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BREAST AND SENTINEL NODE

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INTRODUCTION: BREAST FROZEN SECTION

The historical importance of the breast frozen section in the evolution of surgical pathology practice is the basis for including this topic. The paradigm for clinically relevant immediate decision making in surgical pathology as well as the practical history of intraoperative diagnosis can both be illustrated by the implementation of frozen section related to breast cancer. In the current era, a decline in the number of frozen section diagnoses in the management of breast cancer is a reflection of the significant changes in the clinical detection and therapy of this disease over the last approximately 40 years.

In the premammography era, breast tumors were discovered by palpation, usually by the patient herself or her spouse, partner, or physician. The definitive diagnosis was made by open biopsy, incisional or excisional. While the patient was still anesthetized, a fresh tissue sample, even if grossly benign, was sent to the surgical pathology laboratory for immediate analysis by frozen section. If the frozen section showed carcinoma in any form, in situ or invasive, a mastectomy was immediately done. Since mastectomy was the only therapeutic option, the objective of this sequence was to provide definitive therapy without a second anesthesia. In the later years in which this practice was common, fresh samples of invasive tumors, 0.5 to 1 g, were submitted for estrogen receptor determination, which was done by competitive binding assay. Because tumors were relatively large and biopsy samples were of generous size, there was typically ample tumor to spare.

The advent of screening mammography in the 1970s and subsequent generations of refined imaging techniques have been major factors in changing both the histologic evaluation and therapeutic approach to breast cancer by detecting tumors of small size. The size of the tumors is perhaps best summarized by a premammography era tabulation of 1,355 cases seen at the Memorial Hospital in New York from 1935 to 1942, where more than half the tumors were between 2 and 4 cm and almost 20% were larger than 5 cm (1). In the current era, most tumors are smaller than 2 cm and many are not palpable at all. Diminished tumor size is encountered in both community hospitals as well as referral settings. Table 8.1 illustrates the comparable sizes of invasive breast cancers as encountered at the time of...
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TABLE 8.1 Size of Invasive Breast Cancer in Community and University Setting

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>LGH&lt;sup&gt;a&lt;/sup&gt;</th>
<th>U of C&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>T1mic</td>
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<td>T1a</td>
<td>51</td>
<td>147</td>
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<tr>
<td>T1b</td>
<td>173</td>
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<td>534</td>
</tr>
<tr>
<td>T3</td>
<td>29</td>
<td>130</td>
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<sup>a</sup>Advocate Lutheran General Hospital, 1999 to 2001 (n = 830).
<sup>b</sup>University of Chicago, 2000 to 2011 (n = 2180).
Data from: Cancer Registries at Advocate Lutheran General Hospital and University of Chicago.

diagnosis over several recent years at the Advocate Lutheran General Hospital, a large community hospital in the Chicago suburbs, and the University of Chicago (data supplied by the Cancer Registries in the respective institutions). The decrease in size of the tumors is largely due to screening mammography, which has concomitantly solidified the concept of breast-conservation surgery. The combination of the accepted efficacy of conservation procedures coincident with the radiographic discovery of smaller tumors and the emergence of varied systemic therapies has changed the treatment algorithm for this disease.

Small size is a major disadvantage for frozen section diagnosis for several reasons: (1) the risk of having to freeze the whole tumor which could represent the entirety of the patient’s disease, (2) the introduction of both frozen and paraffin-embedded artifacts, (3) receptor status must be established on formalin fixed paraffin-embedded tissue, (4) there is no emergent therapeutic decision to be made. Therefore, the diagnosis of breast carcinoma is now rarely established by frozen section, but instead by core needle biopsy or aspiration cytology. Immediate definitive surgery is unusual as the patient herself is sure to be consulted about the therapeutic options after the diagnosis. Consequently, the number of breast frozen sections has markedly diminished (2). At the University of Chicago, in 2011, only seven breast tissue specimens were sent for intraoperative diagnosis. Yet, the need to recognize breast cancer by frozen section remains current, primarily as applied to metastatic sites (see below).

The Breast Frozen Section: Major Intraoperative Questions

Current published studies on breast frozen sections are uncommon (3–6). It is perhaps of some relief to pathologists that legal actions related to breast cancer are relatively few for frozen section (7), with the legal burden,
in general, having been shifted to the radiologists (8). While the prior habit of freezing all breast specimens is no longer advocated (9), in the context of individualizing therapy there is an occasional request for a frozen section of a breast mass. Though the circumstances are exceptional, the major question has not changed, that is, to definitively and immediately identify a malignant tumor. The price that has been paid for decreased frequency is that the pathologist is less experienced and perhaps not as confident as in the past. In an attempt to minimize error therefore, interpreting a breast frozen section may negatively influence the therapeutic goal by resulting in a deferred diagnosis or a descriptive nondiagnostic response.

Occasionally, a request may be received for intraoperative assessment of margins on a definitive lumpectomy specimen. The immediate consequence of such evaluations would be a margin re-excision, with possible conversion to a complete mastectomy. Although immediate margin assessment is not a common practice among surgeons and pathologists, and is not performed at the University of Chicago, it is a subject of active discussion. Given the high fat content of such specimens, a frozen section is difficult to execute and interpret, especially related to atypical proliferations at the margins perhaps additionally altered by cautery artifact. Techniques such as freezing with liquid nitrogen have been attempted in this regard (10).

Beyond the technical difficulties, though, are important conceptual considerations (11). First, borderline cytologic and architectural atypia in any part of the sample may be difficult to evaluate even with well-prepared paraffin sections. Trying to do this on a frozen section may be ill advised. Second, no majority consensus currently exists as to what constitutes a clean margin. The range may vary from 1 to 5 mm for invasive carcinoma. Given the lack of rigidity of the tissue and its propensity to shrink, such precise measurements are even more difficult to make on a frozen section evaluation. Last, in this era of improved systemic therapy, the very emphasis on complete surgical removal of microscopic residual tumor is being called into question. For now, the optimal evaluation for breast-conservation specimens under intraoperative conditions requires a good gross assessment; actual frozen sections should be used judiciously (3,4). Definitive microscopic examination should be done on inked, well-fixed, and processed tissue. The decision for margin re-excision can then take into account other information including imaging, lymph node status, and plans for adjuvant therapy.

The Breast Frozen Section and its Interpretation

The most important parameter in the analysis of a breast frozen section is the gross examination. The specimen should be inked according to departmental practice and all sectioned surfaces should be inspected to minimize sampling error (Fig. 8.1, e-Fig. 8.1). To minimize potential artifacts, the freezing of fatty areas should be avoided; the need for sharp blades and cryostats for which the temperature is properly monitored and maintained, cannot be overstated. The histologic examination of the actual
Frozen section requires no special skill or secret maneuver other than attention to traditional morphologic detail: recognition of the standard alterations in growth pattern, under low-power observation, just as would be appreciated on routine paraffin-embedded sections (Fig. 8.2). Employing imprint preparations along with the actual frozen section facilitates the appreciation of cytologic detail (Fig. 8.3, e-Figs. 8.2–8.4). The ability to discriminate infiltrating cancer from a radial scar lesion, inflammatory

**FIGURE 8.1** Cross section of an inked gross specimen with a centrally placed, stellate, gray-white tumor grossly typical for infiltrating carcinoma. The size of the tumor is approximately 1 cm. The margins are free of tumor.

**FIGURE 8.2** Infiltrating ductal carcinoma. Dense fibrous tissue investing poorly oriented cords of large, pleomorphic malignant cells. No normal breast tissue is present.
infiltrates, fat necrosis, sclerosing adenosis, and involutional changes in a papilloma relies on adequate sampling and basic morphology. It is not good practice, not to mention potentially dangerous, for the pathologist to ignore these fundamental morphologic and technical principles.

In part because of early diagnosis and effective treatment, breast cancer has now become a chronic disease. Occasionally, after definitive therapy, an unsuspected metastasis or recurrence may be encountered during a breast reconstruction procedure (Fig. 8.4A,B). Patients may present years after their primary diagnosis with metastatic lesions. The diagnostic context depends heavily on the history and a consideration of breast cancer by the pathologist (Figs. 8.5–8.8). The most important point to remember is that if the frozen section is not absolutely diagnostic of cancer, defer the diagnosis (Figs. 8.9 and 8.10, e-Figs. 8.5–8.7).

INTRODUCTION: THE SENTINEL NODE FROZEN SECTION

The staging and prognostic parameters used to evaluate each new case of infiltrating breast cancer are many. However, the two most important factors remain the size of the primary tumor and the status of the regional lymph nodes. While it is a principle of clinical management that smaller invasive tumors are less likely to have regional node metastases, 10% to 30% of tumors smaller than 1 cm have axillary metastases. It is widely accepted that nodal involvement cannot be accurately predicted on clinical or imaging grounds alone; histologic assessment is also required. In the past, every patient with an invasive breast cancer had at least a low axillary dissection in conjunction with a mastectomy or an excisional lumpectomy. However, postoperatively, the clinical morbidity associated with this
FIGURE 8.4  A: Low-power view of a frozen section of an incidentally discovered intramammary lymph node metastasis in a 48-year-old woman with a history of invasive ductal carcinoma undergoing breast reconstruction. B: High-power view of a field from the lymph node with large tumor cells infiltrating in nests and cords. The procedure was aborted.
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Figure 8.5 A retrograde pyelogram of a 63-year-old woman with a remote history of infiltrating breast cancer who presented with flank pain. Note the kinking of the right ureter with proximal hydronephrosis due to a poorly defined retroperitoneal mass. A surgical ureterolysis was undertaken to ease the external obstruction to the urinary tract.

Figure 8.6 A frozen section of the retroperitoneal mass. Artifactual fold along the top border. Low-power view of a fibrofatty lesion with a seeming mononuclear infiltrate, possibly inflammatory.
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**FIGURE 8.7** High-power view of the previous field showing inflammatory cells and larger polygonal cells focally growing in a single-file fashion, suggesting infiltrating lobular carcinoma.

**FIGURE 8.8** Permanently embedded section of the frozen section, showing infiltrating single files of malignant cells indicative of infiltrating lobular carcinoma. The history of a primary breast cancer with this diagnosis was later confirmed.
FIGURE 8.9 Low-power view of a frozen section of a breast mass in a 65-year-old woman with a history of left breast carcinoma with positive lymph nodes 3 years previously. She was postoperatively radiated. The frozen section of this ipsilateral mass was requested so that an immediate mastectomy could be done if it was malignant. The stellate shape is composed of dense fibrous tissue investing cords and nests of polygonal cells, simulating the growth of an infiltrating carcinoma.

FIGURE 8.10 High magnification of the tumor, demonstrating sheets of polygonal cells with slightly atypical nuclei and abundant, pale to finely vacuolated cytoplasm. At the time of the frozen section analysis, these were interpreted to be histiocytes.
procedure included pain, limitation of motion, lymphedema, and infection. The concept of the sentinel node, first employed with respect to melanoma, has been effectively adapted to breast cancer and has evolved as part of breast-conservation surgery.

A sentinel node is the first lymph node in a drainage basin to receive lymphatic fluid. As such, metastatic deposits are first anticipated in this location. In breast cancer, the sentinel node biopsy procedure allows for the preservation of function and cosmesis without compromising the necessary staging information (12–14). The sentinel node is identified by the injection of radioactive colloid and/or blue dye into the primary breast biopsy site. The affected node or nodes are then excised. The procedure is best applied to small primary tumors (<2 cm) and is well suited for mammographically discovered lesions. Until recently, the standard treatment algorithm mandated that all patients with a positive sentinel node undergo complete axillary dissection. Increasingly, this practice has come into question, culminating in the publication in 2011 of the ACOSOG Z0011 trial (15). This landmark trial concluded that axillary lymph node dissection (ALND) can also be safely omitted in a subset of women who meet the following inclusion criteria: (1) T1-2 invasive breast cancer, (2) one or two sentinel nodes positive by frozen or permanent section, (3) a patient undergoing a lumpectomy with a plan for whole breast irradiation and who has not received neoadjuvant chemotherapy. The findings of Z0011 have been variably adopted; the long-term impact remains to be seen (16–18).

At the University of Chicago, sentinel node examination began in 2000 and frozen section began to increase in 2002. This examination has continued to the present although in markedly decreasing numbers since 2011 (Fig. 8.11). The accumulated experience has been quite accurate: there have been no false positives; of the 12 false negatives from 2002 to 2006, only one was a missed micrometastasis visible on the frozen section. Other false negatives included artifacts of frozen section or sampling. Currently, there is a request on average for one frozen section case of sentinel nodes per week. Though the landscape has clearly shifted and the rate of frozen section sentinel node biopsies for invasive breast cancer is decreasing, it remains a common enough occurrence in clinical practice (19,20). Furthermore, in the age of Z0011, the importance of counting the exact number of positive sentinel nodes has increased, placing even more responsibility on the pathologist.

The Sentinel Node and the Major Clinical Question

The major clinical question is deceptively simple, that is, whether or not the sentinel node harbors a metastasis. Perhaps the question is better formulated as to whether the status of the sentinel node should be reported intraoperatively, that is, immediately by frozen section analysis, or whether the diagnosis should be made under the routine circumstances of fixation and paraffin embedding. If the surgeon is immediately prepared to complete a low axillary dissection in light of a report of a metastatic deposit, then a frozen section can be justified. From the standpoint of the pathologist, the
issues related to sentinel node examination concern the extent of gross sampling, the use of imprints or scrapes, the number of frozen or paraffin (permanent) sections to be examined, the spacing of those intervals, and the use of cytokeratin immunostaining on permanent preparations, to name a few. It may be that the simplest, least intricate approach is optimal (21). The assessment of tumor in a node has become more complex than just positive or negative and concerns the best way to recognize a metastasis and report it, and for the treating physicians to decide what to do about it (22).

The size of the metastasis further illustrates this complexity as it has itself become a source of controversy related to the question of the simple presence or absence of tumor. Macrometastases defined as 2 mm or larger are widely accepted as clinically significant (AJCC Cancer Staging Manual, 7th edition). But the question is what constitutes a clinically significant metastasis, that is, what is the significance of deposits between 0.2 and 2 mm as well as isolated microscopic tumor clusters smaller than 0.2 mm? While this issue is not definitively settled, a recent analysis of NSABP data suggests a small survival advantage for negative sentinel nodes (21). Treating very small and possibly insignificant lesions raises the issue of overtreatment; not treating raises the issue of undertreatment. The frozen section focuses attention on the clinical relevance of the size of a metastasis. An agreement between the surgeon and the pathologist with respect to this issue needs to be worked out in advance of the procedure.

**FIGURE 8.11** Rise and fall of sentinel node evaluation by frozen section at the University of Chicago (2000 to 2012).
Since it is easier for the surgeon to complete a dissection at the time of the sentinel node excision, and if the presence of a predetermined amount of tumor will influence the surgical procedure, a frozen section is reasonable. The actual detection of tumor is, in part, related to the expertise and technique of the examining pathologist. The earlier reported 10% to 30% false-negative rates related to sentinel node frozen section may have been due to sampling, that is, failure to freeze the entire node or to cut more than one level for histologic evaluation (23,24). Although the frequency of sentinel node evaluation by frozen section may vary among institutions, it is now accepted practice. Recently reported sensitivities vary with respect to detection of macrometastases versus micrometastases and isolated tumor clusters. False-negative rates for macrometastases now fall below 3%, depending upon the institution (25,26).

The Sentinel Node Frozen Section and its Interpretation

The gross examination is again key. Any macroscopically visible metastasis is clinically significant and care should be taken to make sure that the area is mounted so that it will appear on the frozen section. Acknowledging that missing a small metastasis is much easier than finding it, freezing the entire node especially in the absence of a gross lesion is essential in dealing with the sampling issue. The standard reference point to justify reporting a metastasis should be detection of a tumor on an H&E-stained frozen section. Imprints and scrapes of an obvious gross lesion (Fig. 8.12) can also be quite useful (27); whether there also needs to be a histologic counterpart should be a practice parameter with which the pathologist is comfortable. More than one level should be examined histologically to

**FIGURE 8.12** Photograph of a gross sentinel node almost totally replaced by white, poorly delineated tumor.
provide for artifacts and tissue falling off slides, although there is no agreement on the number. Our practice is to examine at least two levels. The need to examine the entire node can be complicated by nodes of any size which are invested by fat and hence difficult to trim. However, everyone involved should recognize that at some level sampling error is inherent in the accuracy of this procedure. The false negative is something to accept and to try to minimize, but it cannot be eliminated.

This is not an examination requiring anything other than a well-cut and stained H&E section. The permutations in finding small lesions are many (Figs. 8.13 and 8.14) and would also include tumor present on the frozen but not on the permanent section, present on the imprint but not on the actual frozen (both still regarded as positive). Another problem in this context concerns low-grade infiltrating lobular carcinoma, which occasionally simulates sinus histiocytosis. These cases are lessons in careful examination (Figs. 8.15 and 8.16, e-Figs. 8.8–8.10). The identification of intracytoplasmic lumina in individual tumor cells has long been associated with lobular carcinoma, although not necessarily specific for this tumor type (Fig. 8.16). When present, they are helpful diagnostic adjuncts (28). Last is being aware of the sequelae of previous needle biopsy of axillary lymph nodes, occasionally done for clinically enlarged nodes to bypass formal sentinel node evaluation and proceed directly to an axillary dissection. The capsular reparative reaction includes granulation tissue with endothelial enlargement and atypia as well as fibrosis that can be mistaken for desmoplasia (Figs. 8.17 and 8.18, e-Figs. 8.11–8.13).
**FIGURE 8.14** Low-power view of a frozen section of a sentinel node demonstrating a single intracapsular lymphatic cluster of tumor cells. *Inset:* High-power view of the intracapsular lymphatic group of tumor cells.

**FIGURE 8.15** Low-power view of a frozen section of a sentinel lymph node from a patient with infiltrating lobular carcinoma. Subtle architectural distortion and a suggestion of cytologic atypia.
**FIGURE 8.16** Frozen section. High-power view of a subcapsular area demonstrating diffuse infiltration by malignant cells. *Inset:* Frozen section. High-power view of the tumor cells demonstrating nuclear pleomorphism, pyknosis, and intracytoplasmic lumina. The latter is suggestive of infiltrating lobular carcinoma.

**FIGURE 8.17** Frozen section of perinodal capsule and fat 1 week following a negative needle biopsy of this node. This field demonstrates an actively fibrotic background extending into the fat with associated chronic inflammation and prominent small vessels with atypical endothelial cells. The picture simulates a metastasis.
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**FIGURE 8.18** High-power view of two atypical vascular channels. The endothelial cells are enlarged and the lumina are virtually inapparent.

**REFERENCES**


