Increase of Fat Necrosis after Radiation Therapy Following Mastectomy and Immediate TRAM Flap Reconstruction in High-risk Breast Cancer Patients

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Purpose: This study evaluated the benefit of radiation therapy in high-risk breast cancer patients who have received immediate transverse rectus abdominis myocutaneous (TRAM) flap reconstruction. The evaluation involved examining the effect of radiation therapy on postmastectomy flap fat necrosis and tumor recurrence.

Methods: A retrospective review was performed on 102 patients who underwent mastectomy and immediate TRAM flap reconstruction between 1996 and 2001 at the Asan Medical Center (Seoul, Korea). The mean patient age was 41 years, and the median follow-up time was 33 months. Skin-sparing mastectomy was con ducted in 82 patients (80.4%) and classical mastectomy in 20 patients (19.6%). Of the 21 high-risk patients needing postmastectomy radiation therapy, nine received it.

Results: Moderate or severe TRAM flap fat necrosis occurred more frequently in patients receiving radiation therapy than those not receiving radiation therapy (55.6% vs. 19.4%, P=0.026). In the group with high-risk patients, two tumor recurrences occurred (one-locoregional and one- systemic). Among the 102 patients, thirteen had recurrences, including only two high-risk patients, with almost of them being systemic recurrences except four locoregional recurrences.

Conclusion: Our findings showed that radiation therapy increased flap fat necrosis in high-risk patients underwent immediate TRAM flap reconstruction. Such necrosis can result in poor outcomes for reconstruction. We recommend careful consideration prior to using radiation therapy on high-risk breast cancer patients after immediate TRAM flap reconstruction, where clinicians need to balance the possible positive effects on recurrence with the possible negative effects on flap tissue. **(Journal of Korean Breast Cancer Society 2004;7:17-21)**

Key Words: Breast cancer, Skin-sparing mastectomy, Immediate TRAM flap reconstruction, Radiation therapy, Fat necrosis.

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INTRODUCTION

Recently, skin-sparing mastectomy including immediate reconstruction with autogenous flaps is becoming more widely used in the treatment of breast cancer. This surgery does not appear to affect diagnosis of locoregional tumor recurrence or interfere with subsequent disease treatment.(*1*,*2*) In most cases, skin-sparing mastectomy with immediate reconstruction yields better cosmetic results than delayed breast reconstruction.(*3*)

Three recent, large, randomized trials and a meta-analysis of postmastectomy radiation therapy in high-risk patients receiving adjuvant chemotherapy demonstrated overall survival benefits as well as reduction of locoregional recurrences.(*4-7*) On the basis of these results, postmastectomy irradiation in high-risk breast cancer patients is the current treatment trend, and recommendations and guidelines for postmastectomy radiotherapy have been proposed by the American Society of Clinical Oncology.(*8*)

Increasing use of adjuvant postmastectomy radiation the-

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rapy raises a conflict between the cosmetic benefit of immediate reconstruction and the effect of radiation therapy on the reconstructed flap. The long-term effects of radiation therapy on autogenous flap reconstruction are unclear. Given that all high-risk patients should receive radiation, an important question is whether autologous tissue reconstruction should be done before or after radiation treatment. A consensus at the recent American Society of Plastic Surgeons meeting and several large studies have discouraged immediate breast reconstruction in patients requiring postmastectomy radiation. However, articles concluding to the contrary continue to be published.(*9*)

The present study evaluated the effect of radiation therapy in high-risk patients undergoing immediate TRAM flap reconstruction. Evaluation was achieved by comparing postmastectomy flap fat necrosis and tumor recurrences between a 'no radiation therapy group' and a 'radiation therapy group'.

METHODS

One hundred and two patients who underwent mastectomy and immediate TRAM flap reconstruction between 1996 and 2001 at the Asan Medical Center were evaluated retrospectively. The mean age of patients was 41 years, and the median follow-up time was 33 months. Skin-sparing mastectomy was conducted in 82 patients (80.4%) and classical mastectomy in 20 patients (19.6%). Of 21 high-risk patients needing postmastectomy radiation therapy, nine received radiation therapy and thirteen did not received it because of patient's refusal of radiation therapy.

TRAM flap fat necrosis was classified as follows: No - not detected by clinical evaluation (physical examination, USG); Mild-clinically not palpable, but detected on USG, or clinically small, ill-defined fibrosis or induration; Moderate - clinically definite, small, hard, palpable mass (size＜3 cm); Severe-clinically large, hard, protruding palpable mass needing revision (size≥3 cm), or moderate criteria which had undergone revision. Only moderate and severe categories were considered for this study. Fat necrosis was evaluated at least one year after completion of radiation therapy, and was defined when it presented clinically (by physical examination), radiologically (by USG), or pathologically (by needle biopsy).

Tumor recurrence (locoregional) in high-risk patients was evaluated during the median 33 (10～81) months follow-up. Recurrence patterns of patients were reviewed. The high-risk group comprised 21 patients with tumor size ＞5 cm, or four or more axillary LN metastases in our study. Of these 21 high-risk patients, nine received radiation therapy using tangent fields (50～60 Gy) in the reconstructed breast at 180 cGy per fraction. The supraclavicular fossa and axillary apex were also treated with 50 Gy at 180 cGy per fraction. All high-risk patients received adriamycin-combined chemotherapy or CMF (cyclophosphamide, methotrexate and 5-fluorouracil) chemotherapy.

Statistical analysis was performed using Fisher's exact test. A *P* value of less than 0.05 was considered statistically significant.

Table 1. Patient characteristics

	Number of patients (%)
Mean age (years)	41
Mean tumor size (cm)	2.7
Stage*	
0	7 (6.9%)
I	36 (35.3%)
II	55 (53.9%)
III	4 (3.9%)
Lymph node metastasis (number)	
0	62 (60.8%)
1～3	22 (21.6%)
≥4	18 (17.6%)
Mastectomy type	
Skin-sparing mastectomy	82 (80.4%)
Conventional mastectomy	20 (19.6%)

Conventional mastectomy includes a modified radical mastectomy or a simple mastectomy. *5th AJCC staging system.

Table 2. The effect of radiation therapy on fat necrosis in patients undergoing immediate TRAM flap reconstruction

Fat necrosis	Without postmastectomy RT (n=93)	With postmastectomy RT (n=9)	*P*-value
No/Mmild	75 (80.6%)	4 (44.4%)	
Moderate/ Severe	18 (19.4%)*	5 (55.6%)†	0.026

RT = radiation therapy; *14 of 18 patients had revision; † all 5 patients had revision.

RESULTS

1) The effect of radiation therapy on fat necrosis after immediate TRAM flap reconstruction

Post-operative examination of patients for a median time of 33 months showed that moderate or severe fat necrosis in TRAM flaps occurred more frequently in patients who received radiation therapy (55.6%) compared to those not receiving radiotherapy (19.4%) (P=0.026) (Table 2). Fourteen of 18 patients with moderate or severe fat necrosis in the no radiation therapy group underwent revision, while all five patients with moderate or severe fat necrosis in the radiation therapy group underwent revision.

2) Tumor recurrence in high-risk patients after mastectomy and immediate reconstruction

Of nine high-risk patients who have had postmastectomy radiation therapy during the median 33 months follow-up, two experienced tumor recurrences. One was an axillary lymph node recurrence and the other was an ipsilateral supraclavicular lymph node recurrence and liver metastasis. There was no recurrence in the 12 high-risk patients in the no radiation therapy group.

Among the 102 patients, thirteen patients, including the two high-risk patients, showed recurrences during follow-up. Most cases had systemic recurrences, except for four locoregional recurrences (Table 3).

DISCUSSION

Although skin-sparing mastectomy and immediate autologous flap reconstruction has a good aesthetic outcome, it may not be the ideal procedure for high-risk breast cancer patients requiring postmastectomy radiation therapy. Of the complications after postmastectomy radiation therapy following immediate TRAM flap reconstruction, fat necrosis is considered clinically important as the hard lumps mimic malignant masses, leading to patient concern over recurring malignancy.

Our study found that in patients underwent mastectomy and immediate TRAM flap reconstruction, the incidence of fat necrosis was higher in those received radiation therapy than in those not received radiation therapy.

Exactly which patients should receive adjuvant postmastectomy radiation therapy is not entirely clear. In general, high-risk patients eligible for postmatectomy radiation therapy included patients with four or more positive nodes, patients with tumor size greater than 5 cm, patients with tumor invasion to skin or pectoral fascia, or patients with positive surgical margins.(*7,9,10*) Twenty-one patients of all subjects in our study had tumor size greater than 5 cm, or four or

Table 3. Clinical profiles of patients with recurrence (n=13)

Case	Age (years)	OP type	Tumor size (cm)	LN Met. (no)	Stage*	CTx, HT	RT	First recurrence site	Disease status	F/U (month)
1	34	MRM	4	0	IIA	CMF	No	Lung	Dead	18
2	37	SSM	2.7	0	IIA	CMF, Tam	No	Bone	Alive	30
3	41	SSM	3	1	IIB	CMF	No	Bone	Alive	32
4	31	SSM	1.8	1	IIA	CAF, Tam	No	Lung, Liver	Dead	19
5	29	MRM	3.5	2	IIB	CMF	No	Bone	Alive	28
6	51	SSM	2	1	IIA	AC	No	IMLN	Alive	27
7	39	SSM	1.5	1	IIA	CMF	No	Liver	Alive	44
8	46	SSM	1.8	3	IIA	CMF	No	SCLN	Alive	42
9	44	SSM	4.3	0	IIA	CMF	No	Lung	Alive	39
10	41	SSM	1.2	1	IIA	CMF	No	Chest wall	Alive	39
11	32	SSM	4	0	IIA	CMF	No	Bone	Alive	33
12	33	SSM	4.5	20	IIB	CAF, Tam	Yes	SCLN, Liver	Alive	19
13	52	SSM	3	4	IIB	AC-T	Yes	Axillary LN	Alive	18

MRM = modified radical mastectomy; SSM = skin-sparing mastectomy; CTx = chemotherapy; HT = hormone therapy; RT = radiation therapy; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; CAF = cyclophosphamide, adriamycin, 5-fluorouracil; AC = adriamycin, cyclophosphamide; AC-T = adriamycin, cyclophosphamide Taxol; Tam = tamoxifen; Met = metastasis; IMLN = internal mammary lymph node; SCLN = supraclavicular lymph node. *5^{th} AJCC staging system.

more positive nodes. Although our results are from only a relatively small number of patients and only 33 months of follow-up, there were few recurrences after mastectomy and immediate TRAM flap reconstruction, even in high-risk patients. Furthermore, most recurrences presented as systemic metastasis, with chest wall locoregional recurrence being very rare. It is a little interesting findings, however, it needs longer follow-up evaluation with regard to the recurrence.

Buchholz et al. commented that immediate breast reconstruction has two significant disadvantages in patients with locally advanced breast cancer.(*11*) First, radiation can affect the aesthetic outcome of the reconstructed breast. The second issue concerns the design of radiation fields, which ideally include the chest wall, internal mammary lymph nodes, axillary apex, and supraclavicular lymph nodes, and minimize doses to the heart and lung. This ideal arrangement of radiation, which matches a medial chest wall electron beam field to more laterally placed opposed tangent fields, is not feasible after reconstruction because the sloping breast contour leads to an imprecise geometric matching of the fields.

Regarding the influence of radiation therapy on aesthetic outcomes, Tran et al. reported the incidence of late complications was significantly higher in patients who had immediate autologous tissue reconstruction followed by radiation compared to those having radiation and delayed reconstruction (87.5% vs. 8.6%; P=0.000).(*12*) Fat necrosis was also significantly increased in the former compared to the latter (43.8% vs. 8.6%; P=0.000). These investigators advocated that, in patients who are candidates for TRAM flap reconstruction and need postmastectomy radiation therapy, reconstruction should be delayed until radiation therapy is complete. Interestingly, William et al. reported that the complication rate did not change depending on whether a patient received radiation before or after reconstruction, but the nature of the complication changed i.e. fat necrosis to fibrosis. However, fat necrosis was greater in both radiation groups (15.8～17.6%) compared to no radiation groups (10%).(*13*) In contrast, several published articles suggest postmastectomy irradiation after immediate TRAM flap reconstruction for locally advanced breast cancer appears safe and cosmetically acceptable.(*10,14*)

In addition to skin-sparing mastectomy and immediate breast reconstruction becoming more widely used in the treatment of breast cancer, another current trend is the more liberal use of postoperative radiation therapy. Recent large, randomized trials and a meta-analysis demonstrated locoregional therapy, including radiation therapy, not only reduced local failure but also improved disease-free and overall survival.(*4-7*) Locoregional therapy as well as systemic therapy in management of breast cancer is important according to the synthesis theory of Hellman that breast cancer is "a heterogeneous disease that can be thought of as a spectrum of proclivities...".(*15*)

The number of high-risk patients needing radiation therapy after immediate autologous flap reconstruction will proportionally increase with the increase in patients undergoing skin-sparing mastectomy and immediate reconstruction.(*16*) To reduce complications and improve cosmesis after radiation therapy, radiation techniques and field arrangements for the reconstructed breast need to be considered.

Although the issue of the use of radiation therapy in patients undergoing immediate autologous tissue reconstruction is not yet resolved, the consensus at the recent American Society of Plastic Surgeons meeting, and a multidisciplinary-determined philosophy at the M.D. Anderson Cancer Center, was to avoid immediate reconstruction in patients that require postmastectomy radiation.(*11*) Our results support this recommendation. An interesting finding from our results was that locoregional recurrence, especially chest wall recurrence, was rare during follow-up in high-risk patients, regardless of radiation therapy. However, it needs more longer follow-up evaluation.

There are insufficient data available to make evidence-based guidelines with regard to the integration of postmastectomy radiation therapy and reconstructive surgery. The American Society of Clinical Oncology (ASCO) panel in 2000 reviewed that was reasonable to perform immediate reconstruction in patients with clinical stage I or II cancers. However, their was disagreement within the panel regarding the use of immediate reconstruction in patients with stage IIIB tumors and large T3 tumors.(*9*)

We recommend that radiation therapy in high-risk patients after immediate TRAM flap reconstruction should be applied only after due regard to the likely positive effects on recurrence and the likely harmful effects on the flap. More importantly, careful preoperative evaluation of the disease state may indicate which patients need postmastectomy radiation therapy, in which cases delayed reconstruction appears more appropriate.

CONCLUSION

Our data indicate that in high-risk breast cancer patients underwent immediate TRAM flap reconstruction, subsequent radiation therapy increased flap fat necrosis. Such necrosis will result in poor outcomes for reconstruction. We recommend that radiation therapy in high-risk patients undergoing immediate TRAM flap reconstruction must be carefully considered, with clinicians needing to balance the likely positive effect on recurrence with the likely negative effect on flap tissue.

In addition, careful preoperative evaluation of the disease state will indicate whether a patient needs postmastectomy radiation therapy, in which case delayed reconstruction appears more appropriate.

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