Using Complications Associated With Postmastectomy Radiation and Immediate Breast Reconstruction to Improve Surgical Decision Making

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Objectives: To identify factors independently associated with surgical complications in oncologic and reconstructive surgery and to examine sentinel lymph node (SLN) biopsy data, along with variables that are typically known prior to definitive resection, for their ability to impact the prediction of need for postmastectomy irradiation (PMRT).

Design: Retrospective review.

Setting: University hospital.

Patients: Mastectomy patients with stage I to III breast cancer treated in 2000 to 2008.

Main Outcome Measures: Complication rates of oncologic and reconstructive surgery requiring reoperation and clinicopathologic variables that independently predict complications and/or PMRT administration by multivariate analysis.

Results: Among 100 of 302 mastectomy patients who underwent PMRT, complications occurred in 44% who underwent immediate breast reconstruction (IBR) and 7% who did not (P < .001). Postmastectomy irradiation independently predicted the occurrence of a complication (odds ratio, 3.3; P < .001). Implants were removed in 31% of patients who underwent PMRT and 6% of patients who did not (P = .005). Three percent of patients with T2 or smaller tumors and zero positive SLN required PMRT. Among those with T2 tumors, 49% with a positive axilla lymph node underwent PMRT. Independent predictors of PMRT need were T2 vs T1 tumors, positive axillary lymph node status, and the number of positive SLNs, with odds ratios of 5.8 (P < .001), 14.5 (P < .001), and 2.1 (P = .001), respectively.

Conclusions: Postmastectomy irradiation was associated with a high rate of surgical complications and implant loss among patients who underwent IBR. Determining the number of positive SLNs prior to definitive resection and reconstructive operations may reduce complications and implant loss by guiding surgical decision making. Patients with a negative SLN are unlikely to require PMRT. Those with positive SLN(s) are high-risk IBR candidates with a quantifiable PMRT risk.

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See Invited Critique at end of article

In women with low-stage breast cancer, rates of mastectomy, immediate reconstruction, and postmastectomy irradiation (PMRT) are increasing. These developments magnify an ongoing debate centered on the extent to which PMRT negatively impacts breast reconstruction and which reconstructive strategies can best ameliorate the negative impact of PMRT on the complication rate and cosmetic outcomes. Furthermore, concerns have been raised regarding the impact of reconstructive options on the optimal delivery of PMRT and breast cancer survival. A different oncologic approach that gathers lymph node (LN) data prior to mastectomy may improve surgical decision making because the risk of PMRT would be incorporated into the surgical plans for reconstruction.

Indications for PMRT according to the American Society of Clinical Oncology (ASCO) are a tumor greater than 5 cm and/or greater than 3 positive axillary LNs. At our institution, women who have an indication for PMRT prior to mastectomy, and those deemed likely to require PMRT, are cautioned that immediate breast reconstruction (IBR) is associated with a high complication rate and potentially compromised cosmetic outcome. However, 1 in 5 women with a 1- to 2-cm tumor and nonpalpable LNs have at least 1 pathologically positive LN, and this rate is even higher among premenopausal women, in whom the benefit of PMRT may be greater. Therefore, predicting whether PMRT will be indicated is difficult for the
most common clinical presentation. Additionally, women with tumors near 5 cm, those with aggressive biology, or those who are premenopausal are difficult to assign a risk of whether PMRT indications will be met. Further complicating the risk assessment are data demonstrating that some women with 1 to 3 positive LNs may benefit from PMRT.4,6

Axillary LN metastasis is one of the most important determinants of PMRT need. Postmastectomy irradiation has a significant negative impact on reconstructive surgery outcomes and complication rates.7,12-16 Yet, in a majority of patients, surgical decisions regarding the extent of resection and breast reconstruction are made without axillary LN data because axillary staging is performed concurrently with definitive cancer resections. A sentinel lymph node biopsy (SLNB), undertaken as a separate outpatient diagnostic procedure prior to definitive resection or reconstruction, would be 1 way to obtain LN data prior to definitive surgery. While it would not provide complete axillary LN staging, we wish to examine to what extent the need for PMRT could be predicted by LN data collected by SLNB.

The validity of such a strategy is predicated on 2 assertions that we sought to examine in this study. First, the combination of IBR and PMRT must be associated with sufficiently frequent poor outcomes to justify the separate diagnostic intervention. Second, the knowledge gained by the early SLNB must adequately predict PMRT administration such that surgical decision making is meaningfully affected. If these contentions are both true, then an early SLNB may reduce surgical complications.

To address the first contention, our institution’s experience with mastectomy and breast reconstruction was analyzed to identify factors independently associated with surgical complications. To address the second contention, SLNB data, along with variables that are typically known prior to definitive resection, were examined for their ability to impact the prediction of PMRT need.

METHODS

The institutional cancer registry was used to identify consecutive women treated or diagnosed with a primary nonmetastatic breast cancer at Oregon Health & Science University after November 1999 who underwent mastectomy. Patients with bilateral breast cancer were excluded. Clinicopathologic data were collected from the medical records. Surgical complications that required an additional operation were recorded. The type of breast reconstruction was categorized as autologous tissue transfer, 2-staged reconstruction with tissue expander, or implant reconstructions. A concurrent combination of both tissue and implant reconstructions was categorized as autologous tissue transfer requiring an additional operation were recorded. The variable axillary LN metastasis was limited to patients with T1 or T2 tumors without contraindication to SLNB (n=254). The variable axillary LN status, in contrast, was derived from patients who either had axillary LN dissection and/or SLNB.

RESULTS

Three hundred two women had sufficient medical records available for inclusion. Median follow-up was 31 months (range, 1-101 months).

OPERATIONS

Axillary Operations

One-hundred eighty-three patients (60%) underwent SLNB, of whom 108 (59%) had a final diagnosis of negative for malignancy. Sixty-five SLNB specimens had 1 or more positive SLNs on frozen section analysis. Ten patients whose SLNB specimens were negative on frozen section analysis had a change in diagnosis to positive for malignancy on permanent sections and required a second operation for completion axillary LN dissection. Thus, the false-negative rate of frozen section analysis was 8% (10 of 118).

Reconstructive Operations

One hundred fifty-two patients (50%) underwent breast reconstruction, with IBR performed in 131 patients. Significantly more tissue expander reconstructions were performed in the IBR group (P = .004). Table 1 indicates the type and timing of reconstruction as well as PMRT administration subgroups.

COMPLICATIONS

Complications requiring a return to the operating room occurred in 39 of 302 patients for an overall operative complication rate of 13%. Operative follow-up was not available for 32 patients, 26 of whom underwent PMRT.

Using univariate analysis, complication rates varied by PMRT and whether a reconstructive operation was performed, but not by histological examination results; menopausal status; estrogen receptor, progesterone receptor, or human epidermal growth factor 2 status; or timing of chemotherapy. Trends toward increasing complications with smoking history and increasing T category, N category, and histological grade were present but did not meet statistical significance.

As seen in Table 1, IBR was associated with significantly more complications than no reconstruction. A complication rate of 42% associated with IBR followed by PMRT was significantly higher than the 16% complica-
Complications in the PMRT group who underwent reconstruction are shown in Table 2. The tissue expander/implant loss rate with IBR was 31% among those who underwent PMRT and 6% among those who did not (P = .005). As displayed in Table 3, logistic regression identified PMRT and breast reconstruction as independent predictors of an operative complication for the study population (n=302).

**PREDICTIVE MODELING FOR PMRT**

One hundred patients underwent chest wall PMRT. Actual PMRT administration and ASCO-recommended PMRT administration differed in 32 patients. Seventy-eight of 90 women (86%) who met ASCO-recommended indications underwent irradiation. Postmastectomy irradiation was administered to 20 patients who did not meet ASCO-recommend PMRT indications (20%); a majority of these women were premenopausal with moderately or poorly differentiated tumors that were T2 or greater in size.

Among patients with at least 1 positive axillary LN (n=149) determined by SLNB specimen or axillary LN dissection, PMRT rates for T1, T2, T3, and T4 tumors were 20%, 55%, 100%, and 79%, respectively. Among patients who underwent SLNB (n=183), Table 4 delineates the portion of patients who underwent PMRT according to the number of positive SLNs and T category. None of the 10 patients with a false-negative SLNB specimen subsequently received PMRT.

Table 5 displays independent variables identified by backward logistic regression that were significantly associated with PMRT administration in patients who were candidates for SLNB (n=254). No variable interactions were significant.

**COMMENT**

Postmastectomy irradiation and IBR were each identified as strong independent predictors of complications. Postmastectomy irradiation tripled the risk for an unplanned return to the operating room and IBR increased that risk 8-fold. The combination of IBR and PMRT resulted in nearly 1 of 2 patients returning to the operating room with complications compared with 7% of patients who received PMRT but did not undergo reconstruction.

Two-staged reconstruction offers the benefit of a relatively quick procedure at the initial operation, saves tissue reconstruction as a later option, and can allow expander deflation prior to PMRT so as not to impact PRMT fields. However, Alderman et al, with 2 years of follow-up, reported a 46% complication rate for similarly treated pa-
Wani et al reported that radiation treatment plans after IBR negatively impacts the delivery of PMRT. Mot-failure of reconstruction, there is considerable concern about results with IBR if PMRT may be administered. These results highlight the need for a clear strategy regarding the optimal type of IBR when PMRT is performed or was declined by the patient. Complication rates among patients with tissue expander reconstruction who underwent PMRT were significantly higher than those who did not undergo PMRT, similar to that reported in the literature and, in our view, unacceptably high.

Furthermore, in this series, 31% of women who underwent PMRT required removal of the tissue expander or implant within 3 years. This represents complete failure of reconstructive efforts in almost 1 in 3 women because a subsequent reconstructive operation either could not be performed or was declined by the patient. Complication rates among patients with tissue expander reconstruction who underwent PMRT were significantly higher than those who did not undergo PMRT, similar to that reported in the literature and, in our view, unacceptably high.

Autologous tissue IBR with PMRT did not confer a significant improvement in the complication rate compared with 2-staged reconstruction, although there was a trend toward lower complication rates with autologous tissue (29% vs 44%). The literature is widely disparate regarding the optimal type of IBR when PMRT is administered. These results highlight the need for a clear discussion with patients regarding the inconsistent results with IBR if PMRT may be administered.

Besides significant rates of unplanned reoperation and failure of reconstruction, there is considerable concern that IBR negatively impacts the delivery of PMRT. Motwani et al reported that radiation treatment plans after IBR were compromised in 52% of patients compared with 7% of patients who did not undergo IBR. Huang et al reported that the recurrence rates with or without autologous tissue IBR were not different. However, Nahabedian et al reported a statistically significant difference in recurrence rates of 27% for patients who underwent PMRT and IBR compared with 19% among patients with similarly staged disease who underwent delayed reconstruction, but they lacked sufficient numbers to demonstrate whether the finding was stage specific. The length of follow-up and lack of sufficient statistical power in the current study prevented evaluation of these important outcomes.

Because the complications of IBR may be considered prohibitive when a patient is at high risk for PMRT, delayed reconstruction is the recommended approach by several authors. Spear et al also found no increase in complication rates between IBR and delayed reconstruction in the setting of PMRT, but among patients undergoing delayed reconstruction, they found improved cosmetic results. The Michigan Breast Reconstruction Outcome Study, the only multicenter prospective study, to our knowledge, demonstrated IBR had a 2-fold increased odds for complications compared with delayed reconstruction by multivariate logistic regression. Based on these results, delayed reconstruction is an attractive alternative in women who are at high risk for PMRT.

The approach at our institution is to avoid autologous tissue IBR in patients at high risk for PMRT. Despite this, 7 of 39 patients, nearly 20%, who were considered at low enough risk for PMRT to undergo IBR with tissue required PMRT once final pathology results were available. Therefore, predicting PMRT more accurately would permit avoidance of IBR and its PMRT-associated complications, potentially decreasing the rate of unplanned operations. Conversely, some women are unnecessarily directed away from IBR because of an overestimation of their risk for PMRT. In this series, 12 of 22 patients (55%) who underwent delayed reconstruction did not undergo PMRT. Thus, the strategies currently used to avoid the administration of PMRT to women considering reconstruction may be overapplied, preventing women from undergoing a single-staged procedure at the time of mastectomy.

A strategy is needed that improves the prediction of PMRT so that the combination of IBR followed by PMRT can be avoided but IBR is not denied to patients who are at low risk for PMRT. The second aim of this study was to explore whether the need for PMRT can adequately be predicted prior to making surgical decisions with data obtained from SLNB. We found that negative axillary node status in patients with T1 and T2 tumors predicted 1% and 8% rates of PMRT administration, respectively. Thus, negative axillary LN status was a nearly perfect predictor of not receiving PMRT.

Knowledge of negative axillary LN status prior to undergoing delayed or 2-staged reconstruction could therefore allow many women to consider IBR instead. In the

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### Table 4. PMRT Administration According to T Category and SLN Data

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>No. Positive SLN</th>
<th>1 Positive SLN</th>
<th>2 Positive SLNs</th>
<th>3 Positive SLNs</th>
<th>4 Positive SLNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>100</td>
<td>1/75 (1)</td>
<td>1/17 (6)</td>
<td>1/6 (17)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>T2</td>
<td>61</td>
<td>2/26 (8)</td>
<td>3/16 (19)</td>
<td>10/15 (67)</td>
<td>2/2 (100)</td>
</tr>
<tr>
<td>T3</td>
<td>20</td>
<td>4/6 (67)</td>
<td>9/9 (100)</td>
<td>4/4 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>T4</td>
<td>2</td>
<td>1/1 (100)</td>
<td>0/1 (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; PMRT, postmastectomy irradiation; SLN, sentinel lymph node.

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### Table 5. Predictors of PMRT Among Candidates for SLNB

<table>
<thead>
<tr>
<th>Covariate</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 vs T1</td>
<td>5.8 (2.4-13.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Positive axillary lymph node status</td>
<td>14.5 (4.8-43.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Per positive SLN</td>
<td>2.1 (1.4-3.2)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio; PMRT, postmastectomy irradiation; SLN, sentinel lymph node, SLNB, sentinel lymph node biopsy.
setting of no PMRT, IBR has low complication rates, consistently high patient satisfaction rates, and potential for a single-stage mastectomy and reconstruction. Conversely, 10% of patients with T1 and 55% with T2 tumors received PMRT when 1 or more SLNs were positive or the axilla was clinically positive.

By multivariate analysis, positive axillary LN status increased the risk of PMRT 15.5-fold. Each positive SLN increased the risk of PMRT 2.1-fold. Therefore, while the data gained from a positive SLNB specimen do not yield a final answer as to whether indications for PMRT will be met, it does quantify a significant risk for PMRT that should be considered during surgical decision making. A validated nomogram, such as the one developed by Van Zee et al., could be used to further estimate the risk of additional positive nodes prior to undertaking reconstruction, thereby shedding further light on the risk for PMRT-associated complications of reconstruction.

For patients considering breast reconstruction, performing an SLNB as a separate procedure prior to final decision making is feasible. This approach would involve performing an SLNB as an outpatient procedure, foregoing frozen section analysis, and incorporating final SLNB pathology results in multidisciplinary discussion. Using a data set with more than 4000 patients, Chagpar et al. developed a scoring system to be used intraoperatively, using 1 category, the number of positive SLNB specimens, and the ratio of positive to negative SLNs, that correlated well with whether 4 or more positive LNs would be identified on final pathology results. When SLN pathology results with immunohistochemical results were used, rather than frozen-section hematoxylin-eosin SLN results, the predictive strength of the model was improved from an area under the receiver operating characteristic curve of 0.754 to 0.882. Thus, having final immunohistochemical pathology data available significantly improved the prediction of whether PMRT would be needed from the prediction possible by intraoperative pathology results alone.

It has been established that SLNB can be done as an outpatient procedure with negligible morbidity in an average of 30 minutes. Additionally, unplanned return to the operating room for completion axillary LN dissection after false-negative intraoperative frozen section analysis results would be eliminated. Last, in a small prospective study, reconstructive decisions were modified in 8 of 13 patients who underwent SLNB as a separate procedure prior to mastectomy.

Limitations of this study include the fact that some patients were treated with PMRT outside of ASCO guidelines. This may have introduced bias because it reflects preferences of the institution, radiation oncologist, and other patient factors. Data regarding extracapsular extension, lymphovascular invasion, and the size of the metastatic deposit were not collected in this study but may improve the prediction of whether PMRT indications will be met. Their inclusion may have added insight into factors that predict PMRT administration and warrant further review, but because an early SLNB would be necessary to establish these data points, their inclusion would only strengthen our contention that an early SLNB may better inform surgical planning.

While the results demonstrate PMRT is an independent predictor of complications requiring a return to the operating room, a portion of the complications in the PMRT group occurred before its administration. This raises the possibility that there is not a direct causative link between PMRT and the complication rates found in this study and others. However, meeting PMRT indications, ie, having more advanced cancer, was a marker of an increased propensity for complications. This is supported by the fact that the complication rate was higher in the PMRT group who did not undergo reconstruction as well as trends of increasing complications with increasing histological grade and T and N categories. Additionally, complication rates in the PMRT group may be underestimated because of significantly less operative follow-up in this group, reflecting a referral pattern at a tertiary cancer center from surgeons in the community to the Department of Radiation Oncology. A larger, prospective study would be needed to establish PMRT as a causative, not just associated, factor in complications.

This study determined that PMRT after IBR was associated with high complication rates. A strategy to decrease the coincidence of IBR and PMRT is therefore warranted. Knowledge of axillary LN status significantly contributed to the accurate prediction of PMRT. For patients considering breast reconstruction in whom an indication for PMRT has not already been met, an early SLNB done prior to mastectomy as an outpatient diagnostic procedure would provide crucial prognostic data and meaningfully inform surgical planning. Patients with a negative SLN would be reassured that their risk with IBR is low. Patients with a positive SLN would be identified as having a higher, quantifiable risk of meeting PMRT indications.

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Start by Decreasing Unnecessary Postmastectomy Irradiation

The Christante et al article describes the effect of IBR and postmastectomy chest wall irradiation on postmastectomy complication rates. For patients with no reconstruction, complication rates rose with PMRT from 3% to 7%. For delayed reconstruction, complication rates rose with PMRT from 0 of 12 patients to 2 of 9 patients. For the patients who underwent IBR, complication rates rose with PMRT from 16% (16 of 98) to 42% (14 of 33). To avoid IBR in patients who will have PMRT, they suggest doing IBR only in SLNB-negative patients and those with T1 tumors. Unfortunately, they do not provide the preoperative primary tumor and SLN information to validate this recommendation. The recommendation is too restrictive and would require all potential IBR patients to have an additional operation prior to mastectomy.

A recent review by Kronowitz and Robb showed very similar results and reported a reduction in the complication rates of IBR followed by PMRT by placing an expander at the time of mastectomy, deflation of the expander at the time of PMRT, limiting PMRT to necessary patients and doses, and use of autologous tissue transfer following PMRT. They noted that optimal cosmetic breast reconstruction occurs with preservation of breast skin, which takes much longer to perform and has a higher risk of tissue necrosis. These approaches to optimize reconstruction and limit complications when PMRT is added have not been used in the Christante et al report. Further, more than one-third (6 of 16) of the complications in the patients who underwent IBR and PMRT occurred before the PMRT had been administered. These cannot be attributed to the PMRT-IBR combination.

Current guidelines recommend that patients with a primary tumor more than 5 cm (T3) and/or with 4 or more positive nodes (N2, N3) have PMRT. This recommendation is based on several prospective studies of patients who underwent total mastectomy in the 1970s and...