REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 22 (2017) 277–283

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Adjuvant intraoperative radiotherapy for selected breast cancers in previously irradiated women: Evidence for excellent feasibility and favorable outcomes

Gladys Blandino[a], *Marina Guenzi*[a], *Liliana Belgioia*[a,b,*], *Elisabetta Bonzano*[a], *Elena Configliacco*[a], *Elena Tornari*[a], *Francesca Cavagnetto*[c], *Davide Bosetti*[a], *Alessandra Fozza*[a], *Daniele Friedman*[d], *Renzo Corvò*[a,b]

[a] *Department of Radiotherapy – IRCCS A.O.U. San Martino – IST- Largo Rosanna Benzi 10, 16132 Genoa, Italy*
[b] *Department of Health Sciences (Dissal) – University of Genoa – Largo Rosanna Benzi 10, 16132, Italy*
[c] *Department of Medical Physics – IRCCS A.O.U. San Martino – IST- Largo Rosanna Benzi 10, 16132 Genoa, Italy*
[d] *Department of Breast Surgery – IRCCS A.O.U. San Martino- IST and University of Genoa, Largo Rosanna Benzi 10, 16132, Italy*

ARTICLE INFO

Article history:
Received 15 May 2016
Received in revised form
14 October 2016
Accepted 25 February 2017
Available online 5 May 2017

Keywords:
Breast cancer
Reirradiation
Intraoperative radiotherapy

ABSTRACT

Background: The present report provides preliminary outcomes with intraoperative radiotherapy delivered to women with breast cancer included in a re-irradiation program.
Materials and methods: From October 2010 to April 2014, thirty women were included in a re-irradiation protocol by exploiting IORT technique. The median time between the two irradiations was 10 years (range 3–50). All patients underwent conservative surgery, sentinel lymph node excision and IORT with electron beam delivered by a mobile linear accelerator. Primary endpoint was esthetic result and consequential/late toxicity; secondary endpoints were local control (LC), disease free survival (DFS) and overall survival (OS).
Results: With a median follow up of 47 months (range 10–78), we analyzed 29 patients (1 lost at follow up). Twenty-seven patients (90%) had presented breast cancer local relapse or a new primary cancer in the same breast after a previous conservative surgery plus radiation treatment; three patients (10%) had previously received irradiation with mantle field for Hodgkin Lymphoma. Esthetic result was excellent in 3 pts (10%), good in 12 pts (41%), fair in 8 pts (28%) and poor in 6 pts (21%). 12 (41%) patients showed subcutaneous fibrosis at the last follow-up. LC, DFS and OS at five years was 92.3%, 86.3% and 91.2%, respectively.

* *Corresponding author at*: Department of Radiation Oncology, University of Genoa, Largo Rosanna Benzi 10, 16132 Genoa, Italy. Fax: +39 0105556393.
E-mail addresses: blandinog.81@gmail.com (G. Blandino), marina.guenzi@hsanmartino.it (M. Guenzi), liliana.belgioia@unige.it (L. Belgioia), eli-86@hotmail.it (E. Bonzano), ele.confy@virgilio.it (E. Configliacco), ele.tornari@gmail.com (E. Tornari), Francesca.cavagnetto@hsanmartino.it (F. Cavagnetto), bosetti.davide@yahoo.it (D. Bosetti), ale.fozza@libero.it (A. Fozza), friedman@unige.it (D. Friedman), renzo.corvo@unige.it (R. Corvò).
http://dx.doi.org/10.1016/j.rpor.2017.02.009

Conclusion: Although we analyzed a small number of patients, our results are satisfactory and this approach is feasible even if it could not be considered the standard treatment. Further clinical trials exploring IORT are needed to identify possible subgroups of patients that might be suitable for this type of approach.

1. Background

Breast conservative surgery and adjuvant whole breast radiation therapy are considered the standard care for early breast cancer (BC). Nevertheless, breast relapse may occur in a small proportion of patients.[1] A significantly greater risk of developing breast cancer (BC), compared to the general population, has been demonstrated in women treated with chest radiotherapy (RT) at a younger age for Hodgkin lymphoma (HD) or other neoplasms.[2] In all the clinical situations where radiotherapy was already delivered on site and a new irradiation may be strongly correlated with severe late effects, the standard approach is mastectomy alone that results in a loco-regional control rate up to 90%.[3,4] This radical approach is often not well accepted by patients because of the emotional and physical distress related to mutilating surgery. A novel therapeutic option is treating these patients after re-resection of the recurrent tumor with partial breast irradiation (PBI), assuming that re-irradiation to a limited volume will be effective with limited side effects. Intraoperative radiotherapy (IORT) is one modality of these PBI options which allows to deliver high doses to a small area where microscopic tumor cells may be left after the conservative surgery. The present report provides preliminary favorable outcomes with intraoperative radiotherapy (IORT) delivered to a series of women with breast cancer included in a re-irradiation program.

2. Materials and methods

From October 2010 to April 2014 thirty women affected by early breast cancer were included in a re-irradiation protocol by exploiting IORT technique. All the women had already received radiation therapy for other neoplasms, patients with previous breast cancer received 50 Gy in 25 fraction followed by a sequential boost of 10 Gy in 5 fractions and patients with previous HD, 40 Gy in 22 fractions (median dose: 50 Gy, range: 40–60 Gy); as regard systemic therapy, if indicated, patients received CMF or ABVD based chemotherapy for breast cancer or HD, respectively. The median age at first cancer diagnosis was 57 years (range 24–74) and 68 years (range 48–82) at the second cancer occurrence. In 5 breast cancer patients, recurrence occurred within 5 years since first radiotherapy. The median time between the two irradiations was 10 years (range 3–50). Seventeen patients (57%) were affected by right and thirteen (43%) by left breast disease, all of which but one were postmenopausal at second diagnosis. At the time of second diagnosis, the majority of the tumors were classified as invasive ductal carcinoma (21 patients – 70%), lobular carcinoma (3 patients – 10%), mucinous carcinoma (1 patient 3.3%), clear cell carcinoma (1 patient 3.3%) and DCIS (4 patients – 13.4%); twelve pts (67%) had the same histology of the first tumor. All histology had been included, also lobular carcinoma and DCIS because the patients refused standard treatment (mastectomy) and, following ASTRO guidelines,[5] accelerated partial breast irradiation (aPBI) may be considered cautionary in this group. In seventeen patients (57%), the second cancer was in the same quadrant as in the previous surgery. Axillary lymph nodes metastasis was confirmed in four patients (13%): 2 patients underwent lymph node dissection and one of them also, subsequent node radiotherapy (40 Gy in 16 fractions), in the remaining 2 patients no other additional procedures had been done as micrometastasis in only one node was detected. Characteristics of patients treated were presented in Table 1. Tumors were classified according to molecular characteristics as shown in Table 2.

Table 1 – Patients' characteristics at second diagnosis.

Features	No	%
Age (yrs)		
<50	1	3
50–59	3	10
>60	26	87
Histology		
Ductal ca	21	70
DCIS	4	13.4
Lobular ca	3	10
Mucinous	1	3.3
Clear cell carcinoma	1	3.3
Tumor size (cm)		
<0.5	4	13
0.5–1	9	30
1–2	13	43
Not evaluable	4	13
Surgical margins		
Positive	2	7
Close	3	10
Negative	24	80
Not evaluated	1	3
Grading		
G1	3	10
G2	24	80
G3	2	7
Not evaluable	1	3

2.1. *Intraoperative radiotherapy*

All patients refused mastectomy, despite being informed that this was considered the treatment of choice. Karnofsky index > 80%; signs of multicentric invasive growth pattern and distant metastasis were considered exclusion criteria for the

Table 2 – Molecular characteristics of women' cancer.

Molecular subtype	N pts	%
Luminal A	9	30
Luminal B	6	20
HER 2 Like	2	7
Triple negative	8	27
Not evaluable	3	10

inclusion in the IORT program. All patients underwent conservative surgery, sentinel lymph node excision and IORT with electron beam delivered by a mobile linear accelerator (LIAC SIT-Sordina IORT Technology S.p.A-Vicenza Italy). Patients received a single dose of 18 Gy prescribed to 90% isodose, namely, therapeutic depths are 12, 15, 20, 26 mm with energies or 4, 6, 8, and 10 MeV, respectively. The diameter of the perspex cylindrical applicator used was 6 cm (range 5–7 cm) and the radioprotection of the thoracic wall was achieved using steel-PTFE shielding disks (3 mm + 3 mm) placed between the deep tissues of the residual breast and the pectorals muscle to minimize the wall irradiation; disk diameter was at least 1 cm larger than that of the applicator (range 6–8). Median retreated volume encompassed by the 90% reference isodose is 23 ml (range 10–43 ml). To avoid superficial under-dosage due to entrance dose that is lower at lower energy we selected a higher electron energy (8 or 10 MeV); before irradiation started the surgeon carefully checked if the shielding disk was correctly sited below the therapeutic applicator end. Micro-MOSFET 502-RDM (Best Medical Canada Ltd.) detectors were employed to monitor the exit dose defined as the dose at the deeper part of the target: detectors were placed inside a thin and sterile catheter (6Fr closed-end brachytherapy catheter) and fixed at the center of the PTFE side of the shielding disk before the insertion in the breast.

2.2. *Toxicity evaluation*

Treatment-related toxicity, disease control and breast cosmetic were analyzed in follow-up visits, performed at 6, 12 months after therapy and subsequently, annually. At each follow up time a clinical examination was performed while mammography or/and breast ultrasound; abdominal ultrasound were required once a year. Subacute and late side effects were evaluated according to RTOG/EORTC scale[6] and esthetic result with Harvard scale (v Table 3).[7]

2.3. *Outcomes*

Primary endpoint of this analysis was local assessment of esthetic results and evaluation of consequential/late toxicity;

Table 3 – Harvard scale.

Excellent	Treated breast nearly identical to untreated breast
Good	Treated breast slightly identical to untreated breast
Fair	Treated breast clearly different from untreated breast but not seriously distorted
Poor	Treated breast seriously distorted

Table 4 – Subcutaneous toxicity (fibrosis) at 6 months.

RTOG\EORTC	No pts	%
G0	13	45
G1	6	21
G2	7	24
G3	3	10

secondary endpoints were local control (LC), disease free survival (DFS) and overall survival (OS). LC was defined as the time between the second treatment to any local re-recurrence in the affected breast. DFS was the time between the second treatment and local or distant relapse. Survival curves were constructed using Kaplan–Meier estimates, statistical analysis was performed using IBM SPSS v. 22 (IBM Co., Armonk, NY, USA).

3. Results

Thirty women with early breast cancer were treated with IORT immediately after conservative surgery. Twenty-seven patients (90%) had presented breast cancer local relapse or a new primary cancer in the same breast after a previous conservative surgery plus radiation treatment; three patients (10%) had previously received irradiation with mantle field for Hodgkin Lymphoma. Of the 30 patients treated, one patient was excluded from this analysis because of being lost at follow up. The median follow up of the remaining 29 pts was 47 months (range 10–78). Based on the definitive histological examination 26/29 patients received systemic therapy: 23 (88%) hormonal therapy, 2 (8%) chemotherapy and 1 (4%) both; the last 3 patients underwent anthracyclines and taxanes based chemotherapy schedule and the 2 Her-2 patients received trastuzumab. As to the primary end-point, the overall esthetic result was excellent in 3 pts (10%) good in 12 pts (41%), fair in 8 pts (28%), poor in 6 pts (21%) according to the HARVARD classification. Consequential and late toxicities are reported in Tables 4 and 5. As to secondary end-points, local control at five years was 92.3%. 1 pt developed a local re-recurrence then treated with mastectomy. This patient developed the first recurrence – a clear cell carcinoma (same histology as the first tumor) of 1.4 cm basal like (pT1c-pN0, hormonal receptor: negative, HER-2: negative) – after 8 years since the first treatment and the re-recurrence (rpT1b – the same as previous biological characteristics) after further 4 years. DFS at five years was 86.3%; 2 pts (7%) developed distant metastasis, both four years after re-treatment. Overall survival after re-treatment was 91.2% at five years and 78.2% at six years. At last follow up 26/29 (90%) patients were alive, of these one developed bone metastasis after 39 months from

Table 5 – Subcutaneous toxicity (fibrosis) at last follow-up.

RTOG\EORTC	No pts	%
G0	3	10
G1	8	28
G2	12	41
G3	6	21

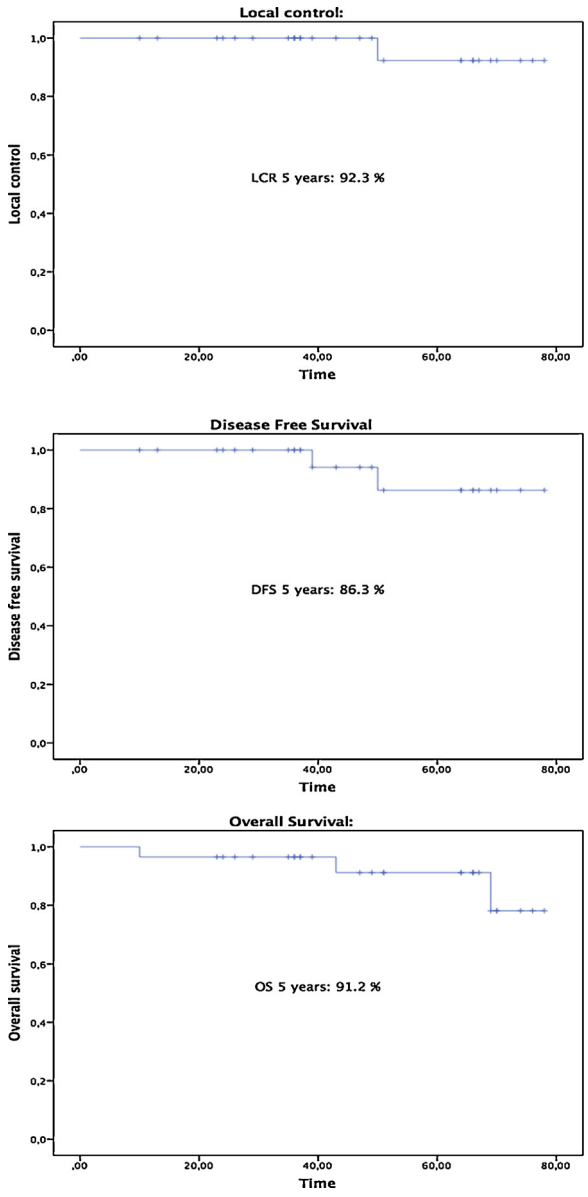

Fig. 1 – Local control, disease free survival and overall survival.

second treatment. The remaining 3 patients died, respectively, for disease progression (local recurrence at 50 months and subsequent metastasis), the occurrence of a fatal lung cancer and for cancer-unrelated causes. Fig. 1 shows LC, DFS and OS.

4. Discussion

After the up-front conservative surgery-adjuvant radiotherapy strategy for early breast cancer the in-breast recurrence rates are nowadays expected to be from 0.4 to 2%.[2] This is the result of advances in breast cancer screening, surgical techniques, pathologic work up and adjuvant local and systemic therapy that improved local control after breast conserving treatment.[1] Moreover, patients who have already been treated for a previous cancer undergo a close follow-up that allows detecting a very small tumor recurrence. Salvage mastectomy represents the standard local treatment strategy in the case of ipsilateral breast tumor recurrence. However, mastectomy significantly affects the quality of life followed by emotional and physical distress and has a negative impact on everyday life, body self-image and sexual performance.[8–10] In literature there are not many data reported on second breast conservative surgery plus re-irradiation and techniques used vary considerably. Partial Breast Irradiation (PBI) presents the advantage to allow delivering a highly conformal dose to the surgical bed, sparing adjacent critical structures, not only the lung, heart, chest wall, but also the breast tissue remote from the lumpectomy cavity.[11] Considering this opportunity, some authors have recently hypothesized that mastectomy may not be necessary in all patients after ipsilateral breast recurrences and that repeat breast-conserving surgery followed by PBI in selected patients might obtain a local recurrence rates similar to those achieved with radical surgery with acceptable toxicity and cosmetic results.[12,13] APBI is a radiation technique that limits the irradiation target to the area of the lumpectomy bed plus a 1–2 cm margin of surrounding normal breast tissue, delivering doses which are biologically equivalent to WBRT in a shorter period of time while minimizing potential side effects on normal tissue.[13] Different PBI techniques are available: interstitial brachytherapy, brachytherapy using MammoSite, 3D conformal external radiotherapy (3D CRT) and intraoperative radiotherapy (IORT). Published evidence is scarce and the proof level of such therapeutic approaches remains low, based on retrospective studies based on a limited number of patients treated and analyzed.[14] In these clinical cases, selection criteria for a second breast conservation attempt were crucial[14] and comparable within all reports; little lesions T0-2, late onset after primary treatment, and no evidence of metastatic disease have been the criteria followed in an attempt to perform a tumor resection with free surgical margins.[2] In addition, the biological characteristics of the tumor must be considered very carefully.[15] In case of re-irradiation for 2nd BCT, interstitial brachytherapy was the oldest and most commonly applied technique using low (LDR), pulsed (PDR) or high-dose rate (HDR).[14–16] The given doses were in a similar range for brachytherapy and biologically comparable to the only series exclusively using EBRT (50 Gy).[2] Oncologic results were similar among the different methods with local control rates ranging between 76% and 100%, and disease free and overall survival rates comparable to mastectomy series. Cosmetic outcomes were reported to be good or excellent in 60–80% of the patients.[2–14] A very small experience analyzing the use of the MammoSite device in the treatment of the previously irradiated breast has been published: the treatment proved feasible and may provide adequate local control as well as acceptable esthetic outcome in carefully selected women, but the number of the patients remains small and the follow up short.[17] With a median follow up of 51.5 months, the analysis of 39 patients treated with re-irradiation using external beam (50 Gy/25 fraction given by accelerated electrons) after conservative surgery for local relapse showed a good local control (76.95%), excellent or good cosmetic outcome in the majority of the patients with no radiation-induced necrosis.[18] An alternative PBI technique, the intraoperative radiotherapy (IORT), allows to deliver a single high dose to the tumor bed immediately after cancer removal, sparing

Table 6 – Main experiences in partial breast re-irradiation.

References	No pts	Type of re-irradiation technique used	Median time follow-up (months)	2nd LR (%)	DFS 5years (%)	OS 5 years (%)
Maulard et al.[24]	38	Brachytherapy (LDR)	48	21%	NA	55%
Deutsch et al.[18]	39	EBRT	51.5	20.50%	68.50%	77.90%
Resch et al.[25]	17	Brachytherapy (LDR)	59	24%	NA	88.20%
Kraus-Tinfenbacher et al.[19]	17	IORT	26	NA	82.30%	94.10%
Chadha et al.[26]	15	Brachytherapy (LDR)	36	7%	89%	100%
Trombetta et al.[27]	26	Brachytherapy (HDR\LDR)	38	4%	88.50%	88.50%
Guix et al.[28]	36	Brachytherapy (HDR)	89	3%	–	–
Kauer-Dorner et al.[29]	39	Brachytherapy (PDR)	57	NA	77%	87%
Hannoun Levi et al.[30]	42	Brachytherapy (HDR)	21	2%	NA	NA
GEC-ESTRO[30]	217	Brachytherapy (HSR\PDR\LDR)	47	7.20%	83.30%	88.70%
Present analysis	30	IORT	47	3%	86.3%	91.2%

LR, local recurrence; DFS, disease free survival; OS, overall survival; LDR, low dose rate; EBRT, external beam radiation therapy; HDR, high dose rate; PDS, pulse dose rate; IORT, intraoperative radiotherapy.

skin surrounding breast tissue, thus limiting the possibility of complications. This approach might be particularly useful in the case of re-irradiation to avoid side effects related to radio-induced toxicity. IORT can be delivered with dedicated linear accelerators in the operation room or novel mobile devices producing low-energy X-rays or electrons. Using low-energy X-rays, the device provides a point source of 50 kV maximum at the tip of a 3.2 mm diameter tube that may be placed at the center of a spherical tumor bed applicator. After tumorectomy, an appropriately sized applicator is inserted into the surgical cavity, and the dose is given at the surface of the cavity. A clinical report relative to 15 patients treated with IORT (50 kV X-rays in single dosages of 14.7–20 Gy at the applicator surface) showed no local recurrence in re-irradiated patients (13 breast cancer recurrences and 2 previously treated for HD) at a follow-up of 26 months.[19] Technical details on IORT have been described by Veronesi et al.[20] In our department we have been treating selected patients with IORT since 2009. Considering the potential results on local control with this novel strategy for conservative treatment, we decided to offer a second tumorectomy accompanied by irradiation of the tumor bed in ipsilateral breast recurrences with IORT. Repeat lumpectomy and high dose electron beam radiotherapy to a series of women with breast cancer included in a re-irradiation program, appears to be a feasible, safe and efficacious treatment, not encumbered by important late toxicity. In this analysis at six months the toxicity is acceptable, with only ten patients showing G2–G3 fibrosis. At the last follow up, 42% of the patients presented G2 fibrosis. This phenomenon could be explained by the fact that in most of the patients the breast had already been subjected to a previous surgery and irradiation. Patients were satisfied with the esthetic results of the treatment which avoided the physical distress associated to a mutilating surgical intervention. Our results here presented showed at 5 years, beyond an excellent clinical feasibility with IORT, a local control rate of 92.3%, DFS of 86.3% and overall survival of 91.2% after re-treatment. These outcomes appear favorable compared with similar experiences, such as that of Orecchia and IEO-Milan researchers: they showed results obtained on 82 patients treated by ELIOT as a single shot (14–21 Gy) after re-quadrantectomy for local recurrences (personal communication): with a median follow-up of 53 months, they obtained a 5-y local DFS of 85.5% (10 pts relapsed). The DFS and OS rates were 80% and 100%, respectively.[2] In Table 6 we summarized the other experiences reported in literature. As to normal tissue tolerance, our results showed excellent technical feasibility, low radiation-induced side effects and good oncological outcomes.[21] Considering that most of the patients analyzed received conservative surgery for the second time, asymmetry from the surgical induced breast volume deficit was in our study a crucial baseline observation before IORT. Despite this, in our retrospective analysis, breast cosmetic was rated as poor only in 6 pts (21%). Moreover, we did not record acute events as delay, dehiscence and infections of healing. This good acute clinical tolerance correlated with very low consequential local effects. The therapeutic approach including IORT should be further explored also in patients previously treated for HD. Although nowadays treatment of lymphoma consists of a multimodal approach with chemotherapy and limited radiotherapy field, mantle radiation (i.e., extended field radiation) represented the standard of care in the past decades for Hodgkin disease (HD).[22] Extended irradiation of HD patients was associated with high long-term survival but increased risk of secondary malignancies such as breast cancer, lung cancer, stomach cancer, and melanoma.[22] In Hodgkin survivors, the risk of breast cancer has been shown to be as high as 35% by the age of 40 years.[23] Our results seem to indicate that, in patients previously irradiated due to HD, this approach may be a feasible and well-tolerated alternative to mastectomy.

5. Conclusions

We recognize that our data are based on a small number of patients and short follow-up and therefore it does not allow us to suggest this method as a standard treatment; nevertheless, this strategy with IORT may be an option to be reserved for selected patients. At any rate, the ultimate decision to accept breast conservative surgery and IORT should be taken after

being well informed about the lack of long term data. Meanwhile, we suggest further clinical trials to explore IORT are needed to identify possible subgroups of patients that might be suitable for this type of approach.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Canavan J, Truong PT, Smith SL, Lu L, Lesperance M, Olivotto IA. Local recurrence in women with stage I breast cancer: declining rates over time in a large, population-based cohort. *Int J Radiat Oncol Biol Phys* 2014;**88**(Jan (1)):80–6.
2. Sedlmayer F, Zehentmayr F, Fastner G. Partial breast re-irradiation for local recurrence of breast carcinoma: benefit and long term side effects. *Breast* 2013;**22**(Aug (Suppl. 2)):S141–6.
3. Anderson SJ, Wapnir I, Dignam JJ, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. *J Clin Oncol* 2009;**27**(May (15)):2466–73.
4. Fowble B, Solin LJ, Schultz DJ, Rubenstein J, Goodman RL. Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment. *Int J Radiat Oncol Biol Phys* 1990;**19**(Oct (4)):833–42.
5. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *J Am Coll Surg* 2009;**209**(Aug (2)):269–77.
6. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;**31**(Mar (5)):1341–6.
7. Olivotto IA, Rose MA, Osteen RT, et al. Late cosmetic outcome after conservative surgery and radiotherapy: analysis of causes of cosmetic failure. *Int J Radiat Oncol Biol Phys* 1989;**17**(Oct (4)):747–53.
8. Rowland JH, Desmond KA, Meyerowitz BE, Belin TR, Wyatt GE, Ganz PA. Role of breast reconstructive surgery in physical and emotional outcomes among breast cancer survivors. *J Natl Cancer Inst* 2000;**92**(Sep (17)):1422–9. Erratum in: J Natl Cancer Inst 2001 Jan 3;93(1):68.
9. Dorval M, Maunsell E, Deschênes L, Brisson J. Type of mastectomy and quality of life for long term breast carcinoma survivors. *Cancer* 1998;**83**(Nov (10)):2130–8.
10. Ganz PA, Schag AC, Lee JJ, Polinsky ML, Tan SJ. Breast conservation versus mastectomy. Is there a difference in psychological adjustment or quality of life in the year after surgery? *Cancer* 1992;**69**(Apr (7)):1729–38.
11. Kacprowska A, Jassem J. Partial breast irradiation techniques in early breast cancer. *Rep Pract Oncol Radiother* 2011;**16**(Oct (6)):213–20.
12. O'Brien MM, Donaldson SS, Balise RR, Whittemore AS, Link MP. Second malignant neoplasms in survivors of pediatric Hodgkin's lymphoma treated with low-dose radiation and chemotherapy. *J Clin Oncol* 2010;**28**(Mar (7)):1232–9.
13. Vila J, Garcia-Etienne CA, Vavassori A, Gentilini O. Conservative surgery for ipsilateral breast tumor recurrence. *J Surg Oncol* 2014;**110**(Jul (1)):62–7.
14. Hannoun-Levi JM, Tarik Ihrai T, Courdi A. Local treatment options for ipsilateral breast tumour recurrence. *Cancer Treat Rev* 2013;**39**:737–41.
15. Ishitobi M, Komoike Y, Nakahara S, Motomura K, Koyama H, Inaji H. Repeat lumpectomy for ipsilateral breast tumor recurrence after breast-conserving treatment. *Oncology* 2011;**81**(5–6):381–6.
16. Poortmans P, Marsiglia H, De Las Heras M, Algara M. Clinical and technological transition in breast cancer. *Rep Pract Oncol Radiother* 2013;**18**(Sep (6)):345–52.
17. Trombetta M, Julian T, Miften M, McWilliams W, Kim Y, Parda D. The use of the MammoSite balloon applicator in re-irradiation of the breast. *Brachytherapy* 2008;**7**(Oct–Dec (4)):316–9.
18. Deutsch M. Repeat high-dose external beam irradiation for in-breast tumor recurrence after previous lumpectomy and whole breast irradiation. *Int J Radiat Oncol Biol Phys* 2002;**53**:687–91.
19. Kraus-Tiefenbacher U, Bauer L, Scheda A, et al. Intraoperative radiotherapy (IORT) is an option for patients with localized breast recurrences after previous external-beam radiotherapy. *BMC Cancer* 2007;**Sep (7)**:178.
20. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomized controlled equivalence trial. *Lancet Oncol* 2013;**14**(Dec (13)):1269–77.
21. Burguer A, Pain S, Peley G. Treatment of recurrent breast cancer following breast conserving surgery. *Breast J* 2013;**19**:310–8.
22. Elkin EB, Klem ML, Gonzales AM, et al. Characteristics and outcomes of breast cancer in women with and without a history of radiation for Hodgkin's lymphoma: a multi-institutional, matched cohort study. *J Clin Oncol* 2011;**29**(Jun (18)):2466–73.
23. Rathore B, Kadin ME. Hodgkin's lymphoma therapy: past, present, and future. *Expert Opin Pharmacother* 2010;**11**(Dec (17)):2891–906.
24. Maulard C, Housset M, Brunel P, Delanian S, Taurelle R, Baillet F. Use of perioperative or split-course interstitial brachytherapy techniques for salvage irradiation of isolated local recurrences after conservative management of breast cancer. *Am J Clin Oncol* 1995;**18**(Aug (4)):348–52.
25. Resch A, Fellner C, Mock U, et al. Locally recurrent breast cancer: pulse dose rate brachytherapy for repeat irradiation following lumpectomy – a second chance to preserve the breast. *Radiology* 2002;**225**(Dec (3)):713–8.
26. Chadha M, Feldman S, Boolbol S, Wang L, Harrison LB. The feasibility of a second lumpectomy and breast brachytherapy for localized cancer in a breast previously treated with lumpectomy and radiation therapy for breast cancer. *Brachytherapy* 2008;**7**(Jan–Mar (1)):22–8, doi: 10.1016/j.brachy.2007.10.006.
27. Trombetta M, Julian TB, Werts DE, et al. Long-term cosmesis after lumpectomy and brachytherapy in the management of carcinoma of the previously irradiated breast. *Am J Clin Oncol* 2009;**32**(Jun (3)):314–8.
28. Guix B, Lejárcegui JA, Tello JI, et al. Exeresis and brachytherapy as salvage treatment for local recurrence after conservative treatment for breast cancer: results of a ten-year pilot study. *Int J Radiat Oncol Biol Phys* 2010;**78**(Nov (3)):804–10.
29. Kauer-Dorner D, Pötter R, Resch A, et al. Partial breast irradiation for locally recurrent breast cancer within a second breast conserving treatment: alternative to mastectomy?

Results from a prospective trial. *Radiother Oncol* 2012;**102**(Jan (1)):96–101.
30. Hannoun-Levi JM, Resch A, Gal J, et al. GEC-ESTRO Breast Cancer Working Group, Accelerated partial breast irradiation with interstitial brachytherapy as second conservative treatment for ipsilateral breast tumour recurrence: multicentric study of the GEC-ESTRO Breast Cancer Working Group. *Radiother Oncol* 2013;**108**(Aug (2)):226–31.