The Impact of Breast Reconstruction on the Oncologic Efficacy of Radiation Therapy

A Retrospective Analysis

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Abstract: Current indications for radiation therapy in women with breast cancer are controversial and continue to be modified. Current indications for breast reconstruction in the setting of radiation therapy are also controversial and poorly defined. The purpose of this study is to analyze oncologic outcomes following various methods of breast reconstruction in the setting of radiation therapy. A retrospective review of 676 women who had breast reconstruction following mastectomy was completed. A total of 146 women had breast reconstruction either before or after radiation therapy and were analyzed. Response variables included tumor recurrence and patient demise for patients having autologous and prosthetic reconstruction. Explanatory variables included patient age, cancer stage, radiation therapy, diabetes mellitus, and tobacco use. Recurrence of tumor occurred in 29 of 146 women (19.8%), of which 27% was when radiation followed reconstruction and 14.9% was when radiation preceded reconstruction. Patient demise occurred in 8.9%, of which 11.9% was when radiation followed reconstruction and 6.9% was when radiation preceded reconstruction. The difference in tumor recurrence in the setting of radiation therapy before or after breast reconstruction was significant for autologous ($P = 0.0146$) and prosthetic ($P = 0.0424$) reconstruction. The difference in patient demise was significant for autologous reconstruction ($P = 0.0380$) but not for prosthetic reconstruction ($P = 0.2827$). These results imply that tumor recurrence and patient demise may be increased when radiation therapy is performed following breast reconstruction. The need for a prospective inquiry is validated.

Key Words: breast reconstruction, radiation therapy, tumor recurrence, loss of life

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The benefit of radiation therapy (RT) in the battle against breast cancer is well documented.[1–3] Studies have demonstrated improved locoregional control when RT is combined with breast conservation therapy (BCT) or mastectomy.[4,5] Other studies have demonstrated improved survival with the addition of systemic therapy.[6] Up until the mid-1980s, many oncologists recommended delaying the breast reconstruction (BR) following mastectomy for cancer to adequately assess for tumor recurrence. Over the past 20 years, the safety and efficacy of immediate breast reconstruction (IBR) have been validated based on the fact that local recurrence and survival are not compromised and the ability to monitor for and detect a recurrence is generally maintained.[7–12] It has been also demonstrated that 85% of recurrences following IBR will occur within 2 years.[13]

The combination of RT and BR has generated significant discussion and controversy.[14–17] One of the main points of discussion has been the timing of RT in relation to BR. The principal issues of concern have related to esthetic and oncologic outcomes. There have been several studies that have evaluated esthetic outcome following BR in the setting of RT.[5,18–28] It is generally accepted that the morbidity is usually increased and esthetic outcome is generally decreased in this setting, although these outcomes are influenced by the specific type of reconstruction.[19] Short-term morbidity related to RT and reconstruction using autologous tissue or prosthetic devices includes cutaneous erythema, irritation, and desquamation. The long-term morbidity for the 2 methods of reconstruction is different. When prosthetic devices are used, morbidity includes capsular contracture, infection, pain, skin necrosis, cutaneous fibrosis, and progressive breast asymmetry.[22,23,27,29] When autologous tissues are used, morbidity includes fat necrosis, flap shrinkage, progressive distortion, and breast asymmetry.[5,18,24–26,28] A question that remains to be answered is whether or not the oncologic outcome based on local recurrence and patient survival is impacted based on the timing of RT.

The purpose of this study was to analyze a set of parameters related to the oncologic outcome following BR using autologous tissue alone, implants alone, or a combination of autologous tissue and implants in the setting of RT delivered either before or after BR. It was initially hypothesized that the timing of RT relative to the BR would not impact local recurrence or patient survival.

METHODS

This was a retrospective review of a prospectively maintained database over an 8-year time interval. During this time, a total of 676 women had BR and were analyzed. The total number of reconstructed breasts was 864 that included unilateral and bilateral cases. Of these women, 198 (29.3%) had BR and RT. To have valid data regarding outcome, inclusion for analysis required a minimum follow-up of 12 months; thus 146 women (21.6%) were included. The mean follow-up was 26.9 months and the range was 12 to 68 months.

All reconstructive procedures were performed by the primary author (M.Y.N.) and at a single hospital. The type of mastectomy performed in this series included non–skin-sparing and skin-sparing mastectomies. These decisions were made by the patient and the surgical oncologist. The decision to proceed with IBR was usually based on traditional parameters that included stage 1 and 2 breast cancer. On occasion, women with locally advanced breast cancer were offered IBR for quality-of-life issues. RT was administered at various hospitals and primarily based on patient residence; thus, it was not possible to obtain records from all institutions to determine the nature and dosimetry of the radiotherapy.

The timing and delivery of RT in relation to the mastectomy or BR were assumed to be standardized based upon RT guidelines. Following mastectomy with chemotherapy, without chemotherapy, or immediate reconstruction, the RT was usually initiated in 3–4 weeks. This interval allowed for complete wound healing based on fibroblast proliferation, as well as normalization of cellular and humeral factors following chemotherapy. Women having delayed BR because of locally advanced breast cancer were usually advised to wait at least 1 year following the mastectomy and 6 months following the RT to assess for recurrence. Chemotherapy was administered in 117 of the 146 women (80%) who had RT. The specific chemotherapy regimens were available in 71 (61%) and included Adriamycin, Cytoxan, and Taxol in 72%; Adriamycin and Cytoxan in 21%; and Cytoxan, methotrexate, and fluorouracil in 7%. The delivery of RT to the chest wall or reconstructed breast was assumed to be standardized, which would include tangential beams delivered in fractionated doses over a 3- to 5-week interval. The total dose was usually 40–50 Gy. An electron boost was occasionally necessary to further radiate the tumor bed. The typical radiation markings are illustrated following mastectomy without reconstruction (Fig. 1) and following mastectomy with reconstruction (Fig. 2).

Outcome measures included tumor recurrence, loss of life, loss of implant, and total flap necrosis. Recurrence was further analyzed based on whether the cancer involved the left or right breast. Relevant factors that could impact outcome were also analyzed and included patient age, cancer stage, chemotherapy, and timing of reconstruction. These factors, as well as the stratification of women based on whether the RT was before or after BR, are listed in Table 1.

Defining the various outcomes was considered relevant. Recurrence of tumor was defined as involving the reconstructed breast, chest wall, or regional lymph nodes. Loss of life was secondary to recurrence of breast cancer and metastatic disease in all cases. For those women who had autogenous BR, the type of flap used is listed (Table 2). Implant reconstruction was performed in 2 stages in all women. Loss of implant was defined as removal of the device for reasons that included but were not limited to patient dissatisfaction, capsular contracture, pain, infection, rupture, and distortion. Loss of the implant was not meant to imply mechanical failure of the device. Cancer stage was assessed based on pathologic evaluation of the mastectomy specimens. The subcategory of "recurrence" was created to include women who previously had BCT and developed a recurrence requiring mastectomy. The initial pathologic staging in this group was not always available.

Statistical analysis was performed using exact logistic regression of the Logistic and Genmode procedures of the SAS system. Not all variables were included in the statistical analyses. Only those variables that could potentially impact

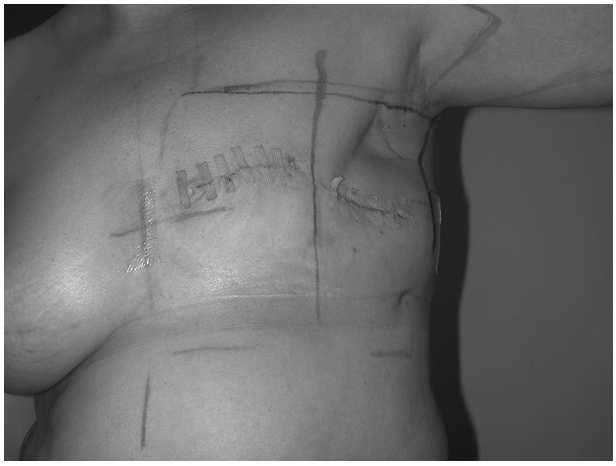

FIGURE 1. The typical chest wall markings for radiation therapy following mastectomy without reconstruction are illustrated.

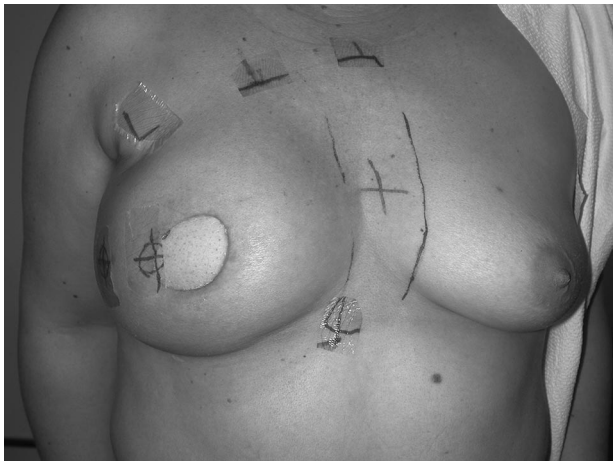

FIGURE 2. The typical markings for radiation therapy following mastectomy and autologous flap reconstruction are illustrated.

TABLE 1. The Various Factors Related to Outcome in Relation to the Timing of Radiation Therapy

Group	Reconstruction	No.	Mean Age	Immediate	Delayed	Chemotherapy
RT before BR	Autologous	57	48	19	38	39
	Implant	27	47	15	12	22
	A + I	3	38	1	2	2
RT after BR	Autologous	37	47	35	2	35
	Implant	20	47	20	0	17
	A + I	2	52	2	0	2
Total		146	47.5	92	54	117

RT, radiation therapy; BR, breast reconstruction, A, autologous; I, implant.

TABLE 2. The Various Autologous Tissue Options That Were Used in the Study

Reconstruction	RT Before BR	RT After BR	Total
Pedicle TRAM	14	2	16
Free TRAM	14	17	31
DIEP	24	17	41
SGAP	1	0	1
Latissimus dorsi	7	3	10
Total	60	39	99

the oncologic outcomes were included. Thus, the response variables included tumor recurrence and patient demise in patients following autologous and prosthetic reconstruction. The explanatory variables included patient age, cancer stage, RT, diabetes mellitus, and tobacco use.

RESULTS

Results were analyzed based on RT after BR and RT before BR (Tables 3 and 4). This included the total number of women for the cohort, as well as the number of women within each reconstructive category. The mean follow-up for each of the 6 subgroups is listed.

Recurrence of Tumor

Recurrence of tumor occurred in 29 of 146 women (19.8%). Of these, 27% was when RT followed BR and 14.9% was when RT preceded BR. The recurrence associated with autologous reconstruction was 38% when RT followed BR and 14% when RT preceded BR ($P = 0.0146$) (Table 5). The recurrence rate associated with implant reconstruction was 10% when RT followed BR and 19% when RT preceded BR ($P = 0.0424$). The recurrence rate associated with reconstruction using a combination of autologous tissue and implants was zero when RT followed and preceded BR. The significance related to the timing of RT was most notable for patients receiving autologous tissue reconstruction. RT delivered after autologous BR increased local recurrence by 4.6-fold compared with RT delivered prior to BR.

Recurrence was also analyzed based on whether the cancer involved the left or right breast. Of the 676 women, there were 393 left-sided breast cancers (58.1%) and 275 right-sided breast cancers (40.7%). Eight women had bilateral prophylactic mastectomy (1.2%). Of the 29 women who developed a recurrence, 18 were left sided (62%) and 11 were right sided (38%). When RT was delivered before BR, there were 7 left-sided and 6 right-sided recurrences. Of these, left-sided recurrence was associated with implant reconstruction in 2 of 5 breasts (40%) and with autologous reconstruction in 5 of 8 breasts (62.5%). When RT followed BR, there were 11 left-sided and 5 right-sided recurrences. Of these, left-sided recurrence was associated with implant reconstruction in 1 of 2 breasts (50%) and with autologous reconstruction in 10 of 14 breasts (71.4%).

Loss of Life

Loss of life occurred in 13 of the 146 women (8.9%). Of these, 11.9% was when RT followed BR and 6.9% was when RT preceded BR. The loss of life associated with autologous reconstruction was 16% when RT followed BR and 7% when RT preceded BR ($P = 0.038$). The loss of life associated with implant reconstruction was 5% when RT followed BR and 7% when RT preceded BR ($P = 0.2827$). The loss of life associated with reconstruction using a combination of autologous tissue and implants was zero when RT followed and preceded BR, albeit, there were only 5 patients in this group. The significance related to the timing of RT was again most notable for patients receiving autologous tissue reconstruction. RT delivered after autologous BR increased patient demise by 7.113-fold compared with RT delivered prior to BR.

Loss of Implant

Removal of the implant was necessary in 23 of 52 women (44%). Of these, 45% were removed when RT followed BR and 43% were removed when RT preceded BR. Removal of the implant associated with reconstruction using implants alone was 45% when RT followed BR and 41% when RT preceded BR. Removal of the implant associated with reconstruction using a combination of autologous tissue and an implant was 50% when RT followed BR and 67% when RT preceded BR.

Flap Failure

Flap failure occurred in 2 of the 99 women (2%). Of these, all occurred when RT preceded microvascular reconstruction (2/57 women, 4%). In both cases of flap failure, the technical aspects of the free tissue transfer were unremarkable; however, postoperative venous obstruction and anastomotic failure was responsible for flap death. There were no flap failures when RT followed BR.

TABLE 3. The Results of Radiation Therapy Following Breast Reconstruction

RT After BR	Number	Recurrence	Loss of Life	Loss of Implant	Flap Failure	Follow-up (mo)
Autologous	37	14 (38%)	6 (16%)	NA	0	29.5
Implant	20	2 (10%)	1 (5%)	9 (45%)	NA	26.5
Autologous + implant	2	0	0	1 (50%)	0	18
All	59	16 (27%)	7 (12%)	10 (45%)	0	28.1

TABLE 4. The Results of Radiation Therapy Preceding Breast Reconstruction

RT Before BR	Number	Recurrence	Loss of Life	Loss of Implant	Flap Failure	Follow-up (mo)
Autologous	57	8 (14%)	4 (7%)	NA	2 (4%)	25.4
Implant	27	5 (19%)	2 (7%)	11 (41%)	NA	28.6
Autologous + implant	3	0	0	2 (67%)	0	17.3
All	87	13 (15%)	6 (7%)	13 (43%)	2 (3%)	26.1

TABLE 5. Statistical Analysis Using Logistic and Genmode Procedures of the SAS System

Factor	Reconstruction	*P* Value	Odds Ratio
Recurrence	Autologous	$P = 0.0146$	5.93
	Implant	$P = 0.0424$	
	Autologous + implant	No significance	
Patient demise	Autologous	$P = 0.038$	7.3
	Implant	No significance	
	Autologous + implant	No significance	

Cancer Stage

Of the 4 parameters, only tumor recurrence and loss of life were relevant to cancer stage. The results are tabulated (Table 6). The total recurrence rate was 19.8% (29/146). In women who had RT after BR, the recurrence rate was 27% (16/59), whereas in women who had RT before BR, the recurrence rate was 15% (13/87). Women with stage 2A breast cancers who had RT before BR were noted to have an increased incidence of recurrence, as well as loss of life (50%, 5/10; 30%, 3/10, respectively). In women who had RT after BR, the recurrence was again increased in women with stage 2A cancer (57%, 4/7), whereas loss of life was most common in women who presented with recurrent disease (25%, 3/12). When analyzing all women, the majority of women having BR and RT had stage 2B cancer (42%, 61/146). Recurrence and loss of life were most common in women with stage 2A cancer (53%, 9/17; 24%, 4/17, respectively). Statistical analysis demonstrated that when controlling for cancer stage, there was no significant association between tumor recurrence and loss of life for both flap and implant reconstruction.

DISCUSSION

The goal of this study was to determine if RT delivered before or after reconstruction made a difference with regard to the oncologic outcome. Based on the results of this retrospective analysis, it appears that RT delivered after BR for all women was associated with a higher local recurrence rate (27% versus 15%) and a higher loss of life (12% versus 7%) when compared with RT delivered before reconstruction. This comparison was statistically significant in the setting of autologous reconstruction and local recurrence ($P = 0.0146$), autologous reconstruction and loss of life ($P = 0.038$), as well as implant reconstruction and local recurrence ($P = 0.0424$). All other outcomes that were analyzed were not statistically or clinically significant. This discussion will focus on possible explanations for these findings.

Prior to analyzing these outcomes, there are several caveats to consider. The first is that this was a retrospective analysis. Our initial hypothesis was that there would be no difference in local recurrence or patient survival based on the timing of RT in relation to the BR. The data presented suggest otherwise, especially in the setting of autologous reconstruction. A prospective analysis would enhance our understanding of this observation. Other caveats are that data regarding specific treatment parameters were not available for some patients due to geographic factors based on patient residence and referral patterns.

It was noteworthy that local recurrence and patient demise occurred with increased frequency when RT was delivered after BR and that they were increased following autologous reconstruction relative to prosthetic reconstruction. Explanations for this observation are complex. Is it because of the mound effect of the reconstructed breast, the altered chest wall anatomy associated with expander/implant reconstruction, or because of alterations in the technique or dosimetry of the radiotherapy? To answer these questions, it is important to appreciate that the effectiveness of RT is based on targeting sites on the chest wall and breast mound that are susceptible to recurrence. This includes the mastectomy skin, pectoralis major muscle, axillary lymph node basin, supraclavicular region, and internal mammary lymph node chain.[3,30,31] The reconstructed breast mound is positioned within these targeted tissues. Following prosthetic reconstruction, the expander or implant is usually placed in the subpectoral position. In this scenario, the chest wall configuration is altered such that the pectoralis major muscle is superficial to the reconstruction. Following autologous reconstruction, the flap is usually placed above the pectoralis

TABLE 6. The Association Between Cancer Stage and Radiation Therapy Delivered Before or After Breast Reconstruction

	RT After BR			RT Before BR			Total		
Stage	**Number**	**Recurrence**	**Loss of Life**	**Number**	**Recurrence**	**Loss of Life**	**Number**	**Recurrence**	**Loss of Life**
0	1	0	0	6	0	0	7	0	0
1	4	0	0	12	0	0	16	0	0
2A	10	5	3	7	4	1	17	9	4
2B	24	4	2	37	3	2	61	7	4
3A	17	5	1	11	2	0	28	7	1
3B	2	1	1	2	1	0	4	2	1
Recurrence	1	1	0	12	3	3	13	4	3
Total	59	16	7	87	13	6	146	29	13

major muscle, leaving the muscle undisturbed and deep to the reconstruction. These configurations have been previously illustrated.[9] The question is whether or not BR and chest wall configuration will affect the efficacy of RT and potentially impact local recurrence and patient survival.

Review of pertinent literature suggests that it is possible but not probable.[31,32] Radiotherapy is directed at the mastectomy site in tangential fields both for the reconstructed and nonreconstructed breast. The advantage is that the radiation beams are maximized at the targeted sites and minimized at the lung and heart. It has been suggested that RT delivered to the reconstructed breast may be compromised because of the steep slope of the breast mound.[14,17,33] It has been demonstrated that breast volume can impact the radiation dose delivered to the breast.[34] Larger breasts have more inhomogeneity with regard to dose and that the greatest inhomogeneity occurs in the lower quadrants. The question that must be considered is whether or not the efficacy of RT delivered to the breast reconstructed with autologous tissue is compromised when compared with the breast reconstructed with prosthetic devices.

Current advancements in radiation oncology have focused on improving delivery systems. Some of these techniques include intensity modulation[35,36] and the use of physical compensators.[37] Intensity modulation involves angling the radiation beams to match the patients' chest contour and minimize the toxicity to normal tissues.[38] Physical compensators are used to equalize dosimetry between right- and left-sided chest wall irradiation to minimize cardiac toxicity. A common approach is to deliver 2 tangential beams directed medially towards the chest wall and internal mammary lymph nodes and directed laterally towards the chest wall. These modifications will theoretically improve the delivery of RT to the targeted tissues.

In a recent manuscript, Buchholz et al[17] have addressed an important question: are the benefits of RT impaired by IBR? Langstein et al[9] have evaluated patterns of recurrence following IBR with prosthetic devices and with autologous tissue and demonstrated that both are safe and effective without adversely affecting oncologic outcome. There were no differences in women who had and did not have adjuvant RT. Hazard has demonstrated that the 5-year local regional control, disease free, and overall survival of women following mastectomy and RT are no different in women who have had IBR (87%, 58%, and 74%) and not had IBR (88%, 57%, and 67%).[39] In a similar study of 25 women, Soong et al[40] have demonstrated a recurrence rate of 8%, with a 5-year local regional control of 89.8% and 5-year survival of 77.9%.

The possibility of dose or technique modulation has been raised as a means to minimize morbidity to the reconstructed breast.[16,32] This phenomenon has been addressed in regard to left- and right-sided chest wall irradiation, but does it also occur in regard to the reconstructed and nonreconstructed chest wall?[32] The morbidity associated with RT and BR has been previously described. In a recent meta-analysis that evaluated the optimal timing of RT in relation to autologous BR, Javaid et al[18] have suggested that RT delivered after BR has deleterious effects on the cosmetic outcome and have cautiously advised delayed reconstruction. Tallet et al[23] have studied the effects of RT on BR with prosthetic devices and demonstrated an overall complication rate of 51%. Further stratification demonstrated a complication rate of 49% and 14% in radiated and nonirradiated patients, respectively, and in 62.5% and 49% when RT was delivered before and after the reconstruction, respectively. Complications included lymphorrhea, hematoma, capsular contracture, pain, infection, necrosis, and implant extrusion. In a study from the M. D. Anderson Cancer Center, Motwani et al[41] have demonstrated that in women who received RT after IBR, the radiation treatment planning was compromised in 52% to minimize the dose delivered to the flap. This was in contrast to a compromised delivery of RT in 7% of unmatched controls that did not have IBR. The delivered dose of radiation to the internal mammary chain was compromised in 23% of women who had flap reconstruction compared with 2% of unmatched controls that did not. In our study, whether the radiation was left or right sided did not make a significant difference, although it was of interest to note that in the group of women who had autologous reconstruction followed by RT, 72% of women had left-sided tumors.

Another observation from this study focused on women who had prior BCT and developed a recurrence requiring a mastectomy and BR. In all women, the recurrence was "in-breast." Studies have demonstrated that the addition of RT following BCT has reduced the generalized regional recurrence rate from 30% to 10%.[42–44] Factors associated with increased local recurrence include patient age less than 50 years, tumor size greater than 3 cm, positive or unknown tumor margins, and extensive intraductal disease.[45,46] Voogd

et al[47] have suggested that early detection of a local recurrence following BCT can improve treatment outcomes. The 10-year overall survival rate in this population was 39%. In our study, it was observed that the likelihood of a second recurrence following failed BCT, mastectomy, and BR was higher when compared with women primary breast cancer regardless of stage (Table 6). Of the 6 women who died when RT was delivered before BR, 50% were women who had recurrence following BCT.

This study also examined esthetic outcomes following BR in the setting of RT comparing implantable prosthetic devices and autologous tissue. It was demonstrated that 43% of prosthetic devices were removed in the setting of RT, whereas the rate of flap failure was 2%. In the setting of implant reconstruction, this was attributed to patient dissatisfaction, capsular contracture, pain, infection, and asymmetry and in the case of flap reconstruction was attributed to failure of the venous anastomosis.

In conclusion, the incidence of tumor recurrence and patient demise appeared to be increased when RT was performed following autologous tissue reconstruction compared with prosthetic reconstruction. Removal of prosthetic devices was necessary in 44% of patients in the setting of RT and did not appear to be influenced by timing of RT relative to reconstruction. Flap failure did not appear to be related to the timing of RT. To validate these conclusions, a prospective analysis should be initiated.

REFERENCES

1. Rutqvist LE, Rose C, Cavallin-Stahl E. A systematic overview of radiation therapy effects in breast cancer. *Acta Oncol*. 2003;42:532–545.
2. Whelan TJ, Julian J, Wright J, et al. Does locoregional radiation therapy improve survival in breast cancer? a meta-analysis. *J Clin Oncol*. 2000;18:1220–1229.
3. Pierce LJ. Treatment guidelines and techniques in delivery of postmastectomy radiotherapy in management of operable breast cancer. *J Natl Cancer Inst Monogr*. 2001;30:117–124.
4. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347:1227–1232.
5. Mehta VK, Goffinet D. Postmastectomy radiation therapy after TRAM flap breast reconstruction. *Breast J*. 2004;10:118–122.
6. Overgaard M, Hansen PS, Overgaard J. Postoperative radiotherapy in high risk premenopausal women with breast cancer who receive adjuvant chemotherapy. *N Engl J Med*. 1997;337:949–955.
7. Feller WF, Holt R, Spear S, et al. Modified radical mastectomy with immediate breast reconstruction. *Am Surg*. 1986;52:129–133.
8. Georgiade G, Georgiade N, McCarty KS, et al. Rationale for immediate reconstruction of the breast following modified radical mastectomy. *Ann Plast Surg*. 1982;8:20–28.
9. Langstein HN, Cheng MH, Singletary SE, et al. Breast cancer recurrence after immediate reconstruction: patterns and significance. *Plast Reconstr Surg*. 2003;111:712–720.
10. Slavin SA, Love SM, Goldwyn RM. Recurrent breast cancer following immediate reconstruction with myocutaneous flaps. *Plast Reconstr Surg*. 1994;93:1191–1204.
11. Howard MA, Polo K, Pusic AL, et al. Breast cancer local recurrence after mastectomy and TRAM flap reconstruction: incidence and treatment options. *Plast Reconstr Surg*. 2006;117:1381–1386.
12. Noone RB, Frazier TB, Noone GC, et al. Recurrence of breast carcinoma following immediate reconstruction: a 13-year review. *Plast Reconstr Surg*. 1994;93:96–106.
13. Sandelin K, Wickman M, Billgren AM. Oncologic outcome after immediate breast reconstruction for invasive breast cancer: a long term study. *Breast*. 2003;13:210–218.
14. Kronowitz SJ, Robb GL. Breast reconstruction with postmastectomy radiation therapy: current issues. *Plast Reconstr Surg*. 2004;114:950–960.
15. Rolles MJ. Radiotherapy in breast reconstruction is mostly safe. *BMJ*. 2005;330:1330.
16. Mathes SJ, McGrath MH, Cordeiro PG, et al. Controversies in breast reconstruction and the surgeon's role. *Contemp Surg*. 2006;62:262–268.
17. Buchholz TA, Strom EA, Perkins GH, et al. Controversies regarding the use of radiation after mastectomy in breast cancer. *Oncologist*. 2002;7:539–546.
18. Javaid M, Song F, Leinster S, et al. Radiation effects on the cosmetic outcomes of immediate and delayed autologous breast reconstruction: an argument about timing. *J Plast Reconstr Aesthet Surg*. 2006;59:16–26.
19. Chawla AK, Kachnic LA, Taghian AG, et al. Radiotherapy and breast reconstruction: complications and cosmesis with TRAM versus tissue expander/implant. *Int J Radiat Oncol Biol Phys*. 2002;54:520–526.
20. Anderson PR, Hanlon AL, McNeeley SW, et al. Low complication rates are achievable after postmastectomy breast reconstruction and radiation therapy. *Int J Radiat Oncol Biol Phys*. 2004;59:1080–1087.
21. Hussein M, Salah B, Malyon A, et al. The effect of radiotherapy on the use of immediate breast reconstruction. *Eur J Surg Oncol*. 2004;30:490–494.
22. Contant CME, van Geel AN, van der Holt B, et al. Morbidity of immediate breast reconstruction after mastectomy by subpectorally placed silicone prosthesis: the adverse effect of radiotherapy. *Eur J Surg Oncol*. 2000;26:344–350.
23. Tallet AV, Salem N, Moutardier V, et al. Radiotherapy and immediate two-stage breast reconstruction with a tissue expander and implant: complications and esthetic results. *Int J Radiat Oncol Biol Phys*. 2003;57:136–142.
24. Rogers NE, Allen RJ. Radiation effects on breast reconstruction with the deep inferior epigastric perforator flap. *Plast Reconstr Surg*. 2002;109:1919–1924.
25. Tran NV, Evans GRD, Kroll SS, et al. Postoperative adjuvant irradiation: effects on transverse rectus abdominis myocutaneous flaps. *Plast Reconstr Surg*. 2000;106:313–317.
26. Tran NV, Chang DW, Gupta A, et al. Comparison of immediate and delayed free TRAM flap breast reconstruction in patients receiving post mastectomy radiation therapy. *Plast Reconstr Surg*. 2001;108:78–82.
27. Ascherman JA, Hanasono MM, Newman MI, et al. Implant reconstruction in breast cancer patients treated with radiation therapy. *Plast Reconstr Surg*. 2006;117:359–365.
28. Spear SL, Ducic I, Low M, et al. The effect of radiation on pedicled TRAM flap breast reconstruction: outcomes and implications. *Plast Reconstr Surg*. 2005;115:84–95.
29. Nahabedian MY, Tsangaris T, Momen B, et al. Infectious complications following breast reconstruction with expanders and implants. *Plast Reconstr Surg*. 2003;112:467–476.
30. Violet JA, Harmer C. Breast cancer: improving outcomes following adjuvant radiotherapy. *Br J Radiol*. 2004;77:811–820.
31. Senkus-Konefka E, Welmika-Jaskiewicz M, Jaskiewicz J, et al. Radiotherapy for breast cancer in patients undergoing breast reconstruction or augmentation. *Cancer Treat Rev*. 2004;30:671–682.
32. Shankar RA, Nibhanupudy JR, Sridhar R, et al. Immediate breast reconstruction: impact on radiation management. *J Natl Med Assoc*. 2003;95:286–295.
33. Schechter NR, Strom EA, Perkins GH, et al. Immediate breast reconstruction can impact postmastectomy radiation. *Am J Clin Oncol*. 2005;28:485–494.
34. Buchholz TA, Gurgoze E, Bice WS, et al. Dosimetric analysis of intact breast irradiation in off-axis planes. *Int J Radiat Oncol Biol Phys*. 1997;39:261–267.
35. Kestin LL, Sharpe MB, Frazier RC, et al. Intensity modulation to improve dose uniformity with tangential breast radiotherapy: initial clinical experience. *Int J Radiat Oncol Biol Phys*. 2000;48:1559–1568.
36. Donovan EM, Bleackley NJ, Evans PM, et al. Dose position and dose-volume histogram analysis of standard wedged and intensity modulated treatments in breast radiotherapy. *Br J Radiol*. 2002;75:967–973.
37. Wilks RJ, Camack T, Bliss P. Improvements in dose homogeneity for tangential fields from a selection of combinations of library compensators. *Br J Radiol*. 2006;79:165–166.
38. Hurkmans CW, Cho BC, Damen E, et al. Reduction of lung and cardiac

complication probabilities after breast irradiation using conformal radiotherapy with and without intensity modulation. *Radiother Oncol*. 2002; 62:163–171.
39. Hazard L, Miercort C, Gaffney D, et al. Local-regional radiation therapy after breast reconstruction: what is the appropriate target volume? *Am J Clin Oncol*. 2004;27:555–564.
40. Soong IS, Yau TK, Ho CM, et al. Postmastectomy radiotherapy after immediate breast reconstruction in primary treatment of breast cancers. *Clin Oncol*. 2004;16:283–289.
41. Motwani SB, Strom EA, Schechter NR, et al. The impact of immediate breast reconstruction on the technical delivery of postmastectomy radiotherapy. *Int J Radiat Oncol Biol Phys*. 2006;66:76–82.
42. Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med*. 2001;345:1378–1387.
43. Bartelink H. Radiotherapy to the conserved breast, chest wall, and regional nodes: is there a standard? *Breast*. 2003;12:475–582.
44. Fisher B, Anderson S, Redmond CK, et al. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med*. 1995;333:1456–1461.
45. Cefaro GA, Genovisi D, Marchese R, et al. Predictors of local recurrence after conservative surgery and whole breast irradiation. *Breast Cancer Res Treat*. 2006;98:329–335.
46. Vicini FA, Eberlein TJ, Connolly JL, et al. The optimal extent of resection for patients with stage I or II breast cancer treated with conservation surgery and radiotherapy. *Ann Surg*. 1991;214:200–204.
47. Voogd AC, van Oost FJ, Rutgers EJT, et al. Long-term prognosis of patients with local recurrence after conservation surgery and radiotherapy for early breast cancer. *Eur J Cancer*. 2005;41:2637–2644.