Safety of Immediate Transverse Rectus Abdominis Myocutaneous Breast Reconstruction for Patients With Locally Advanced Disease

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Hypothesis: Immediate transverse rectus abdominis myocutaneous breast reconstruction combined with postoperative radiation therapy after mastectomy is safe and effective.

Design: Retrospective case series.

Setting: University-based teaching hospital.

Patients: From January 1, 1996, through December 31, 2003, 252 patients underwent mastectomy and immediate transverse rectus abdominis myocutaneous flap reconstruction. Of those, 35 patients received postoperative radiation therapy (stage I, n=1; II, n=17; III, n=15; IV, n=2). Age range was 29 to 72 years (mean, 49.5 years). Follow-up was 1 to 8 years (mean, 48 months).

Main Outcome Measures: Flap loss, fat necrosis, flap volume loss, adjuvant treatment delay, and need for additional surgery.

Results: The rate of flap survival was 100%. Median operative time was 5.5 hours. Average hospital stay was 5.2 days. Fat necrosis occurred in 3 patients, with volume loss requiring additional surgery in 2 patients (6%). Postoperative adjuvant therapy was not significantly delayed (median interval, 32 days). With a median follow-up of 48 months, local recurrence was present in only 1 patient (3%), who underwent successful local salvage, and distant metastasis occurred in 4 patients (11%).

Conclusions: Immediate transverse rectus abdominis myocutaneous breast reconstruction followed by radiation therapy is safe, with minimal morbidity and no significant change in tissue volume. Complications tend to be minor, not delaying adjuvant therapy. Immediate breast reconstruction should be considered after mastectomy, despite the need for postoperative radiation therapy.

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It is now generally accepted that immediate reconstruction after mastectomy is safe, with local recurrence rates similar to those of patients undergoing mastectomy without reconstruction, and without significant delay in diagnosis of recurrence. It has even been suggested that immediate reconstruction can be effective for patients with locally advanced disease.

For patients who require postmastectomy radiation therapy (RT), the optimal timing for transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction remains controversial. A recent series reported an extremely high complication rate after immediate free TRAM reconstruction and RT and suggested that reconstruction should be delayed for all patients receiving both postoperative RT and TRAM flap reconstruction. In light of previous studies demonstrating more acceptable morbidity rates, this most recent series has caused much concern. The purpose of the present study was to determine the influence of immediate autologous tissue breast reconstruction on subsequent treatment and the effect of RT on TRAM flap breast reconstruction.

Methods:

From January 1, 1996, through December 31, 2003, 252 consecutive patients at the Carol Franc Buck Breast Cancer Center at the UCSF (University of California, San Francisco) Comprehensive Cancer Center, San Francisco, underwent modified radical mastectomy with immediate TRAM flap reconstruction. All of the reconstructions were performed by 2 plastic surgeons (R.D.F. and J.P.A.). From this group, data from 35 patients requiring postoperative RT were analyzed separately and form the basis of this study. Patients were all counseled on the risks and benefits, preoperative and postoperative expectations, and reconstructive options by a multidisciplinary team consisting of a general surgeon, a plastic surgeon, an oncologist, and a nursing care specialist before...
surgery. Patients were able to examine photographs of patients who had undergone similar reconstruction, and were given the opportunity to speak with individuals who had received immediate reconstruction and postoperative RT. Contraindications to skin-sparing mastectomy (SSM) included only cancers with direct skin involvement and cancers too close to the skin to achieve adequate margins.

Ages ranged from 29 to 72 years (mean, 49.5 years). Preoperative staging was as follows: stage I, 1 patient (positive resection margins); stage II, 17 patients; stage III, 15 patients; and stage IV, 2 patients (supraclavicular nodes considered stage IV under previous staging scheme). Type and timing of adjuvant therapy, operative time, complications, hospital stay, and follow-up (including local recurrence and distant metastasis) were reviewed by chart review. The median length of follow-up was 48 months (range, 1-8 years). The results for local recurrence rates, the interval to postoperative chemotherapy, and the incidence of distant metastasis were compared with historical data in the literature for patients who underwent modified radical mastectomies without reconstruction for advanced forms of breast cancer.

### RESULTS

#### TIMING OF ADJUVANT TREATMENT

In most cases, postoperative adjuvant therapy was begun by 1 month after surgery. Only 2 patients experienced any delay in treatment. When compared with our own data for patients after modified radical mastectomy without reconstruction (median, 27 days), the postoperative time interval to start adjuvant therapy was not significantly different (median, 32 days; \( P > .05 \)).

#### BREAST RECONSTRUCTION: OUTCOMES AND COMPLICATIONS

In all cases, SSM consisted of sacrificing only the nipple and areola at the level of the skin, with a periareolar incision. The operative time averaged 5.5 hours including the mastectomy, and the average hospital stay was 5.2 days.

There were 13 complications postoperatively. Only 1 case resulted in reoperation in the immediate postoperative period. That patient had an area of central abdominal skin slough after a TRAM flap, requiring skin advancement and primary closure. Four patients with minor epidermolysis of their native skin flaps were treated conservatively with daily dressing changes, and the flaps healed without any further problem. With a minimum follow-up of 1 year, fat necrosis occurred in 3 patients (9%). All 3 cases were noted after RT. Two of those patients (6%) developed volume loss of the flap and required additional surgery, which consisted of implant placement behind the TRAM (1 patient) or mastopexy (1 patient). Volume loss was not noted in any additional patients. Two patients had cellulitis. Three patients were recorded as having ventral hernias, but only 1 had a true hernia, which was periumbilical. The other 2 patients experienced fascial laxity of the lower abdomen, which was treated successfully with mesh placement.

#### LOCAL RECURRENCE AND DISTANT METASTASIS

At an average follow-up time of 4 years, the local recurrence rate was 3% (0 of 1 patient in stage I, 0 of 17 in stage II, 1 of 15 in stage III, and 0 of 2 in stage IV) and the incidence of distant metastases was 11% overall (0 of 17 in stage II, 2 of 15 in stage III, and 2 of 2 in stage IV). This compares favorably with local recurrence and distant metastasis rates in the literature for patients with immediate reconstruction (Table) or without reconstruction\(^2\) after mastectomy. In the 1 patient with a local recurrence, a skin nodule (<1 cm in diameter) was detected within 3 months postoperatively and successfully treated by local excision, followed by RT.

### Table. Studies Evaluating Mastectomy With Immediate Reconstruction for Patients With Locally Advanced Breast Carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Median Follow-up, mo</th>
<th>Local Recurrence, No. (%)</th>
<th>Distant Metastasis, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Godfrey et al,(^9) 1995</td>
<td>21</td>
<td>25.2</td>
<td>3 (14)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Styblo et al,(^10) 1996</td>
<td>21</td>
<td>26</td>
<td>1 (5)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Sultan et al,(^11) 1997</td>
<td>22</td>
<td>28</td>
<td>1 (5)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Newman et al,(^7) 1999</td>
<td>50</td>
<td>58.4</td>
<td>5 (10)</td>
<td>16 (32)</td>
</tr>
</tbody>
</table>

Skin-sparing mastectomy with immediate breast reconstruction has become widely used in early-stage breast cancer,\(^2,13\) and it appears to be safe for patients with locally advanced cancer as well. Local recurrence rates are comparable with those of patients with either a delay in their reconstruction or no reconstruction at all.\(^13,14\) Furthermore, the diagnosis of local recurrences does not appear to be delayed and the aesthetic result of SSM and immediate reconstruction is superior to that of other forms of reconstruction.

Additional concerns about the application of SSM with immediate reconstruction to locally advanced (stages II and III) cases of breast cancer center on adjuvant therapy, which is almost always a part of the treatment for locally advanced breast cancer. The concerns include (1) the risk that prolonged recovery from the surgery will result in delays in postoperative therapy; (2) the risk that preoperative chemotherapy will impair wound healing; and (3) the effect of radiotherapy on flap healing and the cosmetic result.

For many years, women requiring postoperative RT to prevent local recurrences were routinely considered for reconstruction only after the completion of their local and systemic therapy. In the 1990s, several studies

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presented compelling evidence that immediate reconstruction even with planned postoperative adjuvant therapy was both safe and effective. One such study,7 in 1997, concluded that postoperative RT was safe, was effective in locoregional cancer control, and resulted in excellent cosmetic results when immediate TRAM flap breast reconstruction was performed. The same group,15 however, in 2000, arrived at the opposite conclusion because of a very high complication rate and since that time has cautioned against offering immediate reconstruction to any patient expected to receive postoperative radiation therapy. During the past 7 years, as medical opinion has wavered concerning the subject, we have continued to offer immediate TRAM flap reconstruction for patients receiving postoperative RT because we did not note a significant effect on patient outcomes. This series analysis supports that idea. Complications requiring reoperation were relatively few (3 patients [9%]). Postoperative adjuvant therapy was not significantly delayed. Local recurrence and distant metastasis rates were appropriate for comparable staging, and complications directly related to postoperative RT were relatively rare. Flap necrosis and flap volume loss rates were minimal.

Newman et al3 demonstrated no significant differences in local relapse or distant metastasis rates for patients receiving immediate breast reconstruction for locally advanced disease. With the largest series of its kind (50 patients) and the longest median follow-up to date (58.4 months), they have further shown complication rates comparable with those of a similar group of patients who did not undergo immediate reconstruction and a delay in postoperative adjuvant therapy that was only marginally significant (35 vs 21 days; P=.05). The results of our current study suggest that SSM with immediate reconstruction is equally safe and effective for the treatment of advanced stages of breast carcinoma. Local recurrence and distant metastasis rates were consistent with those of Newman et al3 and other studies of immediate reconstruction after traditional mastectomy for locally advanced breast carcinoma3-5,9-11 (Table).

Although median follow-up in the present study was only 4 years, most recurrences are detected as palpable skin flap masses within 3 years of the initial cancer diagnosis.14 Since local recurrences typically present as skin nodules, immediate autogenous tissue reconstruction after SSM should not interfere with local tumor surveillance.

This study has generated promising data and should serve to encourage other institutions to consider SSM with immediate reconstruction for patients requiring postoperative RT. Patients with locally advanced breast cancer are considered to have a poor prognosis. However, this group of patients has a 50% to 80% 5-year disease-free survival rate.12 With the advent of neoadjuvant therapy, physicians will be increasingly able to judge a patient’s response to treatment, which is highly predictive of survival. Most patients have at least a partial response and a reasonable life expectancy. Furthermore, as therapeutic options continue to improve, more women will survive for longer periods, and SSM with immediate reconstruction should be included as an option for women who choose mastectomy.

We understand the inherent biases present in a retrospective study. Because of the patient’s desires and body habitus, such a study cannot be randomized. We recognize that our study group is relatively small and, therefore, it is difficult to draw any final conclusions. Skin-sparing mastectomy with immediate reconstruction represents a significant achievement for the reconstructive surgeon. Its application to patients who require postoperative RT is a significant step toward defining its clinical role.

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REFERENCES

John T. Vetto, MD, Portland, Ore: In recent years survival from breast cancer has improved, and we have therefore set our sights on curing higher-risk lesions (such as locally advanced and inflammatory cancers). As a result, as adjuvant therapy, including chemotherapy and postmastectomy radiation, becomes more commonplace, the issue of when to perform immediate autologous reconstruction is becoming more controversial. Fuel was added to the fire by 2 reports in 2000 and 2001 by Tran et al from M. D. Anderson. Although this was the very institution that had championed immediate reconstruction by such surgically intense techniques as skin-sparing mastectomy and TRAM flap, these reports suggested that cosmetic results are inferior for patients who are slated to undergo the adjuvant treatments I mention, and that reconstruction should therefore be delayed.

The paper we just heard is really about the safety of immediate reconstruction in patients with advanced breast cancer and attempts to refute to some degree the concept that we need to delay autologous reconstruction in these patients. Preferences among plastic surgeons at my own institution reflect this controversy: some of my colleagues have no concerns about aggressive immediate reconstruction in advanced-stage patients, while others routinely require that patients delay reconstruction until up to 2 years after chest wall radiation.

To bring some order to the chaos, it should be said that current surgeons at M. D. Anderson prefer free TRAM—that is, TRAM flaps done with a vascular anastomosis, usually to the axillary vessels—over the older more standard technique of pedicled TRAM, which is based on the inferior epigastric vessels left in situ. I would hypothesize that TRAMs done with microvascular anastomoses are more prone to vascular problems and ischemia or atrophy following radiation. This might account for the change of heart at M. D. Anderson, and for the individual preferences of plastic surgeons at institutions such as ours, depending on the types of TRAM they perform.

The authors present data to suggest that immediate reconstruction for advanced breast cancer is “safe,” and I believe they mean this term in both its oncologic and cosmetic definitions. I accept that it is likely oncologically safe; their data show this, and the concept that reconstruction does not interfere with follow-up has been well demonstrated in the past and will likely become more true in the MRI [magnetic resonance imaging] era. In terms of cosmetic safety and delays to treatment, I am troubled by the fact that they had 10 wound complications in 35 patients. Their data do show a resulting trend toward a delay in adjuvant therapy compared with unreconstructed patients; the fact that this trend did not reach statistical significance may have been a small-numbers phenomenon. To be fair, I should note that a poster at this same meeting yesterday also showed what their data show—an increase in wound complications without a delay in adjuvant therapy. I am puzzled how this can be. The authors attempt to explain it in part by noting a low take-back rate to the operating room for wound revisions, but I do not believe this is an accurate end point, as the decision to go back to the operating room when there are wound problems is somewhat arbitrary and may actually speed the healing process.

In terms of post–adjuvant therapy cosmesis, although the authors followed up their patients for a median of 4 years—which is longer than the M. D. Anderson series and quite commendable—I did not see in the manuscript any data on long-term cosmetic outcomes or patient satisfaction.

The authors did a good job discussing the limitations of the study, so I will only emphasize that both plastic surgery and radiation techniques and outcomes are institutionally dependent, and the results of this study may therefore not be generalizable. Unfortunately, it is unlikely that we will have much prospective randomized data on this issue; a recent attempt at a prospective randomized study of postmastectomy radiation closed early due to poor accrual.

In closing, I have the following questions for the authors:

1. Do the authors believe that the fact that their TRAMs were pedicled influenced their results, and do they recommend that reconstruction be delayed until after adjuvant therapy, especially radiation, if a free TRAM is planned?
2. If reconstruction is delayed until after adjuvant therapy, do the authors use any techniques to preserve skin, and do they believe those techniques alter radiation outcomes?
3. Do the authors have any long-term, ie, post–adjuvant therapy, data on cosmesis and patient satisfaction?
4. What about the opposite situation: when a patient requires (for local recurrence) or requests mastectomy and reconstruction after lumpectomy with radiation? Do the authors think that immediate reconstruction is safe when the patient has already been irradiated, and is there some time limitation they use to decide? I am aware that mastectomy and reconstruction after preoperative radiation is commonly done in some European centers, but in our experience these patients can have major wound problems.

David M. Young, MD, San Francisco, Calif: Many studies have concluded that breast reconstruction is safe in regard to cancer treatment and surveillance and does not delay adjuvant chemotherapy or radiation. The debate, however, has always been the quality of the reconstruction that occurs, whether you do it before or after the radiation therapy. This paper goes a long way toward addressing that issue. Fat necrosis, for people who are not aware, is due to a circulatory problem with the TRAM flap itself. It makes sense that fat necrosis should not be altered by the radiation itself but is rather a product of the TRAM flap reconstruction and whether or not good blood flow is actually kept to the TRAM. The most critical data were not really presented or are not known at this point, which is what the fat necrosis rate is in the group that was not radiated. In your last slide, you did say that that was the next thing you would be looking at, and I think that that would be a critical piece of data, to know that the radiation therapy did not alter your fat necrosis rate.

Have you looked at the quality of the skin in the TRAM reconstruction after the radiation therapy? That is the thing that would be altered by the radiation. If you did the TRAM reconstruction after the radiation, then there would not be any radiation changes because that is outside of your field of radiation. But if you put the TRAM into the field of radiation, would that then cause skin changes that are undesirable? I think that is a critical issue to address within this study.

Dr Esserman: For those of us in breast cancer, this is a really important paper. The contrast of the UCSF and M. D. Anderson results is very important and may allow us to learn quite a bit about some of these techniques as we go forward. It is fairly well established that SSM is safe in terms of complication rates, delay of therapy, and recurrence.

One of the points Dr Vetto brought up was that the lack of delay might be due to a numbers issue. His concern was that there were a number of wound complications. However, many of these wound complications are actually quite minor, mostly skin epidermolysis. Most of our complications involve the mastectomy skin flaps. We are predominantly using a technique of skin sparing, because the more you save the native skin envelope, the more superior the result. Unfortunately, Dr Young, saving the skin precludes saving the skin from the radiation effects. Most of the skin complications result in the formation of eschar or scab. Although patients do not like it, it does heal and it does not delay chemotherapy except in rare cases. Patients need to know that skin flap complications can happen.
We have found a number of technical tricks—using the cutting cautery current or the bipolar instead of the cautery current on the Bovey can minimize skin damage.

One of the things that we also do to avoid any delay in therapy, particularly in these locally advanced cancer patients, is to give neoadjuvant chemotherapy. So we start with chemotherapy. For patients who have locally advanced cancer, their issue is not a local one. Their issue is a systemic one. We start with the most critical therapy, and this has actually a number of major advantages. First of all, when you actually do the surgery, your radiation therapy is immediately following the surgical procedure, and that, as we know from the lumpectomy data, improves local control. It also gives patients time to make decisions and adjust to the idea of mastectomy and reconstruction. We also know that response to therapy dictates surgical choices, and lastly we avoid any kind of chemotherapy delay, which, as I said earlier, is pretty much the most important part of the therapy for these patients.

In terms of recurrence, our data show a 3% local recurrence rate. In a population of locally advanced breast cancer patients, you might expect at least a 5% and maybe 10% local recurrence rate, and we certainly don’t see anything higher than that. Thus, it is very clear that local recurrences in a locally advanced population have more to do with biology and patient’s response to therapy than to surgical technique.

Now, the question was raised about the pedicle vs the free TRAM. I think this is where the insight is in these papers. By the time the M. D. Anderson series had come out, we had already performed immediate reconstruction on maybe half of these patients, and we were not seeing the same kind of results that the M. D. Anderson series had seen. We were not seeing the big volume loss, we were not seeing the significant early contractures, but it is very clear from their papers that major complications occurred in the majority of the M. D. Anderson TRAMs. At a recent talk and report by Dr Robert Allen from Louisiana on the DIEP flaps, he described his results in 1000 patients undergoing reconstruction using a muscle-sparing technique using free flaps based on the inferior epigastric vessels, anastomosed usually to either internal mammary artery. He also reported enormous skin contractures and volume loss after radiation, where the flap shrivels to maybe a third of the volume. I have to presume from these reports that, in fact, the problem is with the free TRAM. The reason the free TRAM was started was to improve the blood supply. Particularly for patients who are smokers, free flaps improve the cosmesis and decrease the fat necrosis rate. The problem is, however, that these flaps may not hold up to radiation therapy at all. We know that one of the problems with radiation therapy is small-vessel disease, and I think that that has to be the initial conclusion. So if you have a patient with locally advanced cancer and you think they are going to have radiation, at this time I would not do a free TRAM. There are enough data here to suggest that pedicle TRAMs are very safe and effective. One of the issues is that skin sparing, being able to save the envelope, really does yield vastly superior cosmetic results, but not, of course, if there is a skin contracture. So you are faced with trying to trade off volume loss or ischemia or any kind of radiation change with being able to preserve the skin envelope. Of course, if you are not going to save the skin, there is not necessarily an advantage to immediate reconstruction. But for patients who know that they want reconstruction, immediate reconstruction with skin sparing gives a superior cosmetic and psychological beneficial result.

Another option for a patient who requires postmastectomy radiation is to again change the sequence of therapy. Radiation can be given prior to surgery and reconstruction performed following both chemotherapy and radiation. In fact, this is standard practice at the Institute Curie in France. They have experience with thousands of patients and their results show that skin-sparing reconstruction following radiation is safe and effective.

In answer to Dr Vetto’s second question, we use skin sparing whenever possible. We are designing a very detailed study comparing 4 patient populations: people who are having DIEP flaps (the muscle-sparing, using either the superficial epigastric artery or the inferior epigastric artery), regular TRAMs, TRAMs with radiation therapy, and lumpectomy and radiation. We are going to look for skin changes, fat necrosis, and volume and contracture loss.

There are measures of cosmesis, but you have to look at them from the patient’s perspective, the surgeon’s perspective, and that of another objective observer, such as a nurse. It is important to separate out radiation effects based on individual biology vs complications secondary to surgical technique. Some of the contractures and problems may be native to the patients and their reactions to radiation therapy. There are now increasing data that there are some biological markers such as transforming growth factor β that may predict radiation necrosis, and whether patients have a lumpectomy and radiation or a TRAM and radiation, you may see changes. The last question that was asked was about local recurrence and radiation therapy. Is it safe to do an SSM in that situation? The answer to that question is yes. We have done many of these cases, particularly if you use TRAM or latissimus flaps. This can be quite safe and the skin can be preserved with new blood supply from the flap to support the skin flaps.

In conclusion, the insights that we gained from this paper are that there is some element of skin necrosis and fat necrosis that is secondary to radiation therapy and the patient’s own native way of reacting to that tissue. We are beginning studies at our institution to try and predict that complication using molecular markers. However, the main conclusion is that free TRAMs or DIEP flaps are not suitable for radiation. There is increasing pressure now from patients who want DIEP flaps. However, if you have a patient who is going to get radiation afterward, it is not an appropriate flap to offer.

Dr Robert Allen’s data are very clear that patients have absolutely terrible outcomes, and having a big flap procedure and have it fail is unconscionable for a patient. So for a patient who is going to get radiation therapy, I think it is clear that a pedicle TRAM is safe, but I would not do a free TRAM of any kind until we get more data.