Intraoperative Assessment of the Breast
Guidelines and Potential Pitfalls

Rodolfo Laucirica, MD

Context.—Intraoperative evaluation of breast tissue has changed as newer imaging techniques and surgical approaches to the treatment of breast cancer have placed the pathologist in a pivotal role in the management of this disease. Assessment of the index lesion and surgical margins are but two of the many tasks we face when the specimen arrives in the surgical pathology laboratory. We are also called on to correlate changes in the mammogram with the gross pathology, particularly in those cases in which the lesion is nonpalpable. More recently, pathologists have been asked to analyze 1 or more sentinel lymph nodes at the time of frozen section to look for metastatic disease. This review discusses many of these issues and also provides a simplified approach to the differential diagnosis of a variety of breast lesions one may encounter intraoperatorively.

Objective.—To provide guidelines for and address potential pitfalls in the intraoperative management of the breast.

Data Sources.—Author’s experience and pertinent literature.

Conclusions.—Careful assessment of the gross specimen coupled with prudent utilization of frozen sections is pivotal to reducing intraoperative error rates and preventing needless anxiety for the patient.

(RArch Pathol Lab Med. 2005;129:1565–1574)

Regardless of the type of breast specimen sent for intraoperative consultation, the pathologist must ask 3 important questions regarding the tissue submitted for frozen section examination. Is there a lesion of sufficient size, such that not all the tissue will be sacrificed for intraoperative analysis (ie, essential diagnostic material will not be lost)? Based on the recommendations of the Directors of Anatomic and Surgical pathology, tumors smaller than 1.0 cm should not be submitted for frozen section examination.1 If only an initial biopsy of a larger lesion is received, will additional material be sent for permanent evaluation? Most importantly, will my diagnosis have an immediate and relevant impact on the operative management of the patient’s breast lesion? If the answer to any of these questions is no, then intraoperative evaluation of the specimen is usually not warranted. Improper utilization of frozen sections can lead to misinformation, unnecessary anxiety, needless additional surgical intervention, and increased costs. In the preoperative setting, effective communication between the radiologist, surgeon, and pathologist will go a long way to prevent errors in the diagnosis and treatment of a variety of breast lesions.

Types of Specimens

At our institution, we receive various types of breast specimens for intraoperative consultation. Depending on the mammographic and clinical findings, they include incisional or excisional biopsies, lumpectomies, and mastectomies.

Incisional Biopsies

Incisional biopsies usually represent small portions of tissue or needle cores from a palpable mass. They are usually performed for 1 of 2 reasons: either an immediate diagnosis is needed so that the surgeon can proceed to definitive surgical treatment (either lumpectomy or mastectomy) as a 1-stage procedure, or the patient has an inoperable tumor and lesional tissue is required for diagnosis and hormonal analysis prior to neoadjuvant cytoreduction chemotherapy or radiation therapy. In the latter case, cytologic imprints (see “Special Techniques”) of the fresh tissue, coupled with judicious sampling for frozen sectioning will, in most cases, prevent freezing of the entire biopsy.

Excisional Biopsies

Excisional biopsies are usually performed to completely remove a palpable or mammographically detected lesion. For mammographic lesions, a specimen radiograph (Faxitron) is obtained (see “Gross Examination”) and compared with the preoperative mammogram to ensure that the lesion in question is present in the biopsy. Inking of all excisional biopsies is recommended prior to sectioning so that microscopic assessment of the margins can be performed. If the specimen has been oriented by the surgeon (which should be strongly encouraged), the various margins can be identified using different-colored inks. With the increased use of stereotactic core biopsies, we now receive excisional biopsies with metallic clips that are placed by the radiologist at the time of the biopsy. These speci-
mens may also be sent to the frozen section laboratory to confirm the presence of the clip, marking the site of the prior core biopsy. Unless there is a justified reason to perform a frozen section, excisional biopsies can be processed for routine sectioning once the lesion of interest is identified by gross or radiographic evaluation.

**Lumpectomies (With or Without Sentinel Lymph Node Mapping)**

Breast conservative surgery is rapidly replacing mastectomies for the surgical treatment of most breast cancers. These specimens are usually marked with sutures for orientation and may have a thin ellipse of skin overlying the breast tissue. Since these patients have a preoperative diagnosis of malignancy, a frozen section for diagnostic purposes is usually not needed. Under certain situations, the pathologist may freeze 1 or more of the margins from the lumpectomy specimen if the tumor grossly approximates a particular margin. Freezing of all margins regardless of the proximity of the tumor should not be undertaken, as this may yield inaccurate information, especially given the difficulties associated with freezing and cutting adipose tissue (see “Artifacts”).

**Mastectomies**

Most mastectomies performed today are undertaken after a diagnosis of malignancy has been made by fine-needle aspiration, core biopsy, or excisional biopsy. It is therefore important to know the prior diagnosis before attempting to evaluate these specimens, since residual disease may be grossly undetectable. Pathologists are usually not asked to perform frozen sections of mastectomy specimens unless there is specific margin that interests the surgeon. In addition, the surgeon may mark the highest node from the axillary dissection if it is clinically suggestive of metastatic disease. A frozen section of this node may be requested to confirm malignancy. Additional nodes may then be removed at the time of surgery, if the highest node is positive.

**GROSS EXAMINATION**

Macroscopic examination of the surgical specimen is of paramount importance, especially when deciding what, if anything, should be submitted for intraoperative evaluation. All excisional biopsies should be measured, weighed, and inked before sectioning. The specimen is then sequentially sliced at 3- to 5-mm intervals (“breadloafed”), and each slice is carefully examined. If a gross lesion is present, it should be described and measured. In addition, the distance to the nearest gross margin should also be noted (Figure 1). A frozen section should not be attempted unless the lesion is grossly suggestive of malignancy and the surgeon needs to remove additional tissue from around the biopsy site to obtain clear margins. The macroscopic appearances of several benign and malignant breast lesions are listed in Table 1. Remember that well-circumscribed lesions are not always benign and stellate lesions are not always malignant. Also, invasive lobular carcinoma frequently presents as a diffuse thickening rather than a distinct mass (Figure 2). Given the fact that hormonal analysis is now routinely done by paraffin immunohistochemistry, we no longer need to sacrifice lesional tissue for these ancillary studies. Sampling for permanent sections should include the tumor and adjacent breast tissue, uninvolved breast parenchyma, and margins. If possible, try to include a section containing the tumor in relation to the nearest inked margin. This will allow for accurate microscopic assessment of the surgical margin.

Excisional biopsies performed for nonpalpable lesions, including those associated with calcifications, require a slightly different approach. A specimen radiograph should be obtained and compared with the preoperative mammogram. Once the index lesion is identified, the
specimen should be serially sectioned and placed in paraffin blocks in such a manner as to maintain its proper orientation. The cassettes should then be radiographed, so that the block(s) with the index lesion can be identified (Figure 3). In this manner, the pathologist can correlate the gross and histologic findings with the preoperative mammogram. The entire lesion along with the peripheral and end margins should be submitted for microscopic evaluation. Portions of breast tissue between the index lesion and the excision margins should also be submitted for pathologic assessment. If the specimen is complicated and requires extensive sampling of several areas, a diagram of the specimen should be made, delineating where the tissue sections were obtained (Figure 4).

When no discrete lesion is present, some laboratories advocate processing the entire specimen for pathologic examination. Remember, given the economic pressures under which we currently practice, we need to balance prudent sampling of the specimen with laboratory costs without compromising patient care. To resolve this issue, criteria have been established for sampling of grossly unremarkable breast biopsies. Schnitt and Wang retrospectively analyzed 384 specimens entirely submitted for histologic examination from biopsies performed for clinically palpable lesions in which no distinct tumor was evident on gross examination. They concluded that significant lesions (i.e., carcinomas and atypical hyperplasias) were identified in fibrous tissue when up to 10 cassettes were submitted per case. This also resulted in an 18% reduction in the number of blocks needed for each biopsy. Based on these findings, the authors recommended submitting up to 10 tissue blocks of fibrous parenchyma and/or fat for each biopsy. If carcinoma or atypical hyperplasia is identified in the initial slides, the remaining tissue may

---

**Table 1. Macrscopic Appearance of Benign and Malignant Breast Lesions**

<table>
<thead>
<tr>
<th>Scar or stellate lesion</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat necrosis</td>
<td></td>
</tr>
<tr>
<td>Radial scar/complex sclerosing lesion</td>
<td></td>
</tr>
<tr>
<td>Microglandular adenosis</td>
<td></td>
</tr>
<tr>
<td>Granular cell tumor</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Carcinomas</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Well-circumscribed/lobulated lesion</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroadenoma and variants</td>
<td></td>
</tr>
<tr>
<td>Phyllodes tumor</td>
<td></td>
</tr>
<tr>
<td>Adenosis tumor</td>
<td></td>
</tr>
<tr>
<td>Intraductal papilloma</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Intraductal papillary carcinoma</td>
<td></td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td></td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td></td>
</tr>
<tr>
<td>Phyllodes tumor (low and high grade)</td>
<td></td>
</tr>
<tr>
<td>Sarcomas</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cystic lesion</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrocystic change</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Rare forms of invasive carcinoma</td>
<td>(squamous and cystic carcinomas)</td>
</tr>
</tbody>
</table>

---

**Summary of sections:**

- **A1** - Lateral margin
- **A2/3** - Representative lateral breast tissue
- **A4/5** - Tissue immediately lateral to the microcalc.
- **A6** - Superior margin
- **A7** - Microcalcifications
- **A8** - Inferior margin
- **A9/10** - Deep margin with microcalcifications
- **A11/12** - Tissue immediately medial to microcalc.
- **A13/14** - Representative medial breast tissue
- **A15** - Medial margin

**Figure 3.** Specimen radiograph of an excisional breast biopsy containing numerous calcifications. The tissue blocks containing the calcifications should be noted in the gross description, and multiple levels of these cassettes can be requested for histologic evaluation.

**Figure 4.** Diagram illustrating an approach to sampling breast specimens for calcifications. In those cases in which the lesion is nonpalpable, use the specimen radiograph as a guide for tissue sampling. Diagram courtesy of Syed Mohsin, MD, Columbus, Ohio.
be processed to look for additional foci of malignancy or atypical hyperplasia.

Lumpectomies should be grossed in a manner similar to excisional biopsies. Remember that the margins should be inked, using multiple colors if necessary. If a portion of skin is present, it should also be inked and sampled for histologic evaluation. Lumpectomies associated with sentinel lymph node mapping can usually be grossed within 24 hours of the surgery without fear of significant radiation exposure, provided the specimen is adequately fixed. Studies have shown that surgeons performing sentinel lymph node mapping and biopsy have minimal radiation exposure. The data state that the expected radiation exposure to a surgeon during a 3-hour sentinel node procedure on a patient administered 20 mCi of technetium-99m sestamibi is approximately 1 mrem per year, and for nonradiation workers it is 500 mrem per year.4 From these data, one can extrapolate that the risk for pathologists handling these specimens is even lower than the risk for the surgeon, given the time that has elapsed since administration of the radioactive solution and the specimen’s arrival in the surgical pathology laboratory. Radiation counts performed at 1 of our affiliated teaching hospitals support the negligible exposure to pathologists handling these specimens. Counts of the sentinel node and breast specimen were less than 2 mrem initially and 0 mrem the following day (~12–15 hours postoperatively). Gross evaluation of sentinel lymph nodes will be discussed under the heading of “Special Techniques.”

Mastectomies should be weighed, measured, and inked prior to sectioning. After performing the gross or intraoperative frozen section consultation, the specimen should be serially sectioned at 3- to 5-mm intervals and placed in formalin for several hours before sections are taken for histologic evaluation. This will ensure that the adipose tissue is adequately fixed before processing of the tissue sections. In most cases, when a mastectomy specimen is sent to the frozen section laboratory, the surgeon is usually interested in the deep resection margin relative to the biopsy site or any residual tumor that is grossly present. If no residual tumor is grossly present, then 4 to 8 sections of the biopsy site (to include the deep margin) should be obtained. Two to 3 sections from each of the 4 quadrants are usually sufficient, if no additional lesions are seen. The skin overlying the biopsy site and nipple/areolar complex should also be sampled. The axillary tail can be arbitrarily divided into thirds, relative to the adjacent breast, for lymph node dissection. If the surgeon has tagged the highest lymph node, it should be submitted separately. In selected cases, gross photographs should be obtained for documentation and teaching purposes. Finally, given the nationwide push for standardization of surgical pathology reports, I am including the College of American Pathologists Web address for those who may want to download the surgical pathology protocol checklists for breast and other organ sites.5

SPECIAL TECHNIQUES

Intraoperative Cytology

Cytologic preparation of the tumor at the time of intraoperative consultation is a useful adjunctive technique that complements frozen section analysis of the tumor. Frozen section artifacts that may impair morphologic assessment of the tumor can largely be avoided if cytologic material is also available for analysis. Smears can be prepared in 1 of 3 ways: (a) cytologic imprints, in which the tumor is directly pressed against a slide; (b) squash preparations, in which a 1-mm fragment of tumor is gently pressed between 2 slides; or (c) scrape preparations, in which a clean scalpel is scraped along the tumor surface and the material is then transferred and smeared onto a slide. The latter technique is quite useful when the tumor is highly fibrotic. No matter which technique is used to obtain the cytologic material, it is imperative that the material is immediately fixed in ethanol for maximum preservation of the cellular detail (Figure 5).

Sentinel Lymph Node Mapping

Sentinel lymph node mapping is now performed on selected patients who opt for conservative surgery to treat their breast cancer. The procedure involves the surgical identification of those axillary lymph nodes that theoretically would be the first “sentinel” nodes to receive the lymphatic drainage from the breast harboring the invasive cancer. If these nodes are pathologically negative, the patient is spared the morbidity associated with a standard axillary node dissection. Surgical identification is based on the peritumoral injection of radioactive solutions and/or colored dyes. The surgeon then massages the breast to facilitate permeation of the solution into the lymphatic system. Several hours after the injection, the patient is taken to the operating room, where the surgeon uses a radioactive counter to locate the “hot” lymph node. If a colored dye has been used, visual inspection of the axilla usually identifies the sentinel lymph node (Figure 6). Usually, the pathologist receives 1 to 3 lymph nodes for evaluation. Some centers use cytologic imprints (see “Intraoperative Cytology”), either with or without frozen section evaluation, at the time of surgery to determine whether the sentinel node is involved by metastatic tumor.6 If the imprints are positive, then the surgeon proceeds to an axillary node dissection. Other hospitals submit their sentinel lymph node biopsies for routine processing without intraoperative consultation. Once the specimen is received in the pathology laboratory, the pathologist must carefully dissect out all the nodes and record the number and sizes. If it is technically feasible, each node should be serially sectioned at 2- to 3-mm intervals, parallel to the long axis, and entirely submitted for evaluation. One hematoxylin–eosin–stained section should be cut from each block for light microscopy (Figure 7). Additional unstained levels may also be requested at the time of sectioning, in the event that immunohistochemical analysis of the node will be required to confirm the diagnosis of metastatic disease. Although some studies advocate using immunohistochemistry on all histologically negative lymph nodes,4 the current College of American Pathologists guidelines state that this procedure is not the standard of care for pathologic evaluation of sentinel lymph nodes in patients with invasive breast cancer.6

FROZEN SECTION EXAMINATION

The percentage of breast specimens evaluated by frozen examination appears to have decreased over the years as new diagnostic modalities have altered the clinical management of breast lesions. Review of our data from Ben Taub Hospital (Houston, Tex) seems to support this con-
Figure 5. Composite photograph of an invasive, no special type (ductal) carcinoma. A, Cytologic preparation of the tumor at the time of frozen section. There are loosely cohesive groups and single cells that display cytologic features of malignancy (hematoxylin-eosin, original magnification ×400). B, The corresponding frozen section of the tumor is depicted in this photograph (hematoxylin-eosin, original magnification ×400). Note that the cellular and nuclear detail of the malignant cells is better preserved in the cytologic material.

Figure 6. An intraoperative photograph of a sentinel lymph node biopsy. Note the blue dye in the sentinel nodes and surrounding lymphatic channels. Photograph courtesy of Anthony Lucci, MD, Houston, Tex.

Figure 7. Sentinel lymph node with metastatic breast cancer. The tumor is present in the subcapsular sinus of the involved node (hematoxylin-eosin, original magnification ×200). This patient subsequently underwent an axillary node dissection.

clusion. Between 1985 and 1995, 20% to 35% of all intraoperative consultations sent to the frozen section laboratory were from the breast. However, during the last 3 years, this percentage has decreased to 4% to 8%. In addition, there has been a change in the type of specimen submitted for frozen section evaluation. Currently, most cases are related to intraoperative evaluation of resection margins, rather than the index lesion. These changes reflect a shift in the current management of breast lesions, with more patients being evaluated in the preoperative setting with either fine-needle aspiration or core biopsy. Also, a larger number of women are presenting with non-palpable disease, given the widespread use of screening mammography in women older than 40 years. As with any other test performed in the laboratory, there is an inherent false-positive and false-negative rate. Data from the literature report that the percentage of false-positive frozen section diagnoses of breast lesions varies from 0.03% to 0.1%, and the rate of false-negative diagnoses varies from 0.5% to 1.0%. Frozen section diagnosis is deferred in 0.5% to 3% of all breast biopsies.

A large retrospective analysis of frozen section diagnoses from a teaching hospital documented that diagnostic errors related to intraoperative consultations can be largely divided into the following 4 groups: those resulting from interpretation (57%), microscopic sampling (24%), gross sampling (9.5%), and lack of communication between the pathologist and surgeon (9.5%). Although meticulous gross and microscopic evaluation can go a long way to reduce errors related to sampling, errors cannot be totally eliminated, especially when dealing with large specimens for which freezing the entire lesion is not justified. Also, it is important that the pathologist keep a mental note of the size of the tissue sample that is being submitted for intraoperative consultation; this way, he or she can be certain that the entire surface of the lesion is sampled for histologic examination. Interpretative errors may result from artifacts of the freezing procedure (see “Artifacts” below) and/or inexperience on the part of the pathologist interpreting the slide. If there is any doubt or concern on the part of the pathologist who is interpreting the frozen section, this issue must resolved before—not after—the intraoperative diagnosis is given. There is no room for what if’s or maybe’s once you have received the mastectomy specimen in the surgical pathology laboratory. Finally, in cases in which there is an equivocal or de-
tell the surgeon the gross distance of the tumor to the closest margin. Given the fact that prognostic markers (estrogen receptor, progesterone receptor, HER-2/neu) are currently evaluated by paraffin immunohistochemistry, freezing of tumor tissue for analysis of these markers is no longer required.

**ARTIFACTS**

Artifacts that may impede intraoperative evaluation of breast specimens may originate from the operative procedure or the frozen section laboratory. Electrocautery instruments used to remove breast tissue may cause extensive thermal damage to the specimen. The most significant effect is severe alteration in the architectural and cytologic detail of the epithelial cells, making it difficult to evaluate epithelial proliferative lesions or to separate benign processes such as sclerosing adenosis from invasive carcinoma. Because the diathermy effect is maximal at the edges or marginal surfaces of the tissue, electrocautery artifacts severely limit the assessment of the margins of excision (Figure 9). In addition, if the electrocautery instrument transects the tumor, this may alter receptor activity and/or hamper the diagnosis or classification of the tumor.12

Crush artifacts may also hamper the frozen diagnosis of a tumor. This issue may arise when the surgeon obtains a core biopsy to confirm the diagnosis of cancer before attempting either a lumpectomy or mastectomy. Given the difficulty of assessing crushed cells in a frozen section, it is best to request additional material before rendering a diagnosis of malignancy. Figure 10 illustrates an example of crushed tumor cells in a core biopsy. Fortunately, diagnostic material was present in one of the other cores.

In the frozen section laboratory, technical problems related to the freezing procedure, tissue, or staining methodology may hamper the intraoperative diagnosis. Careful selection of the tissue sample is an important first step when performing a frozen section. Large samples tend to freeze slowly, thereby causing the formation of ice crystals in the specimen. Also, improper freezing of the specimen may create artifactual spaces around tumor nests that may be erroneously diagnosed as lymphatic or vascular invasion. We all know the difficulty involved in freezing and cutting adipose tissue. Unfortunately, this problem cannot be completely circumvented when freezing breast tissue. When feasible, try to trim off as much adipose tissue as possible before submitting the sample for intraoperative analysis. Sometimes cutting the specimen at a slightly higher thickness (8–10 μm) may help both in sectioning and keeping the tissue on the slide. Properly stained sections begin with adequate fixation. Therefore, one must place the cut sections into the ethanol as quickly as possible so that the cells are immediately fixed, thereby preserving the cellular detail. Most laboratories, including ours, use a rapid hematoxylin-eosin stain for intraoperative analysis. Given that hematoxylin is a water-based stain, removal of all the ethanol is a crucial first step to prevent understaining of the tissue sections. Also, filtering
Figure 9. Composite photograph depicting the diathermy effect at the edge of a breast biopsy. A. The cautery artifact has markedly distorted the epithelial cells within this lobular unit (hematoxylin-eosin, original magnification ×200). B. Given the smudged and elongated appearance of the ductal epithelium, the degree of atypia cannot be determined accurately in this proliferative lesion. The cauterized margin is present along the lower right corner of this picture (hematoxylin-eosin, original magnification ×400).

Figure 10. Crushed tumor cells in a core biopsy of an invasive carcinoma. Although there appears to be an infiltrative pattern in this lesion, the extensive crush artifact precludes accurate evaluation of the cytologic detail of these cells (hematoxylin-eosin, original magnification ×400).

Figure 11. Composite photograph of sclerosing adenosis from a patient with extensive fibrocystic changes. A. There are several compressed ductal structures that exhibit pseudoinvasion between acini of a terminal duct lobular unit (hematoxylin-eosin, original magnification ×400). B. A second focus photographed at a lower power demonstrates the characteristic lobulocentric distribution of sclerosing adenosis (hematoxylin-eosin, original magnification ×100).

Figure 12. Frozen section of a breast biopsy containing a radial scar. This lesion was found on mammography and reported as suspicious for malignancy. Note the central elastosis and peripheral distribution of several sclerotic and hyperplastic lobular units associated with microcalcifications (hematoxylin-eosin, original magnification ×40).
the stains is important for staining clarity and prevention of “tissue floaters” from other cases.

**HISTOPATHOLOGY**

A simple approach to the different lesions encountered in frozen sections of breast specimens is to subcategorize them into the following diagnostically useful groups: benign lesions mimicking cancer, fibroepithelial lesions, invasive carcinomas, and those lesions that fall in the category of “deferred diagnosis.” The following paragraphs discuss the more common examples in these various groups and their associated morphologic pitfalls.

**Benign Lesions Mimicking Cancer**

Overdiagnosis of this group of lesions can lead to disastrous consequences for the patient. They include radial scars/complex sclerosing lesions, sclerosing adenosis, and sclerosing papillomas. These lesions may result in a mistaken diagnosis of malignancy because irregularly shaped glands entrapped within dense fibrous tissue appear to infiltrate the breast parenchyma (“pseudoinvasion”). The occasional presence of glands within perineural spaces in radial scars/complex sclerosing lesions and sclerosing adenosis also adds to the diagnostic confusion. The presence of a 2-cell layer in these entrapped ducts is a useful mor-

---

**Table 2. Differential Diagnosis Between Sclerotic Breast Lesions and Tubular Carcinoma**

<table>
<thead>
<tr>
<th>Histologic Characteristics</th>
<th>Radial Scar</th>
<th>Sclerosing Adenosis</th>
<th>Sclerosing Papilloma</th>
<th>Tubular Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glandular architecture</td>
<td>Haphazard</td>
<td>Lobulocentric</td>
<td>Nodular</td>
<td>Haphazard</td>
</tr>
<tr>
<td>Fibrous reaction</td>
<td>Central</td>
<td>Within lobule</td>
<td>Within papilloma</td>
<td>Evenly distributed</td>
</tr>
<tr>
<td>Margins</td>
<td>Infiltrative</td>
<td>Rounded</td>
<td>Rounded</td>
<td>Infiltrative</td>
</tr>
<tr>
<td>Glandular components</td>
<td>Double layer</td>
<td>Double layer</td>
<td>Double layer</td>
<td>Single layer</td>
</tr>
</tbody>
</table>

---

**Figure 13.** Fibroadenoma excised from a 23-year-old woman. The diagnosis of a fibroadenoma is usually not a diagnostic problem on frozen section. The characteristic intracanalicular growth pattern is evident in this photograph (hematoxylin-eosin, original magnification ×40).

**Figure 14.** Phyllodes tumor removed from a 46-year-old woman. The typical leaflike processes of this tumor is evident in this picture. As noted in the text, one should not try to subclassify these tumors on frozen section. A generic term, such as fibroepithelial lesion may be used pending further histologic sampling (hematoxylin-eosin, original magnification ×20).

**Figure 15.** Tubular carcinoma. There is haphazard arrangement of the tubules in a desmoplastic stroma. Some of the tubules have angulated contours and are lined by a single row of cells (hematoxylin-eosin, original magnification ×400).

**Figure 16.** Invasive lobular carcinoma involving 2 ductal structures. Note the characteristic targetoid growth pattern surrounding the upper duct (hematoxylin-eosin, original magnification ×400).
Figure 17. Epithelial proliferative lesions. A, Florid usual ductal hyperplasia on frozen section. Streaming of the epithelial cells, the irregular spaces, and heterogeneous appearance of the ductal cells are morphologic signs of benignity (hematoxylin-eosin, original magnification ×200). B, Atypical ductal hyperplasia. Three ductal structures are replaced by proliferative lesions exhibiting a greater degree of architectural and cytologic atypia when compared with part A (hematoxylin-eosin, original magnification ×200).

Figure 18. Ductal carcinoma in situ. This patient presented with mammographic and clinical findings that were highly suspicious for malignancy. A frozen section revealed extensive high-nuclear-grade ductal carcinoma in situ associated with necrosis and calcifications. A focus of invasive carcinoma was identified in the permanent sections (hematoxylin-eosin, original magnification ×200).

Figure 19. Atypical papillary lesion. Frozen section from a complex cystic lesion in an elderly woman. The papillary fronds are lined by pseudostratified and papillary tufts of epithelial cells along the right half of the photograph. A cribriform-like area is present near the center. The architectural and cytologic findings are worrisome for an intracystic (intraductal) papillary carcinoma. This finding was confirmed in the permanent sections. No invasive carcinoma was found (hematoxylin-eosin, original magnification ×200).

Figure 20. Malignant lymphoma of the breast. This touch imprint is from a 61-year-old woman with a prior diagnosis of non-Hodgkin lymphoma. A monomorphic population of atypical lymphoid cells is seen. A few multilobated forms and mitotic figures are also present. Flow cytometric studies revealed a monoclonal B-cell lineage, confirming the diagnosis of non-Hodgkin lymphoma (hematoxylin-eosin, original magnification ×400).
phologic clue to their benign nature. Other distinguishing features include the lobulocentric nature of the glandular proliferation in sclerosing adenosis, central elastosis and peripheral radiating ducts in radial scars/complex sclerosing lesions, and papillary projections and dilated spaces seen along the periphery of sclerosing papillomas (Figures 11 and 12). Table 2 summarizes the salient features of these sclerotic proliferative lesions. Other less common entities that should not be attempted on frozen section include microglandular adenosis, tubular adenosis, and granular cell tumors.13,14

Fibroepithelial Lesions

This category includes fibroadenoma and phyllodes tumor. Frozen section evaluations of fibroadenomas usually do not present diagnostic problems (Figure 13). However, differentiating a cellular fibroadenoma from a phyllodes tumor may be almost impossible to do on a frozen section, given the extensive sampling that may be needed to separate these 2 entities. In such cases, the generic diagnosis of “fibroepithelial lesion” is preferred. It also may not be possible to differentiate a low- versus high-grade phyllodes tumor based on the frozen section result, since numerous histologic parameters such as tumor border, stromal cellularity, stromal overgrowth, and mitotic activity need to be assessed in several permanent sections of the tumor.15 Again, the intraoperative diagnosis of fibroepithelial lesion should be used with the caveat that this may turn out to be a phyllodes tumor on the permanent sections (Figure 14). This way, additional tissue can be excised from the margins at the time of the initial surgery, if the diagnosis of phyllodes tumor is a likely possibility.

Invasive Carcinomas

In most instances, identifying a breast carcinoma as invasive is not difficult. The main histologic feature of invasion is the totally disorganized arrangement of the neoplastic cells in association with a desmoplastic stromal reaction. There are, however, certain forms of invasive cancer that may present diagnostic challenges at the time of frozen section. They include tubular carcinoma and the classic form of invasive lobular carcinoma. Tubular carcinomas consist of haphazardly arranged small glands and angulated tubules formed by a single layer of neoplastic cells (Figure 15). The differential diagnosis includes sclerosing adenosis. As mentioned previously, the glandular proliferation in sclerosing adenosis has a lobulocentric pattern at low power, and the glands are formed by 2 rows of cells (inner epithelial and outer myoepithelial layer). Table 2 summarizes the morphologic features of tubular carcinoma versus the sclerotic proliferative lesions that mimic invasive cancer. Invasive lobular carcinoma is often misdiagnosed because of the paucicellular nature of the tumor, coupled with the bland nuclear features of the neoplastic cells. The linear and targetoid growth patterns of this tumor are helpful histologic clues for diagnosis (Figure 16). Given the small size of the tumor cells, they may be mistaken for chronic inflammatory cells. Cytologic smears are a useful adjunct in this differential diagnosis. With invasive lobular carcinoma, one will see cellular cohesion and intracytoplasmic mucin droplets in the neoplastic cells. When faced with an unusual or rare form of invasive breast cancer, a generic diagnosis of invasive carcinoma can be used at the time of frozen section, with the final diagnosis pending histologic sampling of the fixed tissue.

Deferred Diagnosis

Although one should make every attempt to arrive at a specific diagnosis at the time of frozen section, there are instances in which it would be prudent not to do so. All epithelial proliferative lesions should not be diagnosed by means of a frozen section. That includes usual ductal hyperplasia, atypical ductal and lobular hyperplasia, and ductal and lobular carcinoma in situ (Figure 17). With the exception of comedo-type ductal carcinoma in situ, these lesions rarely, if ever, present as a palpable mass requiring intraoperative analysis (Figure 18). Overcalling atypical ductal hyperplasia at the time of frozen section may cause the patient to suffer needless anxiety. Papillary epithelial lesions also should not be diagnosed intraoperatively. The differential diagnosis between an intraductal papilloma and papillary carcinoma is based on extensive sampling of the fixed tissue, looking for a single layer of epithelial cells in the latter diagnosis. If the mammographic and/or clinical findings suggest that the papillary lesion has a high probability of being malignant, then complete excision of the lesion with ample surgical margins should be attempted as a 1-stage procedure (Figure 19). Lymphoproliferative lesions that involve the breast should be handled in a manner similar to lymph node biopsies performed for suspected lymphoma. If the cytologic and/or frozen section is suggestive of non-Hodgkin lymphoma, fresh tissue should be saved for possible flow cytometric studies. Figure 20 illustrates a rare case of non-Hodgkin lymphoma involving the breast. A final diagnosis of B-cell lymphoma was made after correlating the morphology with the flow cytometric studies. Finally, intraoperative diagnosis of soft tissue tumors should also be deferred. This would include entities such as pseudoangiomatous stromal hyperplasia, fibromatosis, and vascular and mesenchymal tumors.

References