Breast Cancer Recurrence after Immediate Reconstruction: Patterns and Significance

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Local recurrence of cancer after mastectomy and immediate breast reconstruction is generally regarded as a poor prognostic indicator. This study was conducted to identify specific patterns of local recurrence following reconstruction and to determine their biological significance. The records of all patients who had undergone immediate breast reconstruction at The University of Texas M. D. Anderson Cancer Center between June 1, 1988, and December 31, 1998, were reviewed. The records of patients who had local tumor recurrence were then carefully analyzed. During this 10-year period, a local recurrence of cancer was found to have developed in 39 of 1694 patients (2.3 percent). Most recurrences were in the skin or subcutaneous tissue ($n = 28$; 72 percent), and the remainder were in the "chest wall" ($n = 11$; 28 percent), as defined by skeletal or muscular involvement. Transverse rectus abdominis myocutaneous flaps were used most often in both groups, but latissimus dorsi myocutaneous flaps and implant techniques were also used in some patients. Patients with subcutaneous tissue recurrence had an overall survival rate of 61 percent at follow-up of 80.8 months, compared with patients with chest wall recurrence, whose survival rate was 45 percent at similar follow-up. Metastases were less likely to develop in patients with subcutaneous tissue recurrence than in those with chest wall recurrence (57 percent versus 91 percent; $p = 0.044$); the former group also had a greater chance of remaining disease-free after treatment of the recurrence (39 percent versus 9 percent), respectively. Metastasis-free survival was higher in patients with subcutaneous tissue recurrence than with chest wall recurrence (2-year and 5-year survival: 52 and 42 percent versus 24 and 24 percent; $p = 0.04$). In both groups, the time to detection of the recurrence was similar (subcutaneous tissue recurrence, 27.1 months, versus chest wall recurrence, 29.5 months). Distant disease did not develop in one patient only in the chest wall recurrence group; this patient remained disease-free at 70 months. From these results, it was concluded that (1) not all local recurrences are the same: patients with subcutaneous tissue recurrence have better survival rates, a decreased incidence of metastases, and a greater chance of remaining disease-free than do those with chest wall recurrence; (2) immediate breast reconstruction (although potentially, it can conceal chest wall recurrence) does not seem to delay the detection of chest wall recurrence; and (3) even if a chest wall recurrence develops, it is highly associated with metastatic disease, and the survival rate is not likely to have been influenced by earlier detection. These data support the continued use of immediate breast reconstruction without fear of concealing a recurrence or influencing the oncologic outcome. (*Plast. Reconstr. Surg.* 111: 712, 2003.)

Plastic surgeons who perform breast reconstruction must be familiar with the behavior and importance of recurrent breast cancer, because they may be the first clinicians to diagnose it. Beliefs about the actual biological significance of such a recurrence have recently undergone a paradigm shift.[1] Breast cancer was originally believed to be a localized process that spreads in an organized fashion to the lymph nodes and then hematogenously. Later, it was thought that breast cancer was primarily a systemic disease,[2] and treatment of a local recurrence was de-emphasized because it was believed to be a manifestation of unrecognized systemic spread. According to this systemic theory, when breast cancer recurs locally following mastectomy, it is merely one of several sites of spread, it should be thought of as a marker for impending distant spread, and it is associated with a uniformly dismal prognosis.[3–5] In many cases, this outcome is actually observed clinically, with metastases frequently diagnosed synchronously with or soon after a local recur-

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rence.[5] However, there seem to be some instances when local recurrences do not behave so aggressively.[6] In the "local" theory of breast cancer, such isolated recurrences can be the only site of disease and, if controlled locally, can be consistent with long-term, disease-free survival.[1,7] Supporting this concept are the findings that radiotherapy following mastectomy in some patients not only reduces the rate of local recurrence, but it also significantly improves survival.[8,9] Local recurrence of breast cancer, therefore, seems to be heterogeneous, with systemic and localized components, and traditional strategies to deal with recurrence may be outdated.

The actual location of the local recurrence, whether subcutaneous or in the deeper tissues of the chest wall, has not seemed to matter historically with regard to outcome,[10] but this, too, is being challenged in light of recent thinking about recurrence. Generally, after a mastectomy without reconstruction, cancer recurs more often in the skin or subcutaneous tissue of the mastectomy flap.[11] Recurrence in the deeper tissues of the chest wall is less frequent. Traditionally, both of these sites have been lumped into one category, "locoregional recurrence," which also includes regional recurrence in the axilla. It is curious that small nodules that recur at the mastectomy site have been considered to have as poor a prognosis as deeper chest wall recurrences.[10] These findings derived from earlier studies[4]; recent improvements in breast cancer treatment may have rendered them obsolete.

When breast reconstruction is performed, the mastectomy site is substantially altered so that autologous tissue or prosthetic material is interposed between the mastectomy flaps and the chest wall.[11] This potentially causes confusion about where recurrences actually originated and how to detect them. In principle, breast cancer recurrence must arise from the native breast skin or the chest wall itself—tissues that might contain residual breast parenchyma or draining lymphatics. The actual recurrence does not arise de novo from the reconstructive tissues, although recurrences can *invade* the reconstruction. Tumors arising from the mastectomy flap may invade the fat of a transverse rectus abdominis musculocutaneous (TRAM) flap and erroneously seem to originate from the chest wall recurrence. Conversely, a chest wall recurrence at the periphery of a TRAM flap may be easily palpable and mistaken for a subcutaneous relapse. Chest wall recurrences in the pectoralis major muscle over an implant may be wrongly categorized as superficial recurrences, because they are more palpable after anterior displacement of the muscle. Because most recurrences are superficial and readily detectable at physical examination, reconstruction may not interfere with detection. On the other hand, there is a greater chance that a flap or implant will delay the discovery of a deeper recurrence.[11] Early studies that validated the oncologic safety of breast reconstruction (mostly those using implants) showed that survival was not adversely affected by that reconstruction.[11–13] These reports did not specifically consider the location of the recurrence, perhaps relying on the widely held notion that if a chest wall recurrence developed, the prognosis was poor and would not have been influenced by earlier detection. Again, many refinements in breast cancer treatment have positively affected the course of the disease, and it is likely that they have affected the biology of recurrence as well. In this light, different locations may be associated with different prognoses.

We undertook this retrospective study to investigate the patterns and locations of breast cancer recurrence in patients who had undergone breast reconstruction, and to determine whether the location of the recurrence had any bearing on the development of distant disease and overall survival. In so doing, we hoped that we would learn more about disease recurrence in reconstructed breasts.

PATIENTS AND METHODS

We reviewed the records of all patients who had undergone breast reconstruction immediately following mastectomy at The University of Texas M. D. Anderson Cancer Center between June 1, 1988, and December 31, 1998. Records of patients who had local tumor recurrences were then carefully analyzed, and patients with axillary regional recurrence were excluded.

The locations of tumor recurrences were classified as either in the skin or subcutaneous tissue of the reconstructed breast or in the chest wall, as defined by skeletal or intercostal muscular involvement, including the pectoralis major muscle. Subcutaneous recurrences were defined as those arising in the skin or the subcutaneous tissue of the mastectomy flap and included lesions anterior to the pectoralis major. Therefore, if a TRAM flap was used,

lesions were classified as subcutaneous tissue recurrence if they were anterior to the rectus abdominis muscle of the flap (or its apparent location), even if they were deeply invading the fat of the flap. When the lesion was posterior to the rectus abdominis muscle and invaded or seemed to arise from the pectoralis major muscle, it was classified as a chest wall recurrence (Fig. 1). By using these definitions, when an implant was placed submuscularly and the pectoralis major was moved anteriorly, recurrences within the muscle (i.e., chest wall recurrences) could easily be palpated beneath the skin and confused with subcutaneous tissue recurrence (Fig. 2). When there was doubt, the report of the pathologic findings was used to ascertain the origin of the recurrence by evaluating the exact site of invasion.

Kaplan-Meier methods were used to estimate survival distributions, and log-rank tests were used to test for differences between groups. Survival was measured from the date of local recurrence. Statistical analyses were performed with SAS software (SAS Institute, Cary, N.C.) and were displayed with Splus 5 (MathSoft Engineering and Education, Cambridge, Mass.). A p value of less than 0.05 was considered statistically significant.

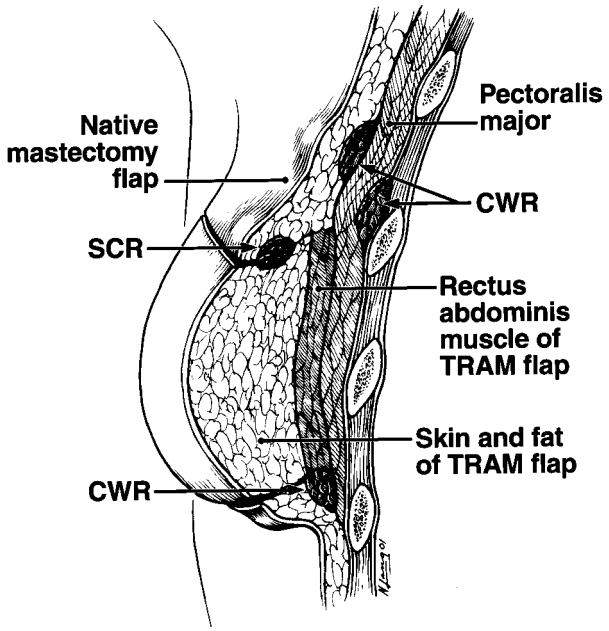

FIG. 1. Possible locations of breast cancer local recurrence following TRAM flap reconstruction. The rectus abdominis muscle of the TRAM is defined as the boundary between superficial or subcutaneous recurrences (*SCR*) and deeper chest wall recurrences (*CWR*).

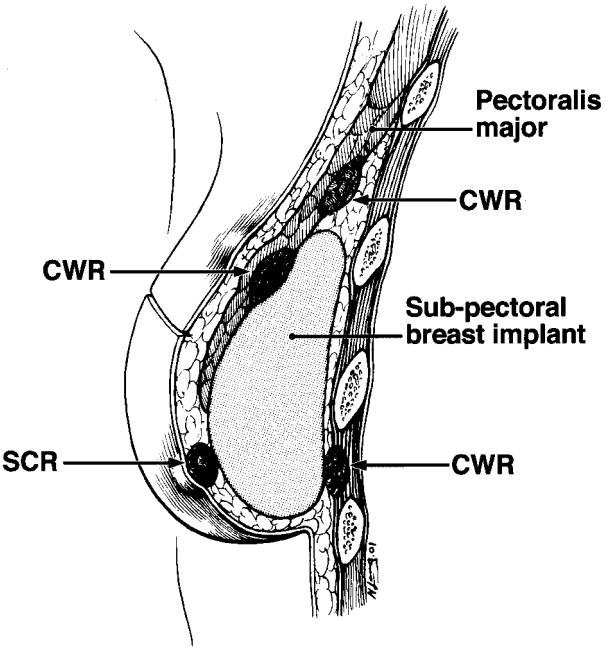

FIG. 2. Possible locations of breast cancer local recurrence following implant breast reconstruction. Lesions anterior to the pectoralis major muscle are defined as skin, superficial, or subcutaneous recurrences (*SCR*), whereas those involving the pectoralis major muscle or deeper structures are termed chest wall recurrences (*CWR*). Note that a submuscular implant can project a chest wall recurrence more anteriorly, making it easily palpable and confused with a subcutaneous tissue recurrence.

RESULTS

During our 10-year study period, of the 1694 patients who underwent breast reconstruction at our institution, local recurrence in the reconstructed breast developed in 39 of those patients (2.3 percent). Most of the recurrences were in the skin or subcutaneous tissue recurrences ($n = 28$; 72 percent), and the remainder were in the chest wall ($n = 11$; 28 percent).

The variables known to influence local recurrence of breast cancer studied in both groups of patients are shown in Table I. No significant differences were found between the two groups of patients with respect to age, initial nodal status, initial tumor size, initial stage, family history of breast cancer, and presence or absence of radiotherapy administered immediately after mastectomy, suggesting that all patients had biologically similar tumors and fairly equal chances of a local recurrence developing. TRAM flaps were the most common reconstruction method in both groups, although implant-based or latissimus dorsi myocutaneous-based methods were also used (Table II).

TABLE I
Breast Cancer Risk Factors by Recurrence Group

	Location of Recurrence			
	Subcutaneous Recurrence		Chest Wall	
Risk Factor	*n*	%	*n*	%
Total (*n* = 39)	28	72	11	
Age (mean years)	39		48	
≤40	15	54	3	27
>40	13	46	8	73
Family history				
Positive	7	27	2	18
Negative	18	73	9	82
Tumor size				
T1	13	48	4	36.5
T2	11	41	4	36.5
T3 (3) + T4 (3)	3	11	3	27
Nodal status				
0	15	53.6	5	45
1	10	35.7	6	55
2	3	10.7	0	0
Stage				
I	10	37.04	3	27.27
II	12	44.44	5	45.45
III (7) + IV (1)	5	18.52	3	18.52
Radiation after mastectomy	3	9	2	18

As expected, the development of local recurrence of breast cancer was highly associated with distant metastasis and low overall survival rates. Of the 39 patients with a local recurrence, metastasis developed in 26 (67 percent), and 17 of the 39 patients (44 percent) ultimately died of breast cancer within a mean follow-up period of 80.8 months. The 2-year and 5-year overall survival rates were 75 percent and 43 percent, respectively.

When the recurrences were stratified by location, some differences became apparent (Table III). Metastasis-free survival rates were statistically higher for patients with subcutaneous tissue recurrence than chest wall recurrence (2-year and 5-year survival: 52 percent and 42 percent versus 24 percent and 24 percent; $p = 0.04$). Overall survival rates were also higher for patients with subcutaneous tissue recurrence, but these results were not statistically significant ($p = 0.62$). Subcutaneous recurrences were also associated with a lower rate of metastasis (57 percent versus 91 percent; $p = 0.04$) and better estimated median overall and metastasis-free survival rates, although of the survival differences, only the metastasis-free survival was significant (Table IV and Fig. 3). In both groups, the time to detection of the recurrence was similar (subcutaneous tissue recurrence, 27.1 months, versus chest wall recurrence, 29.5 months). Second local recurrences were detected in six (15 percent) of the 39 patients (five with subcutaneous tissue recurrences and one with a chest wall recurrence).

At the end of the follow-up period, 12 of the 39 patients (31 percent) remained free of disease after treatment of their recurrence. Of these, 11 had a subcutaneous tissue recurrence and one had a chest wall recurrence. Only one of the 12 patients (9 percent) in the chest wall recurrence group was free of disease at a mean follow-up of 70 months, whereas 11 of the 28 patients (39 percent) with subcutaneous tissue recurrence were disease-free at similar follow-up. There were no differences in survival within the treatment groups (operation/radiotherapy, operation/chemotherapy, operation/chemotherapy/radiotherapy, or other combinations), although the numbers in each group were too small for meaningful comparison.

Discussion

The results of this study confirm that those patients in whom recurrent breast cancer develops immediately after reconstruction are indeed at high risk for the subsequent development of systemic disease; this level of risk is similar to that for patients who never undergo reconstruction. However, the prognosis seems to differ when the recurrence is located in the subcutaneous tissue or the skin compared with

TABLE II
Reconstructions Performed and Recurrence, by Reconstructive Option

	Recurrence Site				
Reconstructive Option	Skin or Subcutaneous Tissue	Chest Wall	Totals	Reconstructions Performed during Study Period	Incidence of Recurrence (%)
Transverse rectus abdominis myocutaneous flap	18	7	25	1191	2.1
Tissue expander/implant	6	4	10	351	2.8
Latissimus dorsi myocutaneous flap without implant	2	0	2	88	2.3
Latissimus dorsi myocutaneous flap with implant	2	0	2	64	3.1
Total	28	11	39	1694	2.3

TABLE III
Two-Year and Five-Year Survival Rates and Metastasis-Free Survival Results

	Overall Survival (%)		Metastasis-Free Survival (%)	
	2 Years	5 Years	2 Years	5 Years
All local recurrences	75*	43	38†	31
Subcutaneous recurrence	80*	45	52†	42
Chest wall recurrence	64*	45	24†	24

* $p = 0.62$.
† $p = 0.04$.

tumors that recur in the deeper tissues of the chest wall. Our study found that patients with subcutaneous recurrences had a lower chance of having metastases develop, a better overall survival rate, and a greater likelihood of remaining free of disease once the recurrence was treated than did patients with chest wall recurrences. (Only the metastasis-free survival rate was statistically significant, but a trend toward a better overall prognosis with a superficial recurrence was apparent.) These findings raise several questions, not the least of which is whether a legitimate biological difference in prognosis exists depending on location of the recurrence.

According to some investigators,[4,5,10,14–18] any reappearance of breast cancer in the vicinity of the original mastectomy site is a chest wall or locoregional recurrence, and distant systemic metastases will also develop in nearly all of these patients before, concurrent with, or subsequent to the local recurrence. Inadequate surgical excision of the tumor is not thought to be responsible for most local recurrences, because even the Halsted radical mastectomy, which removes breast skin and pectoralis major muscle, does not completely eliminate the risk of recurrence.[4,10] In fact, long-term follow-up of Halsted's original series demonstrated a recurrence in 31.9 percent of patients.[19] The extent of resection is, therefore, not the chief determinant of recurrence.[2] Furthermore, locoregional recurrences can range from mastectomy scar nodules to internal mammary nodal disease, and it is perhaps simplistic to believe that a single mechanism is responsible for the behavior of such different recurrences.[20] Toonkel et al.[21] show that mastectomy scar recurrences actually had poorer local control rates than did chest wall recurrences—but no effect on the patient's survival. Our findings also suggest that subcutaneous tissue and chest wall recurrences lead to different prognoses, but that *chest wall recurrences* are more likely to be associated with metastasis and death.

Several factors are known to influence whether breast cancer recurs after mastectomy, but the most important seems to be the pathologic status of the axillary lymph nodes at the time of the mastectomy.[10,16,22] This has been substantiated by the finding in some studies after radical mastectomy that local recurrence jumped from 3 to 8 percent to 19 to 27 percent when nodal disease was present.[10] Other important factors are the size of the primary tumor, histologic grade of the tumor, presence of skin fixation or clinical invasion, gross invasion of the deep fascia, ulceration of the skin, breast edema, and administration of adjuvant therapies, especially radiation. In this study, radiation did not seem to be associated with a survival difference or a change in the location of local recurrence. Of the 28 patients with subcutaneous recurrences, three (approximately 11 percent) received radiotherapy immediately after their mastectomy based on the initial report of the pathologic findings, whereas two of the 11 patients (18 percent) with deeper recurrences had adjuvant radiotherapy. Interestingly, whether the skin resection is limited to a skin-sparing mastectomy or involves more extensive removal does not seem to influence the local recurrence rate.[23–28]

Many other prognostic variables were similar in the two groups in our study, suggesting that a recurrence had similar chances of developing in these patients. In particular, the disease-free interval measured from the time of mastec-

TABLE IV
Survival Differences

			Developed Metastasis		Estimated Median Overall Survival (mo)	Estimated Median Metastasis-Free Survival (mo)
Recurrence Site	*n*	%	*n*	%		
Subcutaneous	28	72	16	57*	60	28
Chest wall	1	28	10	91*	27	10
All local recurrences	39	100	26	67	47	20

* $p = 0.04$.

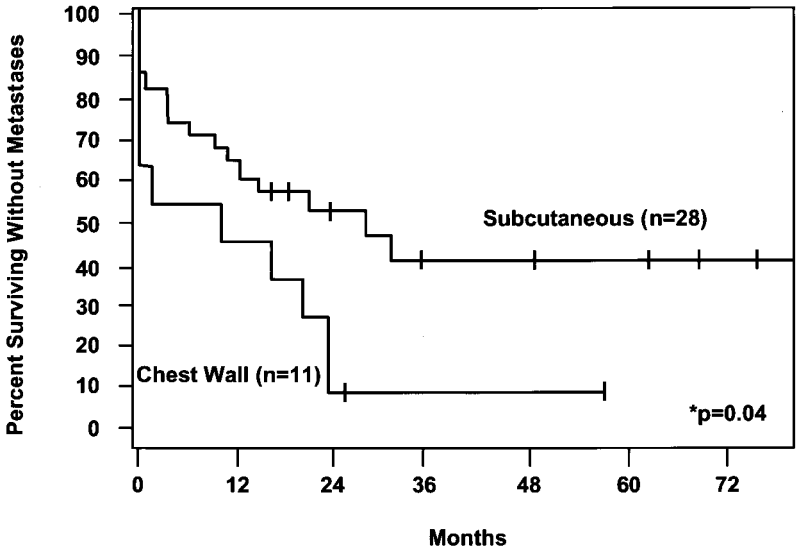

FIG. 3. Kaplan-Meier plot of metastasis-free survival rates by location of breast cancer recurrence.

tomy is thought to be an important prognostic variable.[1,6,20,22,29–31] In this study, the disease-free intervals were similar, giving the patients in each group an approximately equal likelihood of surviving their relapse. Moreover, once recurrence developed, all patients in this study underwent surgical excision, chemotherapy, radiotherapy, or a combination of these treatments to obtain local control of their tumors. Whether one of these methods better controlled the recurrence locally was unable to be specifically evaluated in this study because of the small number of patients who had recurrences, although overall the survival rate was similar. It is unlikely that the choice of one method or another would have influenced the results dramatically, because all patients had been given the "best available treatment" for local control, and all of these methods are roughly similarly effective in eradicating recurrent disease, regardless of technique.

The treatment of locally recurrent breast cancer following reconstruction is not clearly defined. Some investigators have advocated the complete removal of a TRAM flap or an implant along with its periprosthetic capsule, but most have practiced a form of simple reexcision with removal of as much reconstructed tissue as necessary to achieve negative margins. A common strategy now routinely practiced at our institution is surgical resection of the recurrence, followed by a course of adjuvant radiotherapy. If the recurrence is located in the deeper tissues of the chest wall, especially in the sternum and ribs, some data suggest that controlling this "isolated metastasis" (probably originating in the mammary chain nodes) can result in a substantial improvement in the survival rate.[4,10,20,22,32–35] This supports the theory that such recurrence is the only site of disease in some patients, not a universal marker for widespread disease, as some investigators once thought.

As expected, most recurrences in this study were in either the skin or the subcutaneous layer and were detected by physical examination. It could be argued that such recurrences might be more easily detected in patients who have undergone immediate reconstruction, because such patients are followed up frequently as part of their postoperative care, and they may be more motivated to pay attention to changes in their reconstructed breast than in an unreconstructed mastectomy site. A great deal of input from patients is often required after the initial reconstruction to achieve a satisfactory aesthetic result. Furthermore, the reconstruction may push the subcutaneous layer toward the skin surface, compressing the nodule against the skin and improving the ability to detect the nodule. The same cannot be said about chest wall recurrence, although recurrences in the pectoralis major may be more readily detectable in subpectoral implant reconstructions as a result of the anterior shift of the muscle. TRAM flaps have the potential to conceal deeper chest wall recurrences, although many reports have stated that this ei-

ther does not happen or happens very infrequently.[11,12,36–40] In our study, chest wall recurrences and subcutaneous tissue recurrences were detected after similar intervals, suggesting no notable delay in the detection of chest wall recurrences. However, it is known only when these recurrences were found, not when they began to develop, and it is possible that chest wall recurrence started developing earlier and was concealed longer than subcutaneous tissue recurrence. The more important question is whether earlier detection of the chest wall recurrences is clinically meaningful, because if these recurrences are routinely associated with distant spread, then finding them earlier is not likely to influence the patient's survival. In fact, our results showed a strong association between chest wall recurrence and metastasis, and only one of our patients with a chest wall recurrence has survived without further disease. As treatment of metastatic disease improves, simply knowing that chest wall recurrence is a marker for distant spread might prove useful, but, currently, whether it is detected before or after metastasis does not seem to matter.

One explanation for the difference between recurrences in subcutaneous tissue and those in the chest wall is that they result from distinctly different processes. Possibly, some of the subcutaneous tissue recurrence might actually result from either retained breast tissue or unexcised tumor at the mastectomy site. This would easily explain a recurrence in the mastectomy scar itself; it makes more sense biologically that retained tumor cells cause the recurrence rather than that circulating tumor cells just happen to begin growing at the scar. Therefore, it is reasonable to assume that at least some of the patients in our study had subcutaneous tissue recurrences because of unrecognized cancer at the original site or because of residual breast tissue that later became malignant.

The low rate of recurrence in this study may reflect patient selection, because patients who are more prone to having a recurrence are often not encouraged to undergo reconstruction. It is also possible that a recurrence developed in some patients who were treated elsewhere, although most of our patients are observed closely and participate in studies that require them to continue their care at this institution. At the very least, the rate of local recurrence of breast cancer does not seem to be higher in patients who undergo immediate reconstruction than it is in those who do not.[11,13,23–28,36,39,41,42] Also, there is a remote possibility that reconstruction has a salutary effect on breast cancer recurrence, much the way a well-vascularized flap improves the health of irradiated or infected sites; this is the subject of an ongoing investigation at our institution.

How one should search for a local recurrence following reconstruction is still a matter of debate. Simple physical examination revealed most subcutaneous tissue recurrences and even some of the chest wall recurrences in this study. Only a few lesions were so deep that they required mammographic detection, and some were found using ultrasonography, computed tomography, or magnetic resonance imaging when pain or other symptoms indicated that further investigation was necessary. It is unknown whether routine mammography should be performed on patients with TRAM flaps or implants to search for recurrences, although some investigators advocate that practice.[43–46] The most logical use of mammography is for examining patients whose original tumor appeared as microcalcifications on a mammogram, such as with ductal carcinoma in situ.[47,48] Both computed tomography and magnetic resonance imaging have been used for follow-up examinations of reconstructed breasts with some success, but these expensive techniques are infrequently used as screening tools.[49–51] At our institution, mammography is not part of the routine follow-up of patients with reconstructed breasts; physical examination and directed imaging studies are chosen instead. We often perform an ultrasound-directed needle biopsy or a fine-needle aspiration biopsy on suspicious lesions, after which we most often find fat necrosis or scar tissue.

Although published reports suggest that any locoregional recurrence of breast cancer is nearly universally associated with metastasis and death, this study of patients who had undergone immediate reconstruction after mastectomy demonstrated that skin and subcutaneous recurrences are less likely to metastasize than deeper chest wall recurrences. Subcutaneous recurrences actually may not result from circulating tumor cells beginning to grow at the mastectomy site but rather from recalcitrant tumor cells that were separate from the otherwise adequate resection. Chest wall recurrences, as defined in this study, were more highly correlated with metastasis than subcuta-

neous tissue recurrences and were not as likely to have been influenced by earlier detection. Therefore, we suggest that local recurrences of breast cancer are not all the same, especially after immediate reconstruction. Our data further support the continued use of immediate breast reconstruction without fear of concealing a recurrence or influencing the oncologic outcome.

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