity (Grade 1–2 radiodermatitis) was seen in 6.6% and late side effects Grade ≥ 3 (fibrosis, teleangiectasia) occurred in 1.8%. Cosmetic results were excellent/good in 94%.

Wazer et al. [16] analyzed clinical and therapy-related features for their relationship to cosmetic outcome and toxicity rating in a group of 75 women. Suboptimal cosmetic outcome was significantly associated with the number of source dwell positions, V_{150} and V_{200}, and inversely associated with DHI (0.77 vs. 0.73, p=0.05). The risk of Grade 1/2 skin toxicity was significantly associated with V_{150} and V_{200} and inversely associated with DHI (0.77 vs. 8.71, p=0.009). The risk of Grade 0/1 vs. Grade 2–4 subcutaneous toxicity was significantly associated only with a lower value of DHI (0.77 vs. 0.73, p=0.02). The use of adriamycin-based chemotherapy after accelerated partial breast irradiation was found to be associated with a significant increase in the incidence of higher-grade skin toxicity and a higher risk of fat necrosis and suboptimal cosmetic outcomes.

Kuske et al. [17] analyzed the toxicity of RTOG 95-17. From 99 women, 33 were treated with LDR APBI (45 Gy in 3.5–5 days), and 66 were treated with HDR APBI (34 Gy in 10 twice-daily fractions for 5 days). Chemotherapy (>or=2 weeks after APBI) and/or tamoxifen was given at the discretion of the treating physicians. Of the 66 patients treated with HDR APBI, 3% had Grade 3 or 4 acute toxicity (erythema, oedema, tenderness, pain and infection), and of the 33 patients treated with LDR 9% had G3 or G4 toxicity. Late toxicities included skin thickening, fibrosis, breast tenderness and teleangiectasia. No patient experienced Grade 4 toxicity. The rate of Grade 3 toxicity was 18% for the LDR and 4% for the HDR group. Patients receiving chemotherapy had a greater rate of Grade 3 toxicity.

Kaufman et al. [18] published an updated analysis of survival, recurrence rate and toxicity for a cohort of women with early-stage breast cancer treated with high-dose-rate interstitial brachytherapy for accelerated partial breast irradiation between August 1997 and July 2001. There were 32 women with 33 breast cancers (T1-2 tumours with </= 3 axillary nodes positive, nonlobular histology, negative surgical margins, and no evidence of extracapsular lymph node extension). The actuarial local recurrence was 6.1% (3 pts) at 5 years, which is comparable to that seen in conventional whole breast series; all three were elsewhere failures within the treated breast. For the purpose of analysis, toxicity scores were assigned to each of four follow-up intervals: </=6 months, >6 but </=24 months, >24 but </=60 months, and >60

months. Fat necrosis was not seen in the first 6 months after treatment, then appeared in 27.3% of patients from 6 to 24 months, 28.1% from 24 to 60 months, and 17.9% beyond 60 months. Skin toxicity appeared to stabilize with longer follow-up: the percentage of patients showing any degree of skin toxicity was 69.7%, 33.3%, 40.6%, and 28.6% at each successive time interval. Subcutaneous toxicity increased beyond 60 months: moderate to severe subcutaneous toxicity was seen in 15.2%, 18.2%, 18.8%, and 35.7% of patients successively. The percentage of patients with less than excellent cosmetic outcome improved beyond 60 months (21.2%, 21.2%, 21.9%, and 11.1% successively). Only 1 patient experienced more than mild pain at any time. The percentage of patients experiencing any degree of pain improved over time (30.3%, 33.3%, 18.8%, 17.9%).

Polgar et al. [19] reported the seven-year results of a comparative study of HDR brachytherapy alone versus whole breast radiotherapy after breast-conserving surgery. 45 patients with T1 N0-N1mi, nonlobular breast cancer without the presence of an extensive intraductal component and with negative surgical margins were treated with APBI. A total dose of 30.3 Gy (n=8) and 36.4 Gy (n=37) in seven fractions within 4 days was delivered to the tumour bed plus a 1–2 cm margin. During the same period, 80 patients, who were treated with 50 Gy WBRT with or without a 10-16 Gy TBB, were selected as controls. The differences in the 5- and 7-year actuarial rates of ipsilateral breast recurrence were not statistically significant among patients treated with APBI (4.4% and 9.0%), WBRT (4.7% and 14.8%) and WBRT + TBB (5.7% and 9.5%). No statistically significant difference in either the 7-year probability of relapse-free survival or cancer-specific survival was found. The rates of asymptomatic fat necrosis were 20.0% and 20.6% for APBI and WBRT, respectively. Symptomatic fat necrosis occurred in 1 patient (2.2%) treated with APBI. The incidence of Grade 2 or worse late radiation side effects was similar for both groups.

As a result of the small number of patients with a relatively short follow-up in the group, the evaluation of our results – concerning both the toxicity and the local control of the illness – is difficult. Acute toxicity of the treatment was low (two out of twelve patients); furthermore the influence of the surgery and surgical equipment can hardly be differentiated from the influence of the radiotherapy itself.

The small number of patients in our group who showed signs of skin toxicity while being observed does not allow any appraisal of the influence of the dosimetric characteristics on their incidence. As for fibrosis (subcutaneous toxicity), standard deviation (STD) and the number of applicators (inversely associated with fibrosis) were found to be statistically relevant in our file. We observed quite frequent occurrence of fibrosis G1 (42.1% of the patients); nevertheless this fact had no negative impact on patients' evaluation of the cosmetic effect. The incidence of other late side effects of the treatment was low.

We did not evaluate the cosmetic effect of sole HDR-BRT in comparison with the effect achieved with WBRT (± TBB). It was at least similar, without the occurrence of G3 or toxicity, however. Because of the small number of patients it is hard to evaluate the local control in comparison with WBRT; we did not register any in-field recurrence though. Regarding indication of sole BRT after breast-conserving surgery on the number of nodes affected (no nodes vs. </= 3 axillary nodes positive) we included the patients with </= 3 axillary nodes positive and we did not register any nodal recurrence.

CONCLUSIONS

In conclusion, sole perioperative brachytherapy 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 reduce 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), and also accurate optimisation, imaging and evaluation of dose distribution. Owing to the risk of undertreatment, this method is only suitable for patients with a small histologically confirmed carcinoma without negative prognostic factors of local recurrence. Accelerated partial breast irradiation using interstitial high-dose-

rate implants, with proper patient selection and quality assurance, yields similar results and toxicity to those achieved with standard breast-conserving therapy while shortening the total treatment duration. Both the objective and the subjective (evaluated by the patient herself) cosmetic effects obtained by the two therapy methods are comparable. From the patient's point of view the final cosmetic results are 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. However, local disease control comparable with results achieved with standard adjuvant radiotherapy has to be verified in a randomized clinical study.

REFERENCES

1. Astrahan MA, Jozsef G, Streeter OE. Optimization of Mammosite therapy. Int J Radiat Oncol Biol Phys 2004; 58: 220–232.
2. Vaidya JS, Tobias JS, Baum M, Keshtgar M, Joseph D, Wenz F et al. Intraoperative radiotherapy for breast cancer. Lancet Oncology 2004; 5: 165–173.
3. Morrow M, White J, Moughan J. Factors predicting the use of breast conserving therapy in stage I and II breast carcinoma. J Clin Oncol 2001; 19: 2254–2262.
4. Rose CM, Recht A. Accelerated partial-breast irradiation (APBI): Let's give it a good test. Int J Radiat Oncol Biol Phys 2004; 57: 1217–1218.
5. Buchholz TA. Partial breast irradiation – is it ready for prime time? Int J Radiat Oncol Biol Phys 2004; 59: 1214–1216.
6. Clark RM, Whelan T, Levine M, Roberts R, Willan A, McCulloch M et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: An update. Ontario Clinical Oncology Group. J Natl Cancer Inst 1996; 88: 1659–1664.
7. Fisher ER, Anderson S, Redmond C, Fisher B et al. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: Pathological findings from NSABP protocol B-06. Semin Surg Oncol 1992; 8: 161–166.
8. Polgar C, Strnad V, Major T. Brachytherapy for partial breast irradiation: The European Experience. Semin Rad Oncol 2005; 5: 116–122.
9. Veronesi U, Marubini E, Mariani L, Galimberti V, Luini A, Veronesi P et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: Long-term results of a randomized trial. Ann Oncol 2001; 12: 997–1003.
10. Liljegren GG, Holmberg L, Adami HO, Westman G, Graffman S, Bergh J et al. Sector resection with or without postoperative radiotherapy for stage I breast cancer: Five-year results of a randomized trial. J Natl Cancer Inst 1994; 86: 717–722.
11. Polgar C, Sulyok Z, Fodor J, Orosz Z, Major T, Takáczi-Nagy Z et al. Sole brachyradiotherapy of the tumor bed after conservative surgery for T1 breast cancer: Five-years results of a phase I-II study and initial findings of a randomized phase III trial. J Surg Oncol 2002; 80: 121–128.
12. Perera F, Yu E, Engel J, Holliday R, Scott L, Chisela F et al. Patterns of breast recurrence in a pilot study of brachytherapy confined to the lumpectomy site for early breast cancer with six years'minimum follow-up. Int J Radiat Oncol Biol Phys 2003; 57: 1239–1246.
13. Major T, Polgar C, Fodor J. Dose-volume evaluation of HDR interstitial breast implants planned by tradional and image-based dosimetry systems. Radiother Oncol 2004; 71 (Suppl 2): S39 (Abstract).
14. Ott OJ, Pötter R, Hammer J, Hildebrandt G, Lotter M, Resch A et al. Accelerated partial breast irradiation with 192-iridium multicatheter PDR-/HDR-brachytherapy. Preliminary Results of the German-Austrian Multicenter Trial. Strahlenther Onkol 2004; 180: 642–649.
15. Ott OJ, Hildebrandt G, Pötter R, Hammer J, Lotter M, Resch A et al. Accelerated partial breast irradiation with multi-catheter brachytherapy: Local control, side effects and cosmesis outcome for 274 patients. Results of the German-Austrian multi-centre trial. Radiother Oncol 2007; 82(3): 281–286.
16. Wazer DE, Kaufman S, Cuttino L, DiPetrillo T, Arthur D. Accelerated partial breas irradiation: an analysis of variables associated with late toxicity and long-term cosmetic outcome after high-dose-rate interstitial brachytherapy. Int J Radiat Oncol Biol Phys 2006; 62: 489–495.
17. Kuske RR, Winter K, Arthur DW, Bolton J, Rabinovitch RA, White JR et al. Phase II trial of brachytherapy alone after lumpectomy for select breast cancer: toxicity analysis of RTOG 95-17. Int J Radiat Oncol Phys 2006; 65: 45–51.
18. Kaufman SA, Dipetrillo TA, Price LL, Midle JB, Wazer DE. Long-term outcome and toxicity in a Phase I/II trial using high-dose-rate multicatheter interstitial brachytherapy for T1/T2 breast cancer. Brachytherapy 2007; 6(4): 286–292.
19. Polgar C, Major T, Fodor J, Németh G, Orosz Z, Sulyok Z et al. High-dose-rate brachytherapy alone versus whole breast radiotherapy with or without tumor bed boost after breast-conserving surgery: seven-year results of a comparative study. Int J Radiat Oncol Biol Phys 2004; 60: 1173–1181.