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Does post-mastectomy radiotherapy affect the outcome and prevalence of complications in immediate DIEP breast reconstruction? A prospective cohort study☆

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Summary *Introduction:* The decision to perform immediate deep inferior epigastric perforator (DIEP) flap reconstruction in patients requiring post-mastectomy radiation therapy (PMRT) is controversial, and often influenced by the increased potential of complications. We assessed the outcome and complications of irradiated immediate DIEP-reconstructed flaps in a two-surgeon series in our department.
Methods: Data collected prospectively from all patients undergoing immediate DIEP reconstruction under the two senior authors' care over 24 months were reviewed. Patients receiving previous radiation were excluded. Included patients were divided into two groups – requiring or not requiring PMRT. Primary outcome measures were fat necrosis, surgery for removal of fat necrosis, volume loss requiring surgery, wound complications and flap survival. All patients with a clinical diagnosis of post-radiation fat necrosis had an ultrasound scan.
Results: The series included 112 patients with a total of 156 flaps (44 bilateral, 68 unilateral). In 61/156 flaps the patients received PMRT (Group A) whilst 95/156 did not (Group B). Demographics in both groups were similar. Outcomes in PMRT vs. no PMRT, respectively were: fat necrosis 11.5% vs. 6.35% ($p = 0.199$); surgery for removal of fat necrosis 6.6% vs. 4.2% ($p = 0.383$); volume enhancement surgery 4.9% vs. 5.2% ($p = 0.617$); minor wound healing delay, 3.2% vs. 7% ($p = 0.433$); major wound healing delay 2.5% vs. 5.7% ($p = 0.558$). 0/61 flaps were lost in group A and 2/95 in group B.

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Conclusion: Although studies have shown the deleterious effects of post-operative radiotherapy on breast free flaps, our department offers immediate breast reconstruction with the acceptance of the risk/benefit profile. We found no increase in complication rates in patients undergoing immediate DIEP reconstruction receiving PMRT, and the outcome was not adversely affected. As part of an ongoing study, we do not feel that post-mastectomy radiotherapy precludes the decision for immediate free-flap breast reconstruction.

Introduction

The role of post-mastectomy adjuvant radiotherapy (PMRT) in the prevention of locoregional recurrence and the improved overall survival of breast cancer (BRCA) has been well established.[1–6] This has resulted in a steady increase in the rates of patients undergoing this modality of treatment. The application of PMRT in the treatment of patients with T3 or T4 tumours, or four and above involving axillary nodes, has reached international consensus.[1,3,4,7,8] However, results of randomised trials are awaited regarding its role in the management of T1 and T2 tumours and one to three positive axillary nodes.[9–12] This could lead to a marked increase in the number of patients requiring PMRT.[13]

The historical era of BRCA surgery was associated with significant psychosocial morbidity and poor aesthetic results.[14,15] There has since been a paradigm shift towards emphasis on the quality of life, highlighting the importance of aesthetic outcome and benefits of immediate breast reconstruction (IBR).[16–18] The advantages of IBR include superior cosmesis, improved post-operative recovery, and a single operation.[19–22] The use of skin-sparing mastectomy and immediate reconstruction is hence increasing due to the wide acceptance of improved cosmetic results and the evidence of oncological safety.[23–25] An increasing number of patients with BRCA combine radiotherapy and breast reconstruction.[13,26]

Although the adverse effects of radiotherapy after implant-based reconstruction are well documented,[27] there is division of opinion over the outcome of autologous reconstruction when combined with PMRT.[13] Some studies have reported higher rate of complications, volume loss and flap shrinkage, and poor aesthetic outcomes, whereas more recent studies have found acceptable results in particular with modifications of radiotherapy regimes.[28–33] The role of post-ablation breast reconstruction is becoming more complex due to the number of options available to patients. The deep inferior epigastric artery perforator (DIEP) flap has continued to gain popularity in autologous reconstruction due to its excellent cosmetic outcome, natural shape and softness, and low donor-site morbidity.[34] However, some complications such as fat necrosis remain unresolved, and they are thought to be associated with a number of risk factors including radiotherapy.[35] The decision to perform DIEP flap reconstruction in patients requiring PMRT has often been influenced by the increased potential of fat necrosis and volume loss. Our aim was therefore to undertake a prospective cohort study in order to assess the outcome and complications of a consecutive series of irradiated immediate DIEP flaps in a two-surgeon series within our department. The study was designed and executed in keeping with the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology).

Methods

Following discussion at the multidisciplinary meeting, IBR was offered to every patient with operable primary BRCA requiring mastectomy. Bilateral reconstruction was performed in those with BRCA-positive gene status requesting bilateral risk-reducing mastectomy, or in those with proven BRCA on one side and undergoing contralateral risk-reducing surgery. The cohort consisted of all patients undergoing mastectomy and immediate free DIEP reconstruction under the care of two reconstructive surgeons in our department over a 2-year period. The breast surgeons performed the mastectomy and if required axillary clearance, whereas the plastic surgery team was responsible for the immediate reconstruction. Preoperative computerised tomographic (CT) angiography was performed in all cases to determine the location of dominant perforators from the deep inferior epigastric artery. The DIEP flaps were raised in the standard fashion, and they were anastomosed to the internal mammary vessels. In unilateral reconstructions, any tissue with poor perfusion was discarded, and a variable amount of cross-midline tissue was used to reconstruct the breast mound. The flaps were secured down with resorbable sutures, and the skin pocket was closed laterally to reduce the dead space within the cavity.

A prospective database was used to record patient demographics, operative details such as flap weight, ischaemia time, the number and location of perforators, followed by post-operative adjuvant treatment, complications and outcomes. All patients with a delayed reconstruction, previous history of radiotherapy and all muscle-sparing transverse rectus abdominis flaps were excluded from the cohort. Three of the authors were responsible for the review of charts and data extraction. Each patient's hospital and outpatient records were independently reviewed by two out of three authors (cross-covered), and each reviewed approximately 75 charts in order to minimise data extraction errors.

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Those included were divided into two groups, requiring PMRT (A) or not requiring it (B). Patients were reviewed at 6 weeks post-operatively and subsequently at regular intervals. The minimum follow-up was 12 months following the completion of PMRT. Primary outcome measures consisted of fat necrosis, surgery for the removal of fat necrosis, volume loss requiring surgery, wound complications and flap loss. All patients were evaluated for the presence of clinically relevant fat necrosis, and subsequently an ultrasound scan was performed for confirmation. Fat necrosis was defined as any palpable mass/nodule >1 cm, which had been present for >6 weeks following reconstruction. We used the classification system suggested by Caterson et al. to categorise the grade of fat necrosis.[36] Revision surgery was defined as the direct removal of fat necrosis and adjusting the reconstructed breast mound. Surgery for volume loss entailed lipomodelling the flap for the improvement of any contour deficiency. Minor delayed wound healing was defined as any wound requiring dressing change input, and major wound healing entailed debridement or healing by secondary intention.

Statistical analysis

Statistical analysis was undertaken using the Fisher's exact chi-squared test to determine whether there was any significant effect of post-operative radiotherapy on fat necrosis or any of the other outcome-related parameters from the operation to the final follow-up. We compared patient demographics between patients with irradiated and non-irradiated flaps using the *t*-test for continuous variables and chi-squared test for categorical variables. Statistical significance was set at $P < 0.05$. Continuous variables were tested for the normality of distribution using the Kolmogorov–Smirnov test. We used the multivariate logistic regression analysis to account for significant predictors of fat necrosis. The STEPWISE method of logistic regression was used to select the explanatory variables with significant effect. Data analysis was performed using the IBM Statistical Package for Social Science (SPSS) Statistics 17.0. There were no variables in the data set with missing values.

Institutional radiotherapy protocol

PMRT was offered to patients who were at a higher risk of local recurrence, that is, two or more of the following: Grade 3 tumours, >5 cm, >4 positive nodes, vascular invasion, oestrogen/progesterone (ER/PR)-negative status, human epidermal growth factor (HER 2)-positive status and at a young age of <40 years. Following neo-adjuvant chemotherapy, PMRT was also offered to women whose original tumours met the above criteria in addition to the presence of residual tumour or positive axillary nodes.

PMRT was administered using medial and lateral tangential fields with the addition of a field to the supraclavicular fossa (SCF) nodes if indicated. Every patient's treatment plan was delineated using a radiotherapy-planning CT scan, and in unilateral reconstructions, the contralateral breast was used as guidance for the coverage of the target volume of the original breast. Forward-planned intensity-modulated radiotherapy (IMRT) fields were used to achieve an even dose throughout the treatment field. This ensured that no area of the reconstruction received more or less than 95–105% of the 100% prescription dose, and standard linear accelerators delivered 6- or 10-MV (megavoltage) beams. Following the results of the START trial, most patients were treated with 40 Gy in 15 fractions administered daily over 3 weeks.[37] According to clinician preference, a few patients, mainly those with heavily positive nodal status, received 50 Gy in 25 fractions delivered over 5 weeks. In case of clinical concern regarding cutaneous involvement, a few patients received a bolus (a 1-cm tissue – equivalent covering), which was applied to the chest-wall fields in order to achieve a 100% dose delivery to the skin. However, without a bolus, megavoltage radiotherapy 'spares' the skin, as the dose delivered is of the order of 90%; hence, it is perceived to be beneficial in reducing skin reactions to radiotherapy.[38]

Treatment was planned to commence within 4 weeks of mastectomy and immediate reconstruction, or 4 weeks following the completion of adjuvant chemotherapy.

Results

Over the 24-month period, 156 DIEP flaps (44 bilateral and 68 unilateral) performed in 112 patients with a mean age of 47.3 years (range 31–69) were included in the study (although more cases were carried out). PMRT was administered in 61/156 flaps (group A, 39.1%), whereas 95/156 flaps (group B, 60.9%) did not receive PMRT. Patient characteristics were similar in both groups, and there was no significant difference in their co-morbid conditions and demographics other than a higher prevalence of neo-adjuvant and adjuvant chemotherapy amongst those in group A (Student's *t*-test and Fisher's exact test) (Table 1). Group B consisted mostly of patients undergoing risk-reducing surgery in addition to those with lower risk tumours not requiring chemotherapy. Neo-adjuvant chemotherapy had been administered in 14/61 (22.9%) of the flaps in group A, and 6/95 (6.3%) of the non-irradiated flaps in

Table 1 Patient characteristics and demographics in group A (PMRT) and group B (no PMRT). * A higher prevalence of neo-adjuvant and adjuvant chemotherapy was noted in group A. *PMRT: post-mastectomy radiotherapy.*

	Total	A (PMRT)	B (No PMRT)	*P*-value
No. of flaps	156	61	95	
No of patients	112	50	62	
Bilateral	44	11	33	
Unilateral	68	39	29	
Mean age (years)	47.3	47.5	47.1	0.79
Mean BMI kg/m^2	29.9	29.4	30.2	0.35
Active smoking	9	4	5	0.645
Neo-adjuvant chemotherapy	20	14	6	0.012*
Adjuvant chemotherapy	26	17	9	0.014*
Mean follow-up (months)	33	33.3	32.9	0.888

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group B. Neo-adjuvant chemotherapy had no significant effect on the prevalence of fat necrosis, $p = 0.397$ (Fisher's exact test), or other complications. The technical characteristics of the reconstructions were also similar between the irradiated and non-irradiated groups with no statistically significant difference in the number of perforators, flap weight and ischaemia time (Table 2). To precisely demonstrate the effect of PMRT on DIEP reconstruction, we included a subset analysis of recipient-site characteristics (bilateral/unilateral reconstruction, flap weight, ischaemia time, number of perforators, side of breast reconstruction, body mass index (BMI), age, neo-adjuvant/adjuvant chemotherapy, radiotherapy, co-morbidities, diabetes and smoking). Subset binary logistic regression analysis was performed to determine the risk factors for complications while controlling for confounding factors, although the group of patients that developed complications was relatively small, which may have had an effect on the accuracy of the results. Multivariate logistic regression analysis demonstrated that older age was the only significant independent predictor of a higher complication rate (odds ratio (OR): 1.142; $p = 0.033$).

The mean follow-up was 33 months (range 12–62), and it was similar in the two groups: A = 33.3, B = 32.9 months, respectively, $p = 0.888$ (Student's *t*-test).

The overall prevalence of flap loss in the series was 1.28% (2/156), whereby 0/61 flaps were lost in group A, compared with 2/95 in group B. The latter involved a patient with bilateral DIEP reconstructions who lost both flaps due to unexplained intraoperative clotting at the site of arterial anastomosis; she was subsequently referred to the haematologists for further investigation. Radiotherapy had no statistically significant effect on the prevalence of flap loss when comparing the two groups: A = 0%, B = 2.1%, $p = 0.521$ (Fisher's exact test) (Table 3).

Fat necrosis

Thirteen patients presented with clinically relevant fat necrosis (7/61 of the irradiated and 6/95 of the non-irradiated DIEP flaps). Radiotherapy had no statistically significant effect on the prevalence of post-operative fat necrosis when comparing the two groups: A = 11.5%, B = 6.35%, $p = 0.199$ (Fisher's exact test).

Of the 61 irradiated flaps in group A, three (4.9%) were found to have minor, three (4.9%) had moderate and one (1.6%) was noted to have major fat necrosis. Within the group with no PMRT, four (4.2%) had minor fat necrosis, one (1%) moderate and one (1%) was classified as major. Radiotherapy had no statistically significant effect on the severity of fat necrosis, $p = 0.499$ (Pearson's chi-squared test). The prevalence of fat necrosis amongst bilateral flaps was 1/11 (9%) in group A versus 2/33 (6%) in group B. Unilateral flaps in group A experienced a 6/39 (15.4%) fat necrosis rate compared with 2/29 (6.8%) in group B.

Table 2 Flap characteristics in groups A (PMRT) and B (no PMRT) including the number of perforators, flap weight *(grams)* and ischaemia time *(minutes)*. *PMRT: post-mastectomy radiotherapy.*

	A (PMRT)	B (NO PMRT)	*p*-value
Median no. of perforators	1	1	0.598
Range	(1–2)	(1–3)	
Mean flap weight (g)	672.8	682.2	0.789
Range	(336–1447)	(320–1390)	
Mean ischaemia time (min)	85.8	85.3	0.888
Range	30–182	35–178	

Table 3 Complications in groups A (PMRT) and B (no PMRT) including fat necrosis, surgery for the removal of fat necrosis and volume enhancement, and wound complications (minor and major). *PMRT: post-mastectomy radiotherapy.*

	A (PMRT)	B (NO PMRT)	*p*-value
Fat necrosis (%)	11.5	6.35	0.199
Surgery for the removal of fatnecrosis (%)	6.6	4.2	0.383
Surgery for volume enhancement (%)	4.9	5.2	0.617
Minor wound complications (%)	3.2	7	0.433
Major wound complications (%)	2.5	5.7	0.558
Flap loss (%)	0	2.1	0.521

Surgery for the removal of fat necrosis

We found no statistically significant correlation between post-operative radiotherapy and surgery for the removal of fat necrosis: A = 6.6% versus B = 4.2%, $p = 0.383$, (Fisher's exact chi-squared test).

Volume enhancement surgery

Subsequent surgery (i.e., lipomodelling) to enhance volume loss associated with fat necrosis was required in 4.9% of the irradiated flaps versus 5.2% of the non-irradiated group. Radiotherapy did not affect the number of volume enhancement procedures following free DIEP flap reconstruction, $p = 0.617$ (Fisher's exact chi-squared test).

Wound-healing complications

Radiotherapy had no statistically significant effect on post-operative wound healing involving the reconstructed breast. Minor wound-healing delay was seen in 3.2% of the PMRT group versus 7% of the group with no PMRT, $p = 0.433$, whereas major wound-healing delay was noted in 2.5% versus 5.7% in groups A and B, respectively, $p = 0.558$ (Fisher's exact chi-squared test).

Subset binary logistic regression analysis was performed to determine the risk factors for major wound-healing complication while controlling for confounding factors. Subset analysis of recipient-site characteristics in multivariate logistic regression analysis demonstrated that older age and bilateral flap reconstruction were significant

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independent predictors of the development of major wound-healing complications. Specifically, a 1-year change in age increases the odds of developing major wound-healing complications by a factor of 1.2 (OR: 1.197; $p = 0.038$). Bilateral flap reconstructions were almost 14 times more likely to develop major wound-healing complications than unilateral (OR: 13.65; $p = 0.04$). However, as this model seems to be accountable for 23% of the variance in the major complication occurrence, it suggests that there are many other factors that contribute to the possibility of developing major wound-healing complications.

Discussion

Radiation therapy is thought to cause fibrosis within the stroma of fat tissue, resulting in potential cell death and fat necrosis, although the precise mechanism behind this phenomenon is poorly understood.[39,40] Many reports in the literature allude to the increased complications and poor cosmetic outcome following the administration of radiotherapy to the reconstructed breast.[41] Radiotherapy combined with implant-based reconstruction is known to result in poor patient satisfaction and high complication as well as revision rates.[42] Historically, there have been reports of the negative effects of radiation on autologous reconstruction, noting DIEP flaps to be susceptible to fat necrosis after radiation.[39] Garvey et al. in their 10-year institutional review of 625 free abdominal flap breast reconstructions found both DIEP and muscle-sparing free TRAM flaps to have much higher rates of fat necrosis when irradiated. The authors found that IBR with a muscle-sparing free TRAM flap resulted in a similar rate of fat necrosis to a DIEP flap.[40]

A recent systematic review of the literature with 5059 DIEP flaps found a fat necrosis rate of 8.7% among patients with no history of irradiation, which was significantly lower than in patients who underwent pre-reconstruction (11%, $p = 0.022$) and post-reconstruction irradiation (22.3%, $p < 0.001$).[43]

However, a notable observation in existing literature is the division of opinion regarding the deleterious effects of radiation therapy on the outcome of free-flap breast reconstruction, and hence the differing preference in the timing of surgery in relation to PMRT.

Another systematic review by Schaverien has found that the majority of published studies between 1996 and 2013 reported satisfactory outcomes for immediate autologous breast reconstruction with adjuvant radiotherapy; their pooled data analysis demonstrated a similar prevalence of complications in this group when compared with immediate reconstruction without radiotherapy, or delayed reconstruction following radiotherapy.[13]

Different outcomes have been reported regarding the best timing of radiotherapy. Although some support waiting a year or longer after PMRT, there is a trend towards earlier autologous breast reconstruction. Since Kronowitz's earlier description of the use of the delayed–immediate approach in breast reconstruction, the author has undertaken a thorough review of the literature reporting acceptable rates of complications and remarkable cosmetic outcomes with immediate autologous breast reconstruction.[29,44] This is the case in our institution where immediate autologous reconstruction is routinely performed in patients irrespective of their requirement for PMRT. This study demonstrates a successful outcome of immediate DIEP breast reconstruction in combination with PMRT, demonstrating no statistically significant difference in the incidence of fat necrosis, surgery for the removal of fat necrosis, the need for volume enhancement and wound complications.

In our experience, we found a well-planned and well-vascularised DIEP flap to be tolerant of both early and later effects of radiation therapy. Preoperative CT angiography allowed carefully planning of ideal perforators, whereas intra-operatively only well-perfused tissue within the flap was preserved. The close working relationship between the plastic surgery and clinical oncology department has been of paramount importance in planning the radiotherapy regime for our patients.

The strength of this study was its prospective nature as well as the uniform cohort of patients over the 2-year period. Larger numbers and a longer period of follow-up would add strength to our results. The mean follow-up was 33 months, and it was comparable in both radiated and irradiated flaps. During this period, clinical observation did not reveal an increased incidence of fat necrosis, the need for volume-enhancing surgery or the removal of fat necrosis amongst irradiated DIEP reconstructions. It could be argued that the negative effects of radiotherapy continue to evolve with time, and potential skin-envelope shrinkage due to fibrosis is a late sequela of radiotherapy. For this reason, we plan to review our outcomes at a 5-year post-operative time point. The authors recognise the absence of patient-related outcome measures (PROMS) and the Breast Questionnaire (BREAST-Q) to be a limitation of this study. This will be included in our subsequent long-term review of the same cohort. Although all patients underwent preoperative as well as serial post-operative photography, we did not perform a formal evaluation of the aesthetic outcome of irradiated versus non-irradiated DIEP flaps, and this would once again be addressed in the long-term follow-up.

We are aware of the fact that immediate autologous breast reconstruction combined with the preservation of the skin envelope through a skin-sparing mastectomy provides the optimum shape, and it has numerous advantages over delayed or delayed–immediate reconstruction (Figures 1 and 2). It is associated with higher patient satisfaction and quality of life, and it removes the psychosocial morbidity associated with a mastectomy in those patients who have to await a delayed reconstruction.[45] Equally, it is superior to the delayed–immediate technique in which patients have to experience the often-uncomfortable tissue expander for several months after radiotherapy prior to definitive autologous reconstruction.

Conclusion

Despite series reporting the deleterious effects of radiotherapy in free flaps (late complications as high as 87%), we found no statistically significant relationship between PMRT and increased early or late complications in DIEP flaps. Our department offers IBR with the acceptance of the risk/benefit profile. We did not feel that post-mastectomy radiotherapy precludes the decision for immediate free-

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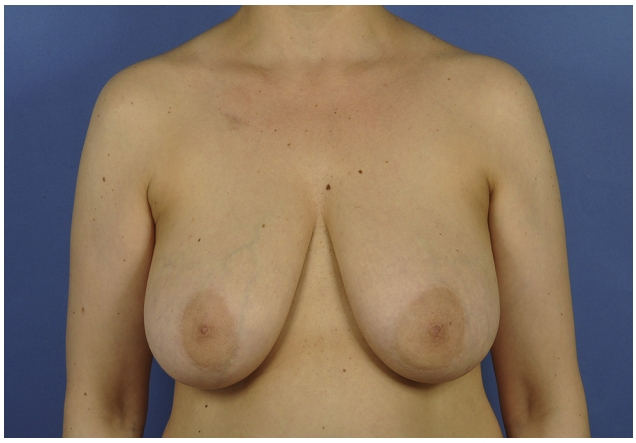

Figure 1 Preoperative view of a patient undergoing a left skin-sparing mastectomy and immediate breast reconstruction with DIEP flap. *DIEP: deep inferior epigastric artery perforator flap*.

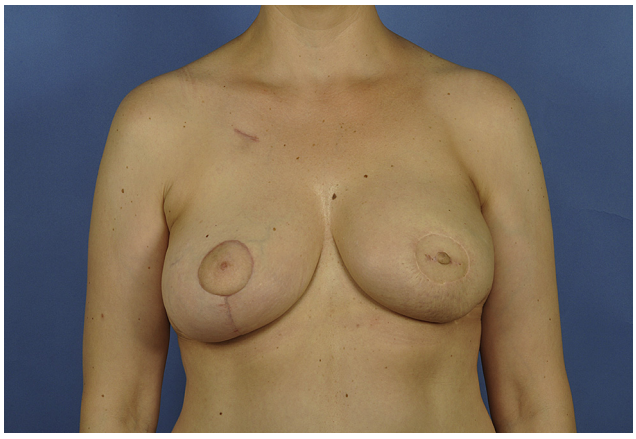

Figure 2 Post-operative result of the same patient 20 months following a left immediate DIEP reconstruction with post-mastectomy radiotherapy, left nipple reconstruction and a right symmetrising reduction.

flap breast reconstruction; however, an evaluation of further long-term results is required.

Conflicts of interest

None.

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None.

References

1. Recht A, Edge SB. Evidence-based indications for post-mastectomy radiation. *Surg Clin North Am* 2003;**83**:995—1013.
2. Recht A, Edge SB, Solin LJ, et al. Post-mastectomy radiotherapy: clinical practice guidelines of the American society of clinical oncology. *J Clin Oncol* 2001;**19**:1539—69.
3. Ragaz J, Olivotto IA, Spinelli JJ, 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**:116—26.
4. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Med* 1997;**337**:949—55.
5. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15 year survival: an overview of the randomized trials. *Lancet* 2005;**366**:2087—106.
6. Benson JR, Jatoi I, keeisch M, et al. Early breast cancer. *Lancet* 2009;**373**:1463—79.
7. Taylor ME, Haffty BG, Rabinovich R. ACR appropriateness criteria on post-mastectomy radiotherapy expert panel on radiation oncology-breast. *Int J Radiat Oncol* 2009;**73**:997—1002.
8. Harris J, Halpin-Murphy P, McNeese M, et al. Consensus statement on post-mastectomy radiation therapy. *Int J Radioat Oncol Biol Phys* 1999;**44**:989—90.
9. Truong PT, Olivotto IA, Kader HA, et al. Selecting breast cancer patients with T1-2 tumours and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;**61**:1337—47.
10. Woodward W, Strom EA, Buchholz TA, et al. Locoregional recurrence patterns after doxorubicin-based chemotherapy and postmastectomy radiation: implications for patients with early stage disease and predictors for recurrence after radiation. *Int J Radiat Oncol Biol Phys* 2003;**57**:336—44.
11. Katz A, Strom EA, Buchholz TA, et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postopera- tive irradiation. *J Clin Oncol* 2000;**18**:2817—27.
12. Sieber DA, Vandevender DK, Albuquerque KV. Intermeshing breast recon- struction and postmastectomy radiation. *Expert Rev Anticancer Ther* 2010;**10**:1273—83.
13. Schaverien MV, Macmillan DR, McCulley SJ. Is immediate autologous breast reconstruction with postoperative radiotherapy good practice?: a systematic review of the literature. *J Plast Reconst Aesth Surg* 2013;**66**:1637—51.
14. Rodman JS. Skin removal in radical breast amputation. *Ann Surg* 1943;**118**:694—7.
15. Champaneria MC, Wong WW, Hill ME, Gupta SC. The evolution of breast reconstruction: a historical perspective. *World J Surg* 2012;**36**:730—42.
16. Atisha D, Alderman AK, Lowrey JC, Davis J, Kuhn LE, Wilkins EG. prospective analysis of long-term psychological outcomes in breast reconstruction: two-year postoperative results from the Michigan breast reconstruction outcomes study. *Ann Surg* 2008;**247**:1019—28.
17. Fitzal F, Gnant M. breast conservation: evolution of surgical strategies. *Breast J* 2006;**12**:165—73.
18. Cordeiro PG. Breast reconstruction after surgery for breast cancer. *N Engl J Med* 2008;**359**:1590—601.
19. Veronesi P, Ballardini B, De Lorenzi F, et al. Immediate breast reconstruction after mastectomy. *Breast* 2011;**20**:104—7.
20. Kronowitz SJ. Immediate vs delayed reconstruction. *Clin Plas Surg* 2007;**34**:39—50.
21. Drucker-Zertuche M, Robles-Vidal CA. 7-year experience with immediate breast reconstruction after skin sparing mastectomy for cancer. *Eur J Surg Oncol* 2007;**33**:140—6.
22. Sandelin K, Wickmanb M, Billgren AM. Oncological outcome after immediate breast reconstruction for invasive breast cancer: a long-term study. *Breast* 2004;**13**:210—8.
23. Lanitis S, Tekkis PP, Sgourakis G, Dimopoulos N, Al Mufti R, Hadjiminas DJ. Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: a meta-analysis of observational studies. *Ann Surg* 2010;**251**:632—9.

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24. Bezuhly M, Temple C, Sigurdson LJ, Davis RB, Flowerdew G, Cook Jr EF. Immediate postmastectomy reconstruction is associated with improved breast cancer-specific survival: evidence and new challenges from the surveillance, epidemiology, and end results database. *Cancer* 2009;**115**(20): 4648—54. 15.
25. Shen J, Ellenhorn J, Qian D, Kulber D, Aronowitz J. Skin-sparing mastectomy: a survey based approach to defining standard of care. *Am Surg* 2008;**74**:902—5.
26. Lee KC, Kim TH, Park SS, et al. Reliability of reconstructed breast flap after chemotherapy and radiotherapy in immediate breast reconstruction. *Arch Plast Surg* 2012;**39**(5):497—503.
27. Mirzabeigi MN, Smartt JM, Nelson JA, Fosnot J, Serletti JM, Wu LC. An assessment of the risks and benefits of immediate autologous breast reconstruction in patients undergoing postmastectomy radiation therapy. *Ann Plast Surg* 2013;**71**: 149—55.
28. Kronowitz SJ, Robb GL. Radiation therapy and breast reconstruction: a critical review of the literature. *Plast Reconstr Surg* 2009;**124**:395—408.
29. Kronowitz SJ. Current status of autologous tissue-based breast reconstruction in patients receiving postmastectomy radiation therapy. *Plast Reconstr Surg* 2012;**130**:282—92.
30. Cinsera CA, Chang EI, Da Lio AL, Festekjian JH, Mehrara BJ. Immediate free flap reconstruction for advanced-stage breast cancer: is it safe? *Plast Reconstr Surg* 2011;**128**:32—41.
31. Albino FP, Kolz PF, Ling MN, Langstein HN. Irradiated autologous breast reconstructions: effects of patient factors and treatment variables. *Plast Reconstruc Surg* 2010;**126**:12—6.
32. Chatterjee JS, Lee A, Anderson W, et al. Effect of postoperative radiotherapy on autologous deep inferior epigastric perforator flap volume after immediate breast reconstruction. *Br J Surg* 2009;**96**:1135—40.
33. Andree C. A single center prospective study of bilateral breast reconstruction with free abdominal flaps: a critical analyses of 144 patients. *Med Sci Monit* 2013;**19**:467—74.
34. Langer S, Munder B, Seidenstuecker K, et al. Development of a surgical algo- rithm and optimized management of complications — based on a review of 706 abdominal free flaps for breast reconstruction. *Med Sci Monit* 2010;**16**(11):518—22.
35. Lee KT, Lee JE, Nam SJ, Mun GH. Ischaemic time and fat necrosis in breast reconstruction with a free deep inferior epigastric perforator flap. *J Plast Reconstr Aesth Surg* 2013;**66**: 174—81.
36. Caterson SA, Tobias AM, Sumner A, Slavin SA, Lee BT. Fat necrosis after autologous breast reconstruction: a classification system and treatment algorithm. In: *American association of plastic surgeons 86th annual meeting*; 2007 [Idaho, United States].
37. Haviland JS, Owen JR, Dewar JA, et al. The UK standardisation of breast radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up of two randomised controlled trials. *Lancet Oncol* 2013;**14**:1086—94.
38. Ha B, Suh HS, Lee J, Lee KJ, Moon BI. Long-term results of forward intensity-modulated radiation therapy for patients with early-stage breast cancer. *Radiat Oncol J* 2013;**31**:191—8.
39. Rogers N, Allen R. Radiation effects on breast reconstruction with the deep inferior epigastric perforator flap. *Plast Reconstr Surg* 2002;**109**:1919—24.
40. Garvey PB, Clemens MW, Hoy AE, et al. Muscle-sparing TRAM flap does not protect breast reconstruction from postmastectomy radiation damage compared with the DIEP flap. *Plast Recon Surg Plast Reconstr Surg* 2014;**133**:223.
41. Clarke-Pearson EM, Chadha M, Dayan E, et al. Comparison of irradiated versus non irradiated DIEP flaps in patients undergoing immediate bilateral DIEP reconstruction with unilateral postmastectomy radiation therapy (PMRT). *Ann Plast Surg* 2013 Sep;**71**(3):250—4.
42. Cordeiro P, Pusic A, Disa J, et al. Irradiation after immediate tissue expander/implant breast reconstruction: outcomes, complications, aesthetic results, and satisfaction among 156 patients. *Plast Reconstr Surg* 2004;**113**:877—81.
43. Khansa I, Momoh AO, Patel PP, Nguyen JT, Miller MJ, Lee BT. Fat necrosis in autologous abdomen-based breast reconstruction: a systematic review. *Plast Recon Surg* 2013;**131**:443—52.
44. Kronowitz SJ, Hunt KK, Kuerer H, et al. Delayed-immediate breast reconstruction. *Plast Reconstr Surg* 2004;**113**:1617—28.
45. Heneghan RS, Prichard R, Lyons PJ, Regan PJ, Kelly JL, Malone C. Quality of life after immediate breast reconstruction and skin-sparing mastectomy- A comparison with patients undergoing breast conserving surgery. *Eur Journ Surg Oncol* 2011; **37**:937—43.

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