

## BREAST CANCER STUDY CASE

### Scenario A

Carol Edwards, a 39 year-old premenopausal woman, had a screening mammogram which revealed an abnormality in the right breast. She had no palpable masses on breast exam. A mammographically localized surgical biopsy was done and revealed a **small (0.9 cm) grade III infiltrating ductal carcinoma with some associated ductal carcinoma-in-situ (DCIS)**. The surgical **margins were not clear** (cancer cells were found at the posterior margin). **Estrogen and progesterone receptors are negative**.

The patient has been given the diagnosis in a telephone conversation with the surgeon a few days after the biopsy, and they are now meeting to discuss definitive treatment. **Surgical treatment must address two issues: local control and staging.**

**LOCAL CONTROL** can be achieved by **mastectomy** or by **wide re-excision** (known as “lumpectomy” or partial mastectomy) **followed by radiation** to the breast. The latter is known as breast conservation therapy (BCT) and it is imperative that margins be clear and cosmetic results acceptable to the patient to qualify for this option. In addition to this, there must be unifocal disease only, not multicentric cancers. If there are multiple foci of carcinoma, the patient should have a mastectomy.

Following healing, radiation to the remaining breast tissue is generally administered over a 6 week period (5 days/week). Side effects are minimal, consisting of fatigue and some local swelling and minor soreness of the breast with associated erythema (and occasionally sloughing of the epidermis which will heal). If chemotherapy is required, the radiation is scheduled to follow the completion of the chemotherapy; radiation and chemotherapy are not, as a rule, administered concomitantly. Radiation following total mastectomy is only recommended in select cases – in patients with inflammatory breast cancer and in patients with locally advanced disease (as manifested by tumor size >5 cm and/ or with 4 or more positive nodes).

**SURGICAL STAGING** (to determine if there are regional metastases) is done by axillary lymph node dissection (ALND). There are no radiologic methods to reliably detect nodal metastases; microscopic confirmation must be achieved by removing some of the axillary nodes. Axillary node status is the single most important prognostic factor in determining breast cancer survival. Regardless of which local control option is desired, mastectomy or lumpectomy with radiation, ALND should be done. In this particular patient the information is especially important as it will determine whether or not adjuvant chemotherapy will be recommended. Because her hormone was hormone receptor-negative, the use of tamoxifen is not an option. For patients with tumors that have a favorable prognosis (as defined by size smaller than 1 cm and negative nodes) the potential benefits of adjuvant chemotherapy are probably outweighed by the risks. However, if nodes are positive, chemotherapy should improve survival.

The information in bold type below is from **UpToDate**:

**INTRODUCTION** – The lymphatic drainage pathways of the breast (axillary, internal mammary [IM], and supraclavicular nodal groups) are the regional areas most likely to be involved with metastatic breast cancer.

**RISK FACTORS FOR AXILLARY NODE INVOLVEMENT** – The axillary lymph nodes (ALNs) receive 85 percent of the lymphatic drainage from all quadrants of the breast; the remainder drains to the IM chain. The likelihood of ALN involvement is related to tumor size and location, histologic grade, and the presence of lymphatic invasion.

**Tumor size and margins** – The likelihood of ALN involvement increases as the size of the primary tumor increases. In one series of 2282 women with invasive breast cancer or ductal carcinoma in situ (DCIS), the incidence of ALN involvement was as follows:

- Tis – 0.8 percent
- T1a – 5 percent
- T1b – 16 percent
- T1c – 28 percent
- T2 – 47 percent
- T3 – 68 percent
- T4 – 86 percent

ALN metastases are relatively common even with invasive breast cancers 1 cm in size. In a second report of 919 such women who underwent ALN dissection (ALND); ALN metastases were detected in 16 and 19 percent of those with T1a (tumor size between 0.1 and 0.5 cm in greatest dimension) and T1b tumors (tumors between 0.5 and 1.0 cm), respectively. Many database series report a higher rate of ALN metastases for T1a than T1b disease. The higher rate in this group may be related to multifocal disease in DCIS, undersampling of the primary tumor, or high grade microinvasive carcinoma.

Nodal positivity rates are also higher in women who are found to have residual tumor after reexcision for positive margins following lumpectomy for breast conservation therapy (BCT). In one series, women with T1b tumors who had residual disease were significantly more likely to harbor ALN metastases than those whose tumors were either excised to a negative margin initially or who had negative reexcisions for an initially positive margin (36 versus 5 percent).

**Histologic features** – Low grade (grade 1) tumors have a significantly lower rate of ALN metastases compared to grade 2 or 3 tumors. As an example, in data derived from the Surveillance, Epidemiology and End Results (SEER) database, the incidence of ALN disease in patients with grade 1 and grade 3 tumors of similar size was 3.4 and 21 percent, respectively. The presence of lymphatic invasion also increases the risk of ALN metastases.

**Tumors that are associated with a less than 5 percent risk of ALN metastases include those with a single focus of microinvasion, <5 mm grade 1 tumors without lymphatic invasion, and pure tubular carcinomas <1 cm.**

**Tumor location — ALNs are more commonly involved with tumors involving the lateral rather than the medial portion of the breast. As an example, in a series of 8422 patients enrolled on International Breast Cancer Study Group trials between 1978 and 1999, the rate of node-negativity for medial compared to lateral/central tumors was 44 versus 33 percent, respectively. The most likely explanation for this difference is preferential drainage of some medial tumors to the IM nodes.**

As with all surgical procedures, there are some risks associated with breast surgery. At the lumpectomy site, the patient may develop a postoperative wound infection or hematoma, but the likelihood is small. These complications can be seen with mastectomy as well. Development of a persistent postoperative fluid collection (known as a seroma) is also a possibility.

Two major motor nerves reside in the axilla, the long thoracic nerve, which innervates the serratus anterior, and the thoracodorsal nerve, which innervates the latissimus dorsi. The likelihood of injury to these is extremely small. Intercostobrachial nerves traverse the axilla as well, supplying sensation to the skin of the axilla and posterior upper arm. These may be divided or otherwise injured during the node dissection, resulting in temporary or permanent numbness.

However, the most feared and significant complication associated with ALND is the development of lymphedema of the upper extremity. This condition occurs in approximately 10-15% of those who undergo ALND and can occur shortly after surgery or several years later. This swelling is felt to be secondary to impeded

lymph flow through the scarred nodal basin and is often triggered by a break in the skin or some other type of inflammation which results in extra fluid in that extremity. The degree of lymphedema is variable but it can be difficult to treat successfully. Patients are urged to avoid injections, phlebotomy and placement of venous catheters in that extremity, and must be encouraged to exercise extra caution while performing simple tasks in the kitchen, the garden or at work to avoid breaks in the skin.

**Arm morbidity — Shoulder stiffness, and numbness and paresthesias in the upper arm are common complaints following ALND; although they do not usually interfere with daily living, they may impact on quality of life (QOL). In one series, 42 percent of women had subjective or objective arm impairment (eg, pain, reduced grip strength) one year postoperatively. The likelihood of arm edema is higher in women who undergo more extensive ALND, and combined axillary surgery and RT. The use of SLN biopsy is associated with fewer arm complications than full ALND.**

**SENTINEL NODE BIOPSY — According to the sentinel lymph node (SLN) hypothesis, tumor cells migrating from a primary tumor colonize one or a**

few lymph nodes (LNs) before involving other LNs. Peritumoral injection of a vital blue dye permits identification of an SLN in the majority of patients, and its status accurately predicts the status of the remaining regional LNs.

The concept of lymphatic mapping and SLN biopsy (SLNB) was initially developed for penile cancer and has been best studied in melanoma. In breast cancer, SLNB has been explored as a less morbid alternative to axillary lymph node dissection (ALND). In theory, a properly performed negative SLNB should eliminate the need for completion ALND. The risk of lymphedema is significantly lower after SLNB than ALND.

Although many surgeons have adopted this approach, whether SLNB adversely influences survival compared to ALND is not yet proven. Since the magnitude of such a survival difference, if it exists, is expected to be 5 percent or less, definitive proof requires a very large trial. At least four are underway.

Preliminary reports from the NSABP and ALMANAC trials presented at the 2004 San Antonio Breast Cancer symposium are encouraging, suggesting that short term survival and recurrence rates are similar with and without ALND. At least in the ALMANAC trial, QOL was superior with SLNB. Nevertheless, until long-term follow-up is available for these and other trials, there will be persisting concerns about a possible survival detriment if ALND is not performed.

**Technique** — Lymphazurin blue dye or radioactive colloid is injected into the vicinity of the tumor, enters lymphatic channels, and then passively flows to LNs. One or a few LNs are labeled, making it possible to identify those first receiving drainage from the tumor. The SLN can be variably located, but is usually within the low axilla (level I).

**Blue dye** — The patient is prepped and draped in the operating room (OR). The surgeon injects 5 mL of blue dye around the tumor periphery, at the Pg. palpable edge of the biopsy cavity, or into the dermis overlying the tumor. Breast massage is then carried out to dilate breast lymphatics. The axillary fascia is entered through an inferior axillary incision. A careful search is made for a blue lymphatic channel leading to a blue-stained LN. Care must be taken to identify the most proximal blue node in the axilla, because the dye transit time is rapid and blue staining of distal, nonsentinel axillary LNs is not uncommon. Failure to identify both a blue lymphatic channel and an associated blue LN, and failure to remove the most proximal blue LN are the two most common technical errors with SLNB.

**Radioactive colloid** — SLN identification with radiocolloid is less well standardized. The radioactive material (technetium sulfur colloid or technetium-labeled human serum albumin) is injected intraparenchymally and often in the retroareolar region as well as in the dermis of the areola.

The radioisotope dose is usually larger than that needed for SLN mapping in melanoma because the breast lymphatics are not so rich as those in skin. Injection should be done at least 30 minutes before, and preferably within eight hours of surgery. Lymphoscintigraphy is performed in the OR with a

sensitive hand-held gamma probe to identify areas of increased radioactivity ("hot spots"), which are then marked on the skin. A small skin incision is made over the hot spot and the probe, along with blunt dissection, is used to guide the surgeon to the labeled LN. Because this technique is easier to learn, proficiency is attained sooner than with blue dye.

Although excellent results are reported in single institution series using either radioactive colloid or dye, combined use of both tracers appears to be complementary, minimizing the false negative rate. In one series of 966 SLNBs, the variables associated with successful SLN localization using either approach were not identical. However, others report no advantage to using both agents, even for surgeons learning the technique, and many institutions utilize blue dye alone.

Adding blue dye to radiocolloid may be particularly helpful to identify the first draining node in patients with a large number of radiolabeled nodes, which may be due to inconsistencies in particle size of the injected tracer. Alternatively, individual radioactive counts can be used to rank order each node. Ideally, the SLN should be hot and stained blue.

### **Accuracy**

**Radiocolloid** — Two large-scale multicenter studies have been conducted using radiolabeled colloid in early breast cancer.

- An American multicenter trial demonstrated that the technique could be learned and successfully applied by a diverse group of surgeons spanning private and academic practice. All patients underwent SLNB followed by completion ALND; pathologic analysis was limited to routine

hematoxylin and eosin staining (H&E). The surgeons were able to identify a "hot spot" in 93 percent of cases, and at least one SLN was identified in 98 percent. Nonaxillary SLNs were identified in 8 percent (histologically positive in 3 percent). The accuracy of the SLN in predicting the final axillary status was 97 percent, the positive predictive value was 100 percent, and the predictive value of a negative SLN was 96 percent. When the ALND specimen was positive, the SLN was falsely negative in 11.4 percent, a value that ranged from 0 to 29 percent among various surgeons.

False negatives were not due to inadequate sampling. When deeper sectioning and immunohistochemical staining (IHC) were applied to the false negative cases, occult metastases were found in only 18 percent; the majority (82 percent) were still false negative. When deeper sections and IHC were performed on both the SLN and the non-SLN nodes, the false negative rate for both occult (1.4 percent) and non-occult (11.9 percent) metastases was 13.3 percent.

- An Italian trial randomly assigned 516 patients with breast cancer <2 cm to SLNB plus ALND, or SLNB followed by ALND only for a positive SLNB. In the SLN plus ALND group, 8 of 174 patients with a negative SLNB had missed metastases (false negative rate 8.8 percent [8 of 91 node-positive

patients missed], negative predictive value 95.4 percent).

**In another series, 162 women undergoing successful SLNB followed by ALND were compared with a concurrently treated but nonrandomized group of 134 women who underwent ALND alone. Axillary metastases were more frequent in the SLN group than in the ALND group (42 versus 28 percent), an effect that was attributed to more focused evaluation of a single node using both routine H&E and IHC.**

**In order to confirm the SLN as the first draining LN, non-SLN nodes were examined with the same careful IHC technique used to examine the SLNs. When the SLN was tumor-free by both routine H&E and IHC, the risk of non-SLN node involvement was 0.09 percent (1 of 1087). However, in this series, the non-SLN nodes were extensively evaluated only when the SLNs were negative by their extensive work-up, a method different from that described in the University of Vermont series where non-SLN nodes were examined regardless of the status of the SLNs.**

**Subsequent reports have confirmed the efficacy of either or both techniques, although selection criteria and technique of SLN identification have varied widely. Despite these variations, an SLN has been consistently identified in between 92 and 98 percent of cases, and the accuracy of predicting the status of the remaining ALNs is 95 percent or better in single institution series. False negative rates range from 0 to 14, averaging 5 percent with experienced surgeons. Axillary recurrence rates in patients undergoing SLNB with or without ALND are lower (less than 1.5 percent in one large series than those reported after ALND (approximately 3 percent)).**

In summary, there are two major options for surgical treatment of early invasive breast cancer. Breast conservation consists of **lumpectomy with axillary node dissection followed by radiation**. Total mastectomy with axillary node dissection is referred to as **a modified radical mastectomy**. Long-term survival rates are approximately the same for these two treatment options. Patients undergoing lumpectomy and radiation are, however, at risk for local recurrence in the treated breast as well as for the development of a new primary tumor in the remaining breast tissue. Local recurrences can generally be managed with mastectomy; overall survival is equivalent to that of women who underwent mastectomy at the time of initial diagnosis. There may, however, be a significant cost to the patient in terms of anxiety about recurrence, as well as the morbidity and potential mortality associated with undergoing a second surgical procedure.

On the other hand, patients who choose mastectomy as their initial surgical treatment face the psychological consequences of losing a breast. Although they are at slightly lower risk for local recurrence than patients who choose lumpectomy, axillary node dissection, and radiation, their overall survival does not seem to be significantly improved. Each physician and each patient must weigh the inconvenience and potential complications of radiation therapy and the risk of local recurrence against the value of breast preservation, keeping in mind that the choice between procedures appears to have no significant effect on survival.

**When mastectomy is necessary or desired, reconstruction should be discussed thoroughly with the vast majority of patients.** Reconstruction is

best done at the time of the mastectomy (immediate reconstruction) when the tissues are not scarred and skin-sparing techniques can be maximally utilized. However, many patients have misconceptions about reconstruction. Some have unreasonable fears, either of the additional surgery required or of the presence of foreign materials such as implants. Others possess expectations that are far too high; they are invariably disappointed with the results. Some who know they need chemotherapy are concerned about delays that might result because of the reconstruction. It is often best to urge the patient to consult a plastic surgeon before any final decision (for or against reconstruction) is made so she can make informed decision. Whether a mastectomy is strongly recommended or simply chosen by the patient who is a candidate for breast conservation, the ultimate decision regarding reconstruction must be hers (unless, of course, there is a strong contraindication to it).

## Scenario B

Carol Edwards is a 39-year-old who had **TWO** nonpalpable abnormalities on mammography of the right breast, one in the upper outer quadrant (UOQ) and one in the lower outer quadrant (LOQ). She underwent mammographically localized excisional biopsies of both areas. **Both lesions were shown to be malignant, the RUOQ one an grade III infiltrating ductal carcinoma measuring 0.9 cm with clear margins, and the RLOQ one a focus of ductal carcinoma in situ (DCIS) measuring 0.6 cm in greatest diameter but with positive margins. Estrogen and progesterone receptors are negative.**

This patient has been told the diagnosis over the phone several days after the biopsy and she is now meeting with the surgeon to discuss definitive surgical treatment: mastectomy. The presence of multicentric cancer is a contraindication to breast conservation therapy. The presence of invasive disease presents the same argument for axillary node dissection for staging as in Scenario A.

**Immediate reconstruction** should be discussed with this patient. This is generally done by a plastic surgeon, usually immediately following a skin-sparing modified radical mastectomy performed by the general/breast surgeon. The types of reconstruction fall into two major categories: those using only tissue expanders/implants, and those using the patient's own tissue in the form of a myocutaneous flap, sometimes in conjunction with an implant and/or a contralateral breast reduction. In some ways the expander/implant is simpler, but it obviously involves using a foreign body. A temporary saline-filled expander with an attached subcutaneous resealable port for future expansions is placed under the pectoralis muscle following the mastectomy. In the weeks following the procedure, saline is intermittently added to the expander to gradually stretch the skin. When sufficient size is achieved to give symmetry with the contralateral breast, the expander can be replaced by a more permanent implant as an outpatient procedure.

The reconstructions that utilize the patient's own tissues are either the TRAM (transverse rectus abdominus myocutaneous flap) or the latissimus dorsi myocutaneous flap. These are extensive procedures that require a long general anesthesia period (some last 4-8 hours after the mastectomy) and sometimes result in significant blood loss. The recovery period is more difficult and prolonged. Patients with obesity, diabetes, and/or a heavy smoking history (as well as those with other major underlying diseases) are not good candidates for these procedures. However, for those patients who qualify, the cosmetic results

are often very good. Not all patients are interested in reconstruction. Obviously, this is a highly personal choice, but frequently patients' initial decisions against reconstruction are based on fear or misconceptions, so they need to be fully appraised of the options/benefits/risks/complications before a final decision is made.