Medical Oncology (2019) 36:48
https://doi.org/10.1007/s12032-019-1275-z

ORIGINAL PAPER

Postmastectomy radiation therapy using VMAT technique for breast cancer patients with expander reconstruction

Fiorenza De Rose[1] · Antonella Fogliata[1] · Davide Franceschini[1] · Salvatore Cozzi[1] · Cristina Iftode[1] · Antonella Stravato[1] · Stefano Tomatis[1] · Giovanna Masci[2] · Rosalba Torrisi[2] · Alberto Testori[3] · Corrado Tinterri[3] · Andrea V. E. Lisa[4] · Luca Maione[4] · Valeriano Vinci[4] · Marco Klinger[4] · Armando Santoro[2,5] · Marta Scorsetti[1,5]

Received: 1 March 2019 / Accepted: 19 April 2019 / Published online: 25 April 2019

Abstract

Postmastectomy radiotherapy (PMRT) following immediate breast reconstruction is increasingly adopted in the management of breast cancer patients. We retrospectively evaluate the complication rates of PMRT using VMAT technique to immediate tissue expander-based reconstructions and the possible impact of tissue expander volume on radiotherapy planning. We reviewed the data of patients who underwent immediate expander breast reconstruction and received PMRT with VMAT (50 Gy in 25 fractions) on the reconstructed breast and axillary levels III–IV. Neoadjuvant or adjuvant systemic therapy was administered in most of the patients. Autologous fat grafting was routinely performed at the time of second-stage reconstruction. Between 2015 and 2017, PMRT was delivered to 46 consecutive patients (median age 50 years) with expander reconstruction. Median follow-up was 27 months (range 10–41). Two patients (4.3%) had a reconstruction failure, as expander rupture and infection, following the first- and the second-stage reconstruction, respectively. In most cases expanders were completely inflated before PMRT (65.2%). Median expander volume before PMRT was 425 cm^3 (range 150–700 cm^3). The amount of expander inflation did not significantly affect dosimetry, except for skin dose, with a surface receiving more than 30 Gy of 36.6 ± 0.9 cm^2 and 47.0 ± 2.5 cm^2 for a volume expander below or above the median, respectively. However, this variable was not predictor for complications. Disease progression was recorded in 15.2% of patients. PMRT using VMAT technique for breast cancer patients with expander reconstruction is associated with a very low complication rate. The expander volume before PMRT does not significantly compromise radiotherapy dose distribution.

Keywords Postmastectomy radiotherapy · VMAT · Immediate breast reconstruction · Tissue expander · Autologous fat grafting

Introduction

During the past decade, literature data and metanalysis confirmed a significant improvement of local control and overall survival in breast cancer patients with locally advanced disease or pathologically involved lymph nodes who underwent postmastectomy radiotherapy (PMRT) [1–3].

The benefit of PMRT and the increasing clinical practice of immediate reconstruction have raised many questions about their optimal integration that became crucial in the management of breast cancer patients [4].

Despite its therapeutic advantages, PMRT is associated with a moderate increase in complications such as skin fibrosis, infection, distortion of breast shape, volume loss, fat necrosis, implant exposure, that translate in poor satisfaction, cosmesis, and quality of life [5–7].

✉ Antonella Fogliata
antonella.fogliata@humanitas.it

1 Radiotherapy and Radiosurgery Department, Humanitas Research Hospital, Milan, Rozzano, Italy

2 Medical Oncology Department, Humanitas Research Hospital, Milan, Rozzano, Italy

3 Breast Surgery Department, Humanitas Research Hospital, Milan, Rozzano, Italy

4 Plastic Surgery Department, Humanitas Research Hospital, Milan, Rozzano, Italy

5 Department of Biomedical Sciences, Humanitas University, Milan, Rozzano, Italy

Moreover, difficulties in irradiating a reconstructed breast may lead to sub-optimal radiotherapy treatment dose coverage of target volumes, particularly when locoregional nodes need to be treated together with the chest wall. In addition, immediate reconstruction could compromise the delivery of radiotherapy, resulting in increasing dose to the organs at risk (OARs) such as heart and lungs. Although not entirely solved, these limits have been minimized by recent advances in both plastic surgery and radiotherapy techniques, which have simplified the ways to integrate PMRT in the setting of breast reconstruction [4, 8, 9].

Intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) improve the plan quality for PMRT allowing adequate and homogeneous target coverage and acceptable doses to the OARs [10, 11].

On the other hand, the introduction of autologous fat grafting (AFG) as a part of a two-stage breast reconstruction could be useful to reduce complication rate and to improve cosmetic outcome [12, 13].

Through this study, we aim to retrospectively evaluate the complication rates of PMRT using VMAT technique to immediate tissue expander-based reconstructions, and the possible impact of tissue expander volume to radiotherapy planning.

Materials and methods

Patients

Clinical data of patients with immediate tissue expander (TE) reconstruction and PMRT for stage II to III breast cancer were retrospectively reviewed. Neoadjuvant or adjuvant systemic therapy was administered in most of the patients.

All patients were treated in agreement with the Helsinki Declaration of 1975 and revised in 1983. Our institutional ethical committee does not require a formal approval in case of retrospective studies; however, a formal consent for patient medical data handling was obtained from each patient at the time of the admission.

Breast reconstruction

All patients received mastectomy and first-stage breast reconstruction with an expander placement under pectoralis major and serratum plane (complete sub-muscular pocket). Radiation treatment started within 9 weeks from mastectomy and within 6 months if adjuvant chemotherapy was indicated following our oncological guidelines. Before radiotherapy, the expander was inflated trying to fill it as much as possible, while during radiotherapy we stopped inflation. When it was not possible to complete the expansions, we restarted (infiltrating 50 cc at most every 3 weeks) one to 3 months after radiotherapy, according to local signs, and we performed fat grafting during expander substitution [14].

At the time of second-stage breast reconstruction, in rare cases of severe radiodermatitis we performed a skin incision at the level of new inframammary fold, otherwise we preferred to use mastectomy scar.

A key point of this procedure is to decrease capsular retraction by capsulotomy during the second time reconstruction, maintaining a relationship between final expander volume and final implant volume without losing expansion volume. Patients underwent radiotherapy before stage two so that during expander substitution we could perform capsulotomy having more space to insert the implant.

Autologous fat grafting

AFG was performed during the surgical procedure of expander removal and implant position. The abdomen and/or trochanteric areas represented preferable donor sites given the easier access to abundant amounts of adipose tissue. We performed the technique according to the Coleman technique since we are convinced about its ability of increasing stem cells potential [15]. The adipocyte fraction was injected using an 18-gage angiographic needle with a snap-on wing in the irradiated area. The adipose tissue fraction was inserted into the dermo-hypodermic junction in all cases, with the use of small syringes described above. Through the same incision, many radiating passages were made, in order to distribute fat in different directions according to an ideal form of a web to support damaged areas and to restore subcutaneous tissue. In case of severe thinning of subcutaneous tissue, we performed fat grafting without the implant inserted in order to increase its thickness without damaging the implant itself while we performed the final refinements, after obtaining adequate subcutaneous thickness, with implant inserted. The amount of fat graft was variable (35–90 cm^3, mean value 55 cm^3) according to local areas of actinic damage. The amount of injected fat at each passage was minimized to avoid irregularities and clusters, which were eventually eliminated with external digital manipulation after procedure. The treated area was covered with a dressing for 1 week and the patient was instructed to avoid pressure and friction in order to reduce the displacement of fat infiltration.

Radiotherapy planning and treatment

After the reconstructive surgery with the expander implant, patients received radiotherapy treatment to the reconstructed breast and axillary levels III–IV.

All patients were set-up in supine position, with both arms above the head. The internal guidelines foresee the computed tomography (CT) dataset with 3-mm thick

adjacent slices acquisition for simulation and planning. The clinical target volumes (CTV) of the thoracic wall and level III-IV were delineated according to the ESTRO guidelines [16]. No patient received prophylactic irradiation of the internal mammary nodes. We generally included the internal mammary chain (IMC) in the target volume only if it resulted involved at staging on CT or CT-PET imaging. The filled expander was included in the CTV delineation. Planning target volumes (PTV) were obtained from CTV by adding a margin of 5 mm in all the directions. The PTVs were limited to 5 mm within the skin surface for planning and plan evaluation purposes. No bolus was applied to any patient during treatment.

The total dose was prescribed to PTV mean dose as 50 Gy in 25 fractions, over 5 weeks for both chest wall and nodal regions, and planned with VMAT technique with 6 MV beams on different Varian linear accelerators (TrueBeam, Unique or Clinac DHX). From 2016, young patients with left-sided breast cancer were treated with gated delivery in deep inspiration breath hold. The majority of the patients treated unilaterally were planned with single isocentre and four partial arcs with gantry angles ranging from the medial tangential beam to an almost posterior entrance (from the PTV side). The bilateral treatments (two cases in this study) were planned with double isocentre and four arcs per isocentre in one case, and with single middle isocentre and five arcs the second case. The PRO optimization algorithm was used, and final dose calculation was estimated with the AAA algorithm implemented in the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, USA, version 11). To account for the set-up uncertainties and patient breathing in a superficial target, the skin flash strategy described by Nicolini et al. [11] was adopted with a virtual expansion of 1 cm. The CT density was corrected for the artifacts generated by the metallic part of the expander, by assigning appropriate densities.

Target-related plan objectives concerned the target coverage and dose homogeneity. For PTV, $D_{95\%} > 95\%$, $D_{2\%} < 107\%$, where D_x is the dose delivered to at least (>) or at most (<) x% of the structure volume. The delineated OARs and their plan objectives were as follows: ipsilateral lung mean dose < 20 Gy, $V_{20Gy} < 20\%$ (the volume receiving more than 20 Gy should not exceed the 20%); mean heart dose < 5 Gy; minimize the contralateral lung and breast irradiation, with mean doses < 3–5 Gy.

During the treatment, daily cone-beam CT or 2D–2D matching allowed assessing the correctness of the patient positioning before the treatment.

Clinical evaluation and statistical analysis

The patients were clinically evaluated during the PMRT once a week. Acute skin and esophageal toxicity at the end of the PMRT were scored according to the RTOG acute radiation morbidity scoring criteria. Clinical evaluation was assessed as outcome of the surgical intervention, as well as clinical outcome during the follow-up period.

Possible relationships between PMRT acute toxicity with clinical and dosimetric data were assessed with a Chi-squared Pearson test, setting the significance value as 0.05.

Dosimetric data were analyzed in particular against the expander filling, stratified according to the median and quartiles volumes. The filling was measured by delineating the expander on the planning CT, and checking the volume consistency with the value recorded during the expander placement. The measured and stated volumes were in good agreement, within 3%.

Data analysis was performed using the SPSS software (Statistical Package for Social Science, version 21.0).

Results

Between January 2015 and May 2017, PMRT was delivered at our institution to 46 consecutive patients with expander reconstruction. Median age was 50 years (range 36–73). Median follow-up was 27 months (range 10–41 months) from PMRT. Most of the patients had a Luminal B subtype and presence of lymph vascular invasion. Regarding chemotherapy, 65% of the cohort received an adjuvant treatment. Patients and tumor characteristics are summarized in Tables 1 and 2. Two patients were treated with radiotherapy bilaterally, in one case the mastectomy and expander placement were bilateral, while in the other case this was performed only on the right breast, having the left been treated with conserving surgery. Other two patients received also a contralateral prosthesis placement, without expander, for aesthetic reasons.

Dosimetric results are reported in Table 3 as average values of some parameters with their standard deviation of the mean. A typical dose distribution for PMRT with TE is shown in Fig. 1.

Skin and esophageal toxicities were recorded at the end of the PMRT treatment. Skin toxicity was reported as G1 in 20 cases (43.5%), G2 in 21 cases (45.7%), and G3 in one case (2.2%). Esophageal toxicity was recorded as G1 and G2 in 18 (39.1%) and 3 (6.5%) cases, respectively.

The toxicity was correlated with diabetes for skin ($p = 0.001$) and a trend was shown also for esophageal toxicity ($p = 0.052$). However, only three patients had diabetes, decreasing the power of the result, although statistically significant. No other clinical or dosimetric correlation was found. In particular, skin toxicity was not significantly correlated with expander size ($p = 0.77$ with the expander size stratified in quartiles, $p = 0.52$ when

Table 1 Patients characteristics

Patients	Total number	46
Age	Median (range) years	50 (36–73)
Body mass index	Median (range)	24.5 (19.5–38.8)
	Mean ± std error of the mean	25.4 ± 0.7
Smoking habit	Yes	13 (28.3%)
	No	30 (65.2%)
	Ex smoker	3 (6.5%)
Diabetes	Yes	3 (6.5%)
	No	43 (93.5%)
Autoimmune diseases	No	44 (95.7%)
	Yes	2 (4.3%)
Chemotherapy	No	2 (4.3%)
	Adjuvant	30 (65.2%)
	Neoadjuvant	14 (30.4%)
Trastuzumab	Yes	15 (32.6%)
	No	31 (67.4%)
Hormone therapy	Yes	36 (78.3%)
	No	10 (21.7%)
Mastectomy	Total	30 (65.2%)
	Nipple sparing	12 (26.1%)
	Skin sparing	4 (8.7%)
Axillary dissection	Yes	36 (78.3%)
	No	10 (21.7%)

stratified according to the median), nor with the mean dose to the skin or the skin area receiving at least 30 Gy ($p = 0.41$).

In most cases (34 patients, 73.9%), the expander was completely filled before PMRT. In Fig. 2, the filling volumes during all phases for all the 46 patients are shown. The median expander volume before PMRT was 425 cm^3 (range 150–700 cm^3). The amount of expander filling did not significantly affect the dosimetry, except for the skin dose. The skin area receiving at least 30 Gy increased with increasing the expander size, being in average 36.6 ± 0.9 and 47.0 ± 2.5 cm^2 for the groups with expander size below or above the median inflation value. However, this variable was not a predictor for complications.

Only two patients (4.3%) experienced reconstruction failure, in one case due to expander rupture, and in the other one due to infection, following the first and the second-stage reconstruction, respectively.

Disease progression (local or distant) was recorded in seven patients (15.2%). Five patients presented a progression of disease with distant metastases: in three cases (two pulmonary and one brain) before the second-stage reconstruction, while in other two patients (one liver and one bone) during the follow-up. In addition, we recorded two cases of locoregional progression.

Table 2 Tumor characteristics

Side	Left	21 (45.7%)
	Right	23 (50%)
	Bilateral	2 (4.3%)
TNM—pT	pT1	1 (2.2%)
	pT2	18 (39.1%)
	pT3	11 (23.9%)
	pT4	2 (4.3%)
TNM—ypT	ypT0	4 (8.7%)
	ypT1mic	1 (2.2%)
	ypT1a	1 (2.2%)
	ypT1b	1 (2.2%)
	ypT1c	1 (2.2%)
	ypT2 m	2 (4.3%)
	ypT3	2 (4.3%)
	ypT3 m	1 (2.2%)
	ypTis	1 (2.2%)
TNM—pN	pN0	1 (2.2%)
	pN1a	8 (17.4%)
	pN2a	11 (23.9%)
	pN3a	12 (26.1%)
TNM—ypN	ypN0	7 (15.2%)
	ypN1mic	2 (4.3%)
	ypN1a	1 (2.2%)
	ypN2	1 (2.2%)
	ypN2a	2 (4.3%)
	ypN3a	1 (2.2%)
Grading	G2	21 (45.7%)
	G3	21 (45.7%)
	Gx	4 (8.7%)
Ki-67 (%)	≤ 20	21 (45.7%)
	> 20	25 (54.3%)
Molecular subtype	Luminal A	0
	Luminal B	27 (58.7%)
	Triple negative	3 (6.5%)
	Her2+	16 (34.8%)
Vascular invasion	No	15 (32.6%)
	Focal	7 (15.2%)
	Extended	24 (52.2%)

Discussion

One of the most relevant issues related to the association of PMRT and immediate reconstruction with TE is the increase of complication rate. Previous studies reported reconstruction failure rates varying from 4.8 to 40% when PMRT was delivered to the TE [17–21].

Prospective results published in 2016 by Santosa et al. [22] evidenced no difference between patients who received PMRT to the TE and those irradiated to the permanent implant, with an overall reconstruction failure rate of 10.7%.

Table 3 Dosimetric results

Heart (left-sided breast)	Mean (Gy)	5.37 ± 0.27
	V_{20Gy} (%)	2.3 ± 0.4
Heart (right-sided breast)	Mean (Gy)	3.93 ± 0.20
	V_{20Gy} (%)	0.1 ± 0.1
Lung ipsilateral	Mean (Gy)	11.30 ± 0.24
	V_{20Gy} (%)	15.3 ± 0.6
	V_{5Gy} (%)	73.1 ± 1.7
Lung contralateral	Mean (Gy)	3.85 ± 0.11
	V_{20Gy} (%)	0.1 ± 0.1
	V_{5Gy} (%)	27.5 ± 1.5
Skin	Mean (Gy)	33.59 ± 0.19
	V_{30Gy} (%)	67.8 ± 0.7
	A_{30Gy} (cm^2)	41.8 ± 1.5
Breast contralateral	Mean (Gy)	3.45 ± 0.12
PTV breast expander	Mean (Gy)	49.90 ± 0.08
	$V_{107\,\%}$ (cm^3)	1.3 ± 0.5

Moreover, the absence of significant differences in the complication rate for these two subgroups of patients was confirmed in Lee's metanalysis [23].

In our study, only 4.3% of patients reported a reconstruction failure, with a median follow-up of 27 months. Regarding acute skin and esophageal toxicity, we recorded only one case of G3 erythema in supraclavicular region, with G2 of 45.7% and 6.5% in terms of skin and esophageal toxicity, respectively.

On the other side, the grade of the TE inflation could play a role in the final cosmetic result and, at the same time, could cause a worsening in the target dose coverage and sparing of OARs.

A heterogeneous behavior prevails among radiation oncologists, therefore, the current practice regarding deflation or not before PMRT is still debated. Different experiences reported the attitude to deflate the expanders prior to the radiation treatment to improve the dosimetric optimization of radiotherapy planning [24, 25]. Other authors

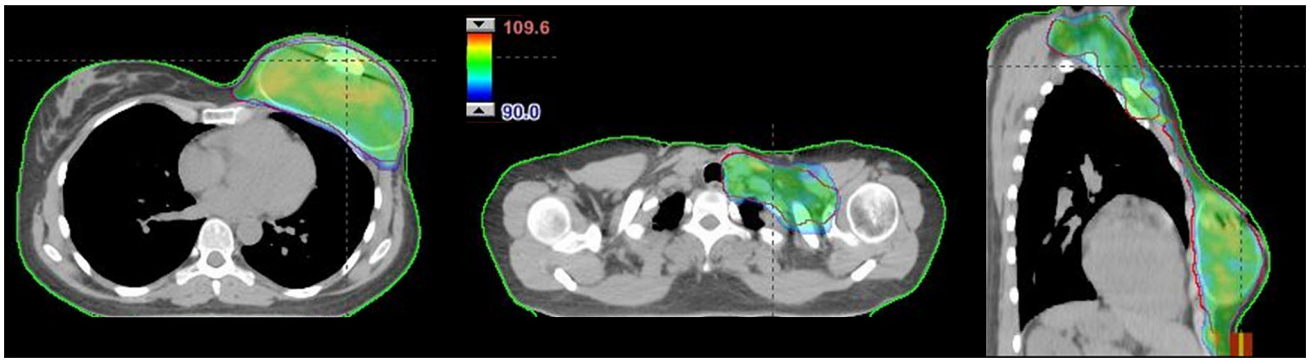

Fig. 1 Typical dose distribution

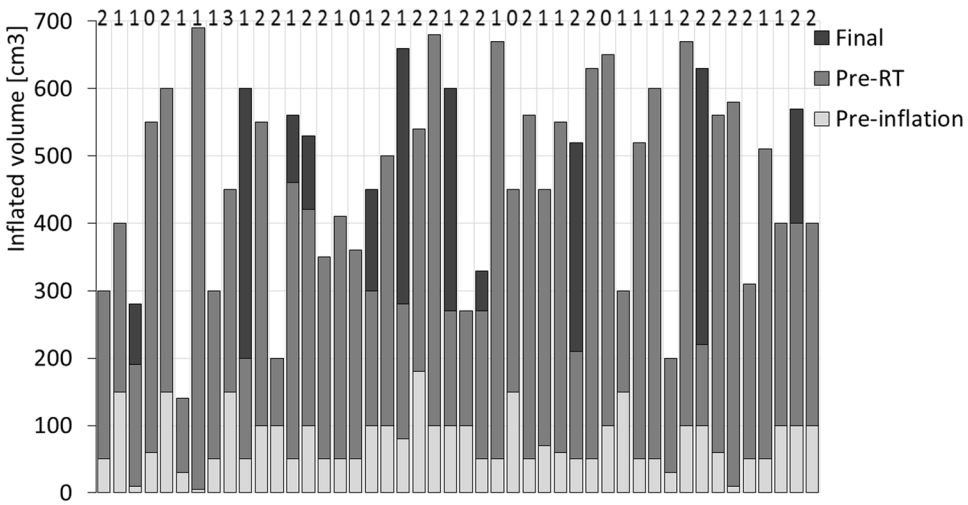

Fig. 2 Sequence of expander filling for all the patients. The numbers on the top of the plot refer to the acute skin toxicity grade for each specific patient

described their clinical practice to irradiate the inflated expanders or, directly, a permanent implant with the aim to improve cosmetic outcomes [26, 27]. A single experience of comparison between full deflation and maximal inflation in a small cohort of patients before PMRT was published by Woo et al. [28]. They reported a complication rate significantly higher in the deflation group.

To evaluate the impact of the TE inflation when VMAT is used, we analyzed the variation in the dose parameters related to different grades of inflation. Our analysis showed no statistically significant differences in target coverage and dose to the OARs, including contralateral breast, in the two or four subgroups defined using a median or quartile cut-off size of the expander volume.

This point could lead to the idea that the complete filling of the expander before the VMAT-PMRT is not detrimental for toxicity nor dosimetry, while it fastens the overall time of expander to prothesis substitution. Considering all these features, VMAT technique seems to be an ideal choice for patients who have to receive PMRT, regardless of the grade of tissue expander inflation.

Probably, both the use of VMAT technique and the routine AFG at the time of expander implant exchange provided a reduction of complication rates and an increase of the patients' compliance and tolerance to the treatments. Different previous studies confirmed that arc therapies improved the optimization of radiotherapy planning in the setting of PMRT compared to 3D conformal treatments [29–31]. Moreover, recent experiences have investigated the role of innovative procedure in plastic surgery, such as the association of AFG, to achieve a better cosmetic outcome [12, 13].

AFG has been already adopted to treat irradiated breasts by other authors [13, 32] demonstrating a positive effect in reducing complication rate, but their approach implied a delayed breast reconstruction or multiple fat graft sessions, while our patients were submitted to immediate breast reconstruction having shorter overall time of reconstruction. In particular, compared to others, our practice is the shortest in procedures number and duration, resulting in a less invasive therapeutic approach with positive effects on patients' quality of life [33, 34].

To our knowledge, this is the first study to report data on a homogeneous cohort, including only patients who have undergone mastectomy and first-stage reconstruction with TE, PMRT using VMAT technique and, finally, second-stage reconstruction with definitive implant and AFG.

Nevertheless, this study is characterized by some limitations that do not allow to draw definitive conclusions: the small sample size, the retrospective nature of the analysis, and lastly, the absence of a systematic assessment of cosmetic outcome.

Further studies, prospective or randomized, including a large cohort of patients with longer follow-up, are needed to definitely assess the role of the VMAT technique and to confirm these preliminary data.

Conclusion

Postmastectomy radiation therapy using VMAT technique for breast cancer patients with expander reconstructions is associated with a very low complication rate after both first- and second-stage reconstructions. The expander volume before PMRT does not significantly compromise target dose coverage or increase dose to organs at risk.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All patients were treated in agreement with the Helsinki Declaration. Our institutional ethical committee does not require a formal approval in case of retrospective studies; however, a formal consent was obtained from all the patients for patient medical data handling.

Informed consent Formal informed consent was obtained from all individual patients included in the study, for patient medical data handling.

References

1. EABCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383(9935):2127–35. https://doi.org/10.1016/S0140-6736(14)60488-8.
2. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005;97(2):116–26. https://doi.org/10.1093/jnci/djh297.
3. Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. Adjuvant radiation therapy of regional lymph nodes in breast cancer—a meta-analysis of randomized trials- an update. Radiat Oncol. 2015;10:258. https://doi.org/10.1186/s13014-015-0568-4.
4. Ho AY, Hu ZI, Mehrara BJ, Wilkins EG. Radiotherapy in the setting of breast reconstruction: types, techniques, and timing. Lancet Oncol. 2017;18:e742–53. https://doi.org/10.1016/S1470-2045(17)30617-4.

5. Woo KJ, Paik JM, Bang SI, Mun GH, Pyon JK. The impact of expander inflation/deflation status during adjuvant radiotherapy on the complications of immediate. Two-stage breast reconstruction. Aesth Plast Surg. 2017;41:551–9. https://doi.org/10.1007/s00266-017-0864-5.
6. Classen J, Nitzsche S, Wallwiener D, Kristen P, Souchon R, Bamberg M, et al. Fibrotic changes after postmastectomy radiotherapy and reconstructive surgery in breast cancer. A retrospective analysis in 109 patients. Strahlenther Onkol. 2010;186:630–6. https://doi.org/10.1007/s00066-010-2158-6.
7. Sullivan SR, Fletcher DR, Isom CD, Isik FF. True incidence of all complications following immediate and delayed breast reconstruction. Plast Reconstr Surg. 2008;122:19–28. https://doi.org/10.1097/PRS.0b013e3181774267.
8. Schechter NR, Strom EA, Perkins GH, Arzu I, McNeese MD, Langstein HN, et al. Immediate breast reconstruction can impact postmastectomy irradiation. Am J Clin Oncol. 2005;28(5):485–94.
9. Aristei C, Kaidar-Person O, Tagliaferri L, Arenas M, Coles CE, Offersen BV, et al. The assisi think tank meeting and survey of post mastectomy radiation therapy after breast reconstruction: the ATTM-SMART report. Eur J Surg Oncol. 2018;44(4):436–43. https://doi.org/10.1016/j.ejso.2018.01.010.
10. Kuo L, Ballangrud ÅM, Ho AY, Mechalakos JG, Li G, Hong L. A VMAT planning technique for locally advanced breast cancer patients with expander or implant reconstructions requiring comprehensive postmastectomy radiation therapy. Med Dosim. 2018. https://doi.org/10.1016/j.meddos.2018.04.006.
11. Nicolini G, Fogliata A, Clivio A, Vanetti E, Cozzi L. Planning strategies in volumetric modulated arc therapy for breast. Med Phys. 2011;38(7):4025–31. https://doi.org/10.1118/1.3598442.
12. Cogliandro A, Barone M, Tenna S, Morelli Coppola M, Persichetti P. The role of lipofilling after breast reconstruction: evaluation of outcomes and patient satisfaction with BREAST-Q. Aesthet Plast Surg. 2017;41(6):1325–31. https://doi.org/10.1007/s00266-017-0912-1.
13. Ribuffo D, Atzeni M, Guerra M, Bucher S, Politi C, Deidda M, et al. Treatment of irradiated expanders: protective lipofilling allows immediate prosthetic breast reconstruction in the setting of postoperative radiotherapy. Aesthet Plast Surg. 2013;37(6):1146–52. https://doi.org/10.1007/s00266-013-0221-2.
14. Lisa A, Caviggioli F, Maione L, Forcellini D, Vinci V, Klinger F, et al. Outcomes of immediate tissue expander breast reconstruction followed by reconstruction of choice in the setting of postmastectomy radiation therapy. Ann Plast Surg. 2015;74(2):270–1. https://doi.org/10.1097/SAP.0000000000000324.
15. Ibatici A, Caviggioli F, Valeriano V, Quirici N, Sessarego N, Lisa A, et al. Comparison of cell number, viability, phenotypic profile, clonogenic, and proliferative potential of adipose-derived stem cell populations between centrifuged and noncentrifuged fat. Aesthet Plast Surg. 2014;38(5):985–93. https://doi.org/10.1007/s00266-014-0372-9.
16. Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol. 2015;114:3–10. https://doi.org/10.1016/j.radonc.2014.11.030.
17. Cordeiro PG, Albornoz CR, McCormick B, Hudis CA, Hu Q, Heerdt A, et al. What is the optimum timing of postmastectomy radiotherapy in two-stage prosthetic reconstruction: radiation to the tissue expander or permanent implant? Plast Reconstr Surg. 2015;135:1509–17. https://doi.org/10.1097/PRS.0000000000001278.
18. Anderson PR, Freedman G, Nicolaou N, Sharma N, Li T, Topham N, Morrow M. Postmastectomy chest wall radiation to a temporary tissue expander or permanent breast implant—is there a difference in complication rates? Int J Radiat Oncol Biol Phys. 2009;74:81–5. https://doi.org/10.1016/j.ijrobp.2008.06.1940.
19. Nava MB, Pennati AE, Lozza L, Spano A, Zambetti M, Catanuto G. Outcome of different timings of radiotherapy in implant-based breast reconstructions. Plast Reconstr Surg. 2011;128:353–9. https://doi.org/10.1097/PRS.0b013e31821e6c10.
20. Hvilsom GB, Holmich LR, Steding-Jessen M, Frederiksen K, Henriksen TF, Lipworth L, et al. Delayed breast implant reconstruction: is radiation therapy associated with capsular contracture or reoperations? Ann Plast Surg. 2012;68:246–52. https://doi.org/10.1097/SAP.0b013e318214e69c.
21. Fowble B, Park C, Wang F, Peled A, Alvarado M, Ewing C, et al. Rates of reconstruction failure in patients undergoing immediate reconstruction with tissue expanders and/or implants and postmastectomy radiation therapy. Int J Radiat Oncol Biol Phys. 2015;92:634–41. https://doi.org/10.1016/j.ijrobp.2015.02.031.
22. Santosa KB, Chen X, Qi J, Ballard TN, Kim HM, Hamill JB, et al. Postmastectomy radiation therapy and two-stage implant-based breast reconstruction: is there a better time to irradiate? Plast Reconstr Surg. 2016;138:761–9. https://doi.org/10.1097/PRS.0000000000002534.
23. Lee KT, Mun GH. Optimal sequencing of postmastectomy radiotherapy and two stages of prosthetic reconstruction: a meta-analysis. Ann Surg Oncol. 2017;24:1262–8. https://doi.org/10.1245/s10434-017-5819-1.
24. Kronowitz SJ, Lam C, Terefe W, Hunt KK, Kuerer HM, Valero V, et al. A multi-disciplinary protocol for planned skin-preserving delayed breast reconstruction for patients with locally advanced breast cancer requiring postmastectomy radiation therapy: 3-year follow-up. Plast Reconstr Surg. 2011;127:2154–66. https://doi.org/10.1097/PRS.0b013e3182131b8e.
25. Moyer HR, Pinell-White X, Losken A. The effect of radiation on acellular dermal matrix and capsule formation in breast reconstruction: clinical outcomes and histologic analysis. Plast Reconstr Surg. 2014;133:214–21. https://doi.org/10.1097/01.prs.0000437255.01199.42.
26. Cordeiro PG, Albornoz CR, McCormick B, Hu Q, Van Zee K. The impact of postmastectomy radiotherapy on two-stage implant breast reconstruction: an analysis of long-term surgical outcomes, aesthetic results, and satisfaction over 13 years. Plast Reconstr Surg. 2014;134:588–95. https://doi.org/10.1097/PRS.0000000000000523.
27. Hirsch EM, Seth AK, Dumanian GA, Jy Kim, Mustoe TA, Galiano RD, et al. Outcomes of immediate tissue expander breast reconstruction followed by reconstruction of choice in the setting of postmastectomy radiation therapy. Ann Plast Surg. 2014;72(3):274–8. https://doi.org/10.1097/SAP.0b013e318268a7ea.
28. Woo KJ, Paik JM, Bang SI, Mun GH, Pyon JK. The impact of expander inflation/deflation status during adjuvant radiotherapy on the complications of immediate two-stage breast reconstruction. Aesthet Plast Surg. 2017;41(3):551–9. https://doi.org/10.1007/s00266-017-0864-5.
29. Osman SO, Hol S, Poortmans PM, Essers M. Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation. Radiother Oncol. 2014;112(1):17–22. https://doi.org/10.1016/j.radonc.2014.04.004.
30. Ranger A, Dunlop A, Hutchinson K, Convery H, Maclennan MK, Chantler H, et al. A dosimetric comparison of breast radiotherapy techniques to treat locoregional lymph nodes including the internal mammary chain. Clin Oncol (R Coll Radiol). 2018;30(6):346–53. https://doi.org/10.1016/j.clon.2018.01.017.
31. Lauche O, Kirova YM, Fenoglietto P, Costa E, Lemanski C, Bourgier C, et al. Helical tomotherapy and volumetric modulated arc therapy: new therapeutic arms in the breast cancer radiotherapy.

World J Radiol. 2016;8(8):735–42. https://doi.org/10.4329/wjr.v8.i8.735.
32. Serra-Renom JM, Munoz-Olmo JL, Serra-Mestre JM. Fat grafting in postmastectomy breast reconstruction with expanders and prostheses in patients who have received radiotherapy: formation of new subcutaneous tissue. Plast Reconstr Surg. 2010;125:12–8. https://doi.org/10.1097/PRS.0b013e3181c49458.
33. Caviggioli F, Maione L, Klinger F, Lisa A, Klinger M. Autologous fat grafting reduces pain in irradiated breast: a review of our experience. Stem Cells Int. 2016;2016:2527349. https://doi.org/10.1155/2016/2527349.
34. Maione L, Vinci V, Caviggioli F, Klinger F, Banzatti B, Catania B, et al. Autologous fat graft in postmastectomy pain syndrome following breast conservative surgery and radiotherapy. Aesthet Plast Surg. 2014;38(3):528–32. https://doi.org/10.1007/s00266-014-0311-9.