Chapter 2
Assessment of the Surgical Margins

The local treatment of breast cancer has evolved significantly in the last 100 years. This was based on the notion that the removal of the entire breast and its lymphatic drainage area (axilla) would achieve not only local but also distant disease control. This Halstedian approach changed to modified radical mastectomy (MRM), when a better understanding developed that the treatment failure despite such a radical procedure was due to early dissemination of tumor cells, prior to surgical intervention. The pivotal study National Surgical Breast and Bowel Project (NSABP) B-04 showed equivalency of simple mastectomy plus radiation to MRM. A series of subsequent studies established that conservative surgery with whole breast radiation did not affect survival, as compared to total mastectomy (Table 2.1).

The National Institutes of Health (NIH) recommended breast conserving surgery (BCS) as the preferred surgical treatment for early breast cancer in 1991. Similarly, National Accreditation Center for Breast Cancer requires a BCS rate of at least 50%. The BCS rates have been reported to be as high as 90% in the published studies, but in general, most institutions reached the rates of about 65–70%. Recently, there has been an increase in mastectomy rates, which appears to be related to several factors, including genetic testing, improved breast reconstruction techniques, patient demand, and increased detection of multifocal tumor due to use of sensitive imaging modalities, such as magnetic resonance imaging (MRI).

The value of adequate surgical margin in decreasing local recurrence rates has been established both in invasive and in situ breast cancers. A summary of long-term studies looking at recurrence rates by margin status is provided in Table 2.2.

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TABLE 2.1 A summary of large prospective trials comparing survival after conservative breast surgery and radiation versus mastectomy.

Trial	Follow up (years)	Overall survival (%)	
		BCS + RT	Mastectomy
Milan	20	42	41
NSABP B-06	20	46	47
NCI	18	59	58
Institut Gustave-Roussy	15	73	65
EORTC	10	65	66

BCS + RT *breast conserving surgery + radiation therapy,* NSABP *National Surgical Adjuvant Breast and Bowel Project,* NCI *National Cancer Institute,* EORTC *European Organization for Research and Treatment of Cancer*

TABLE 2.2 Local recurrence rates by margin status in breast cancer.

Study site	No. of patients	Follow-up (year)	Recurrence rates by margin status (%)		
			Negative	Close	Positive
Fox Chase	1,262	6.3	7	14	12
Netherlands	1,026	6.5	2	6	16
Univ. of Penn	1,021	6.1	8	17	10
Yale	984	13	2	2	18
Gustave-Roussy	757	9	6	NA	14
Tufts	498	10	5	9	17
Stanford	289	6	2	16	9
Duke	259	3.8	2	NA	10

NA data not available

The local management of breast cancer continues to change and at the present time, BCS is the most common approach in all early breast cancers, typically detected by screening mammography. The goal of the breast surgeon is to get clear margins in one surgical procedure, whenever possible. A second surgical procedure is not desirable due to patient discomfort, costs, and risks associated with anesthesia and major surgery. Therefore, the evaluation of surgical margins during the surgical procedure is desirable by the surgeon. However, dealing with fatty breast tissue is difficult for the pathologist. Over the years, the pathologists have tried at least three methods for intraoperative margin assessment: gross examination after slicing the specimen, frozen section (FS), and touch imprints (TI). There has been variable success using these

methods and the field of intraoperative assessment of surgical margins of breast specimens has evolved. In general, the surgeons have changed their practice from completely relying on intraoperative pathologic assessment to better preoperative and intraoperative imaging modalities to obtain adequate surgical margins.

GROSS EXAMINATION FOR SURGICAL MARGINS

In cases with a palpable mass, a careful gross examination after the specimen has been inked and thinly sliced, should allow the pathologist to assess the margins. A combination of close inspection and gentle palpation helps demarcate the extent of the tumor (Fig. 2.1). The margins can then be measured and reported to the surgeon. This method has not been reliable in accurately identifying the distance of the tumor to surgical margins. In one of the studies of 181 patients, followed for 5 years, grossly positive margins were associated with 21% local recurrence rate, as compared to cases with negative margins showing no recurrence. In another study of 254 patients, spread over a 6-year period, tumor within

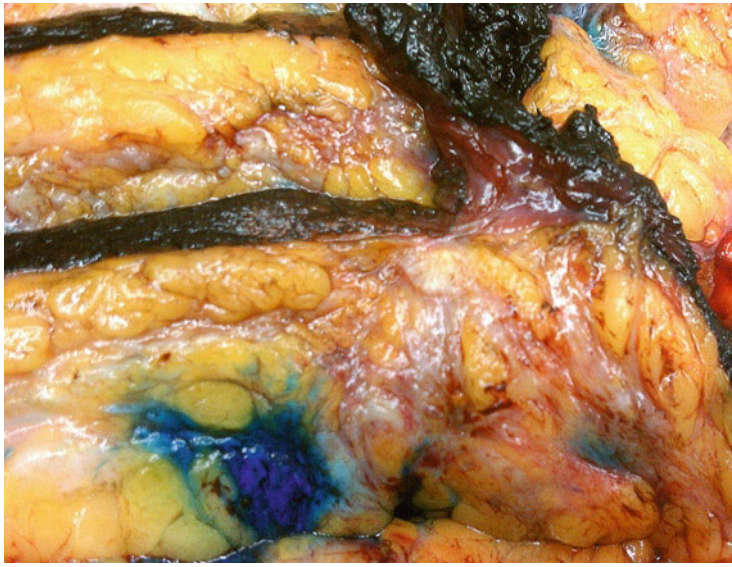


FIGURE 2.1 Invasive tumor involving the deep margin and pectoralis muscle. There is an irregular tumor mass in this mastectomy specimen. The *blue dye* represents injection at the previous lumpectomy site, used for sentinel node mapping. The tumor is very close to black-inked deep margin. A small piece of *brown* pectoralis muscle is present, as tumor abuts the fascia at this focus.

2 mm of the inked surface was considered margin-positive and >2 mm as margin-negative. Gross examination in this series did not accurately reflect the final margin status in 25% of the cases, when compared to the margin status in the final pathology report. Therefore, the surgical margin evaluation by gross examination alone has limited value in intraoperative assessment. However, in selected cases with well-demarcated, single tumor focus, 3–5-mm rim of normal appearing adipose tissue can be reliably considered as a negative margin. In most cases, the information that tumor is very close to the margin, may be sufficient for the surgeon to obtain additional tissue during the first surgical procedure. However, certain locations, such as anterior margin in a centrally located tumor, tumors close to medial edge of breast and in some cases tumor close to the inframammary crease may not leave much tissue to remove with good cosmesis. In such cases, an accurate assessment of close margins can be of significant value to the surgeon and the patient and other methods to evaluate the surgical margins, e.g., FS or TI should be considered.

FROZEN SECTION FOR SURGICAL MARGINS

It is difficult to obtain good sections of fat around the tumor and complete reliance on FS alone can lead to an erroneous interpretation of margin, i.e., closer than the actual distance. Tumors within 2–3 mm of the inked margins can be evaluated by frozen section. When mainly fibrous tissue is present around the tumor, then the likelihood of an accurate assessment of distance between the tumor and the margin is high (Figs. 2.2–2.8). On the other hand, normal adipose tissue around the tumor would most likely result in an underestimation of true distance to the margin (Figs. 2.9–2.11). In both these cases, a relatively small piece of tissue with tumor should be placed in a larger sized tissue disc to allow for a rim of OCT gel, which can be very helpful in obtaining a good section. Another helpful point is to consider cutting the FS at a thickness of 8–9 mm, in order to get reasonable complete sections (Fig. 2.12). During the process of FS, evaluation of frozen tissue in the cryostat, after the frozen tissue block has been faced can be very helpful to see the relationship between the tumor, which appears white or gray-white against bright yellow adipose tissue and the inked surface (Figs. 2.13 and 2.14). The advantage of a good frozen section is that it allows measurements of margins in millimeters rather than a qualitative assessment as positive or negative. The reliability of FS in assessing surgical margins in breast cancer has been reported in a few studies (Table 2.3). This limited data suggest that FS can be a fairly reliable method for surgical margin assessment.

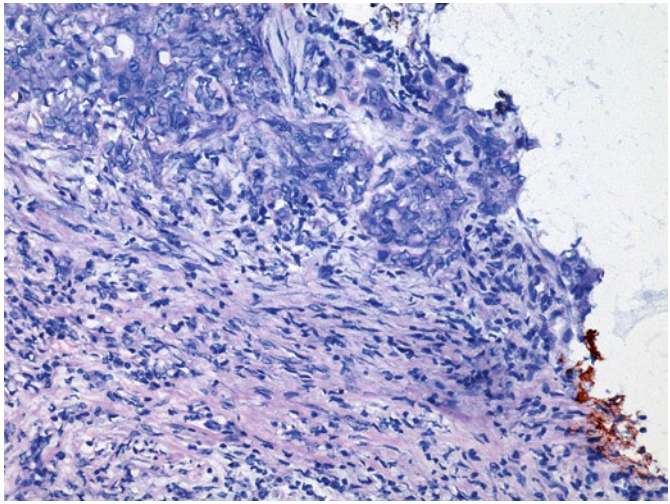


FIGURE 2.2 An invasive tumor is transected at the margin. There is significant frozen artifact in the tumor cells but they are recognizable, as compared to inflammatory cells elsewhere in the section.

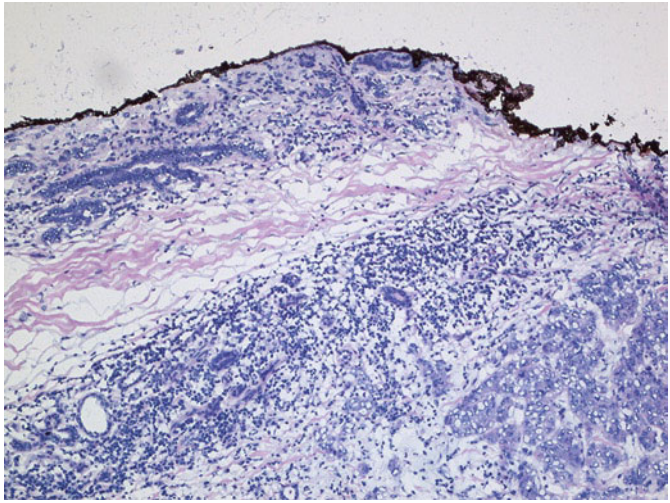


FIGURE 2.3 Very close margin on frozen section. This is a high power view of section from Fig. 2.2. There is an inflamed normal breast unit at the inked margin.

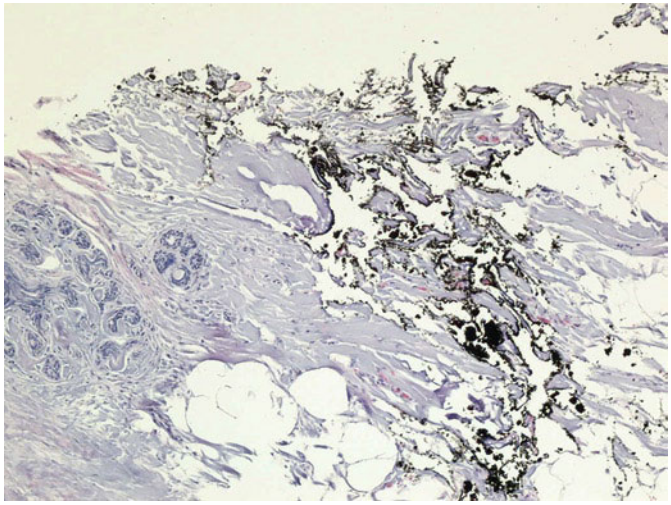


FIGURE 2.4 Negative margin on frozen section. The tissue is fragmented and ink has seeped into the tissue. However, the histologic features are easy to read and show benign breast epithelium and stroma.

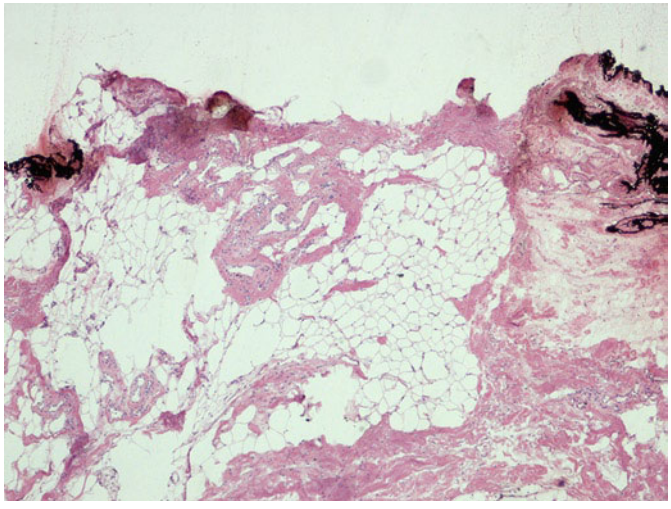


FIGURE 2.5 Optimal frozen section due to fibrous tissue at the margin. Due to less fat in the tissue, an optimal section can be prepared and it shows negative surgical margin.

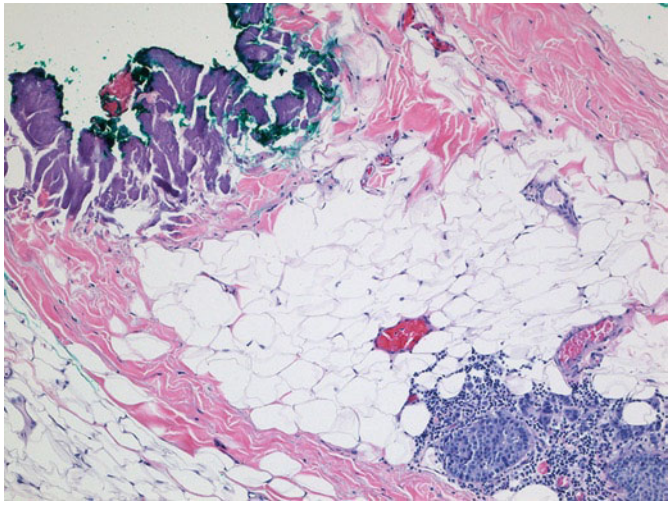


FIGURE 2.6 Close but negative margin on frozen section. The inked and cauterized margin is present in the left upper corner. There is a small focus of DCIS and associated invasive tumor with fat between the tumor and the inked margin. Therefore, the margin is negative but close.

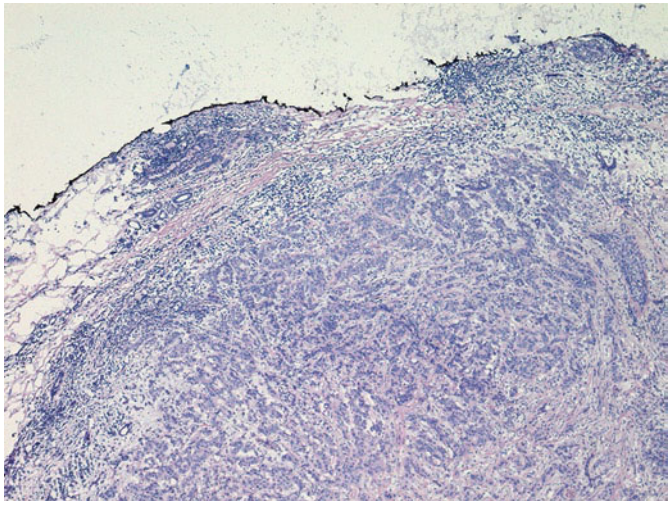


FIGURE 2.7 Close margin for invasive tumor on frozen section. The invasive tumor has a relatively circumscribed edge and it is within 1 mm of the inked margin. It appears that there is rim of benign tissue at the margin.

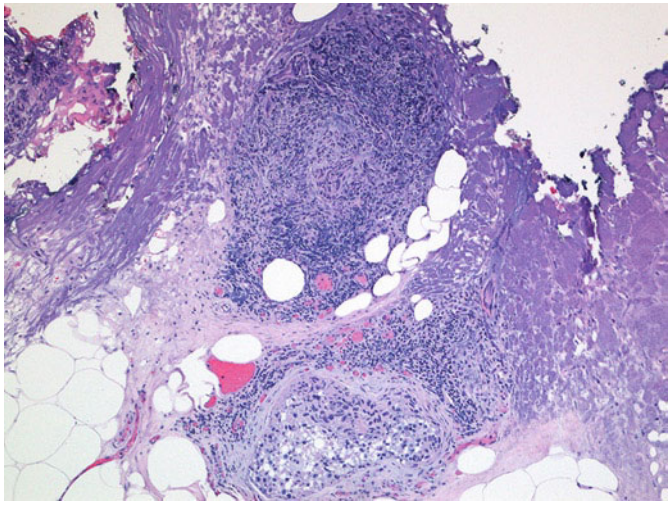


FIGURE 2.8 Indeterminate margin on frozen section. There is marked cautery artifact with crushed cells, which cannot be reliably interpreted. There is a small intact focus of DCIS. On close examination, it appears that DCIS is very close to the margin and there is a piece of cauterized epithelium on the left. Overall, the margin evaluation is indeterminate in this case.

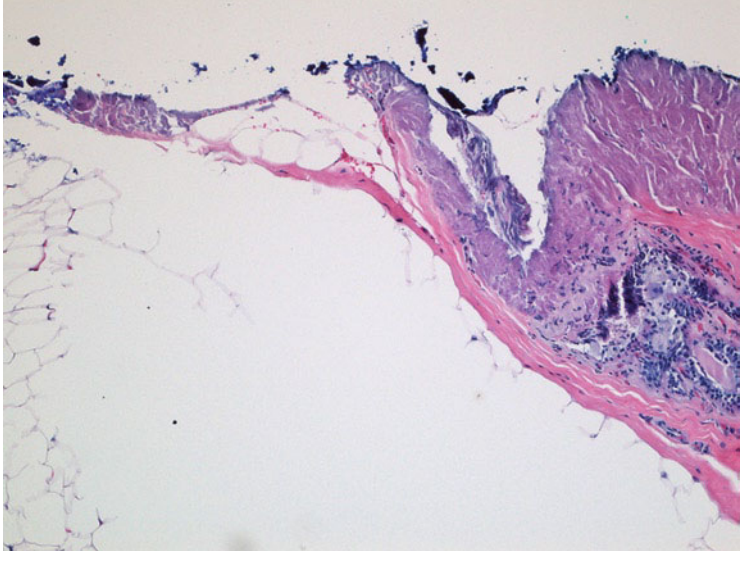


FIGURE 2.9 The main limitation of frozen section for margins is inability to obtain complete sections of fatty tissue. This is a fairly good quality frozen section showing small amount of benign breast epithelium in fibrous stroma. However, most of the fatty tissue is missing in the section.

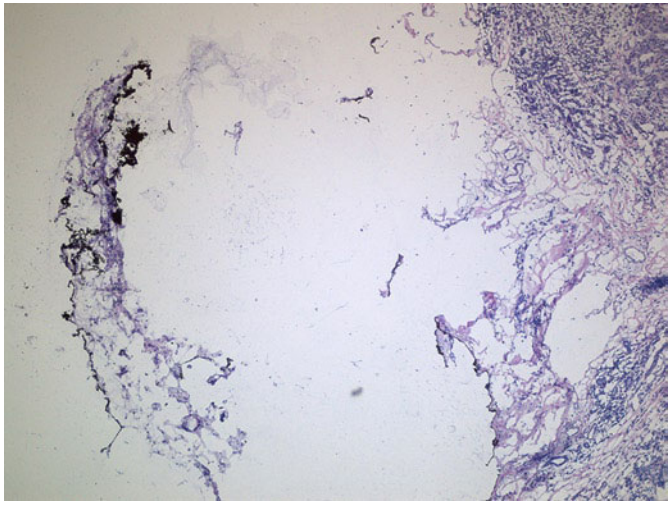


FIGURE 2.10 Difficult frozen section due to fat. Due to mainly fat, there is a large piece of tissue missing in this section. The tumor is on the right and there is some benign breast tissue after the tumor. The margin can be reported as negative with confidence; however, the actual distance cannot be measured in frozen section.

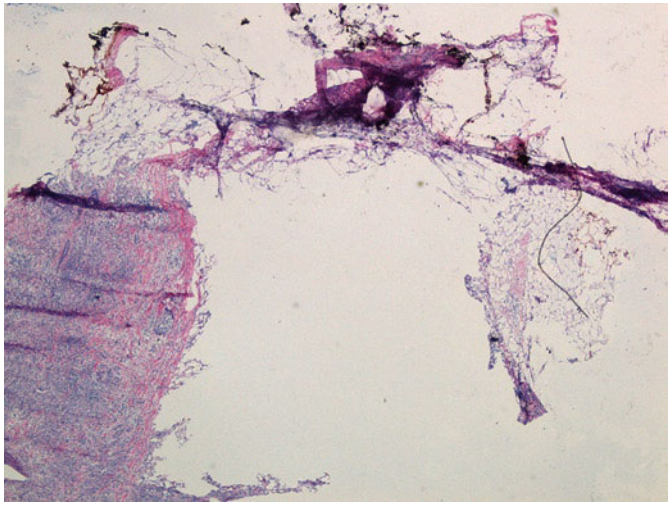


FIGURE 2.11 Fatty tissue at the margin precludes reliable assessment of the actual surgical margin. The tissue has folded over due to pure fat between the tumor and the inked surface. The margin appears negative but it is impossible to measure the exact distance between the tumor and the actual margin.

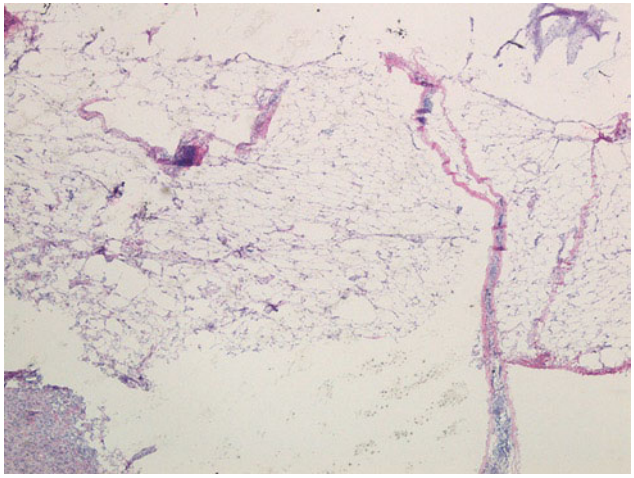


FIGURE 2.12 Technique to cut full sections of fatty tissue. One of the ways to obtain reasonable quality section of fatty breast tissue is to increase the section thickness in the cryostat. In the section illustrated here, the section was cut at 8-mm thickness, leading to a fairly complete section of fat. The tumor is seen at the bottom and true distance between the tumor and the inked margin can be measured.



FIGURE 2.13 Examination of the frozen tissue block in cryostat. This is a trimmed frozen section block for margin evaluation. The examination of block in the cryostat is a helpful adjunct during the intraoperative assessment. One can see that the entire tissue is composed of fat and the possibility of getting a good frozen section is very low.



FIGURE 2.14 Examination of the frozen tissue block in cryostat. A close examination of trimmed frozen tissue block is very helpful in studying the topography of margin and rest of the tissue. In this case, the tissue appears to be fibrous at the margin. The frozen section preparation is expected to be reasonable.

TABLE 2.3 Studies evaluating the utility of frozen section in assessing surgical margins in breast cancer.

Authors	No. of patients	Sensitivity (%)	Specificity (%)
Olson et al.	290	90	100
Weber et al.	140	91	100

TOUCH IMPRINT FOR SURGICAL MARGINS

Touch imprint or preparation of the surgical margin is another way to perform intraoperative margin assessment. An appropriately labeled glass slide is touched to each of the five or six surfaces, depending on whether there is any attached skin to obtain cells for evaluation. A simple and quick stain, such as Diff-quik or Toluidine blue can be used on air-dried slides. For surfaces, measuring more than 5 cm, two imprints are prepared for each surface

to adequately sample the surgical margin. The other options include use of rapid H&E or Papanicolaou stain on alcohol-fixed slides. The slides are then screened to look for malignant epithelial cells. This method yields either no epithelial cells or rare clusters of benign epithelial and nonepithelial cells, when the margin is negative versus atypical or malignant epithelial cells in case of a positive margin (Figs. 2.15–2.25). This method has been successfully used by several laboratories, and on average takes about 10 min per specimen. Some of the studies that have evaluated the value of TI in evaluating surgical margins are summarized in Table 2.4. These studies suggest that the use of TI in this setting is not highly reproducible and has low sensitivity in low-grade tumors. This may be related to differences in technique and lack of expertise among interpreting pathologists. However, Moffitt Cancer center in a series of publications has shown this to be reproducible in their hands and their long-term follow-up study on 701 patients showed a low recurrence rate of 2.7% at 3.5 years

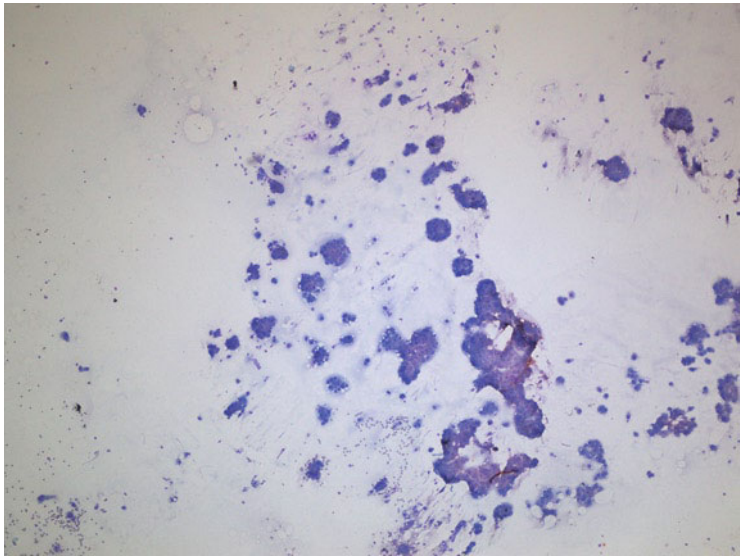


FIGURE 2.15 Low power screening of imprint cytology preparation for margin evaluation. This is an air-dried preparation for margin evaluation, stained with diff-quik. The low power examination at scanning objective is extremely useful. This imprint slide is very cellular and shows cell clusters of variable size and shape, consistent with positive margin.

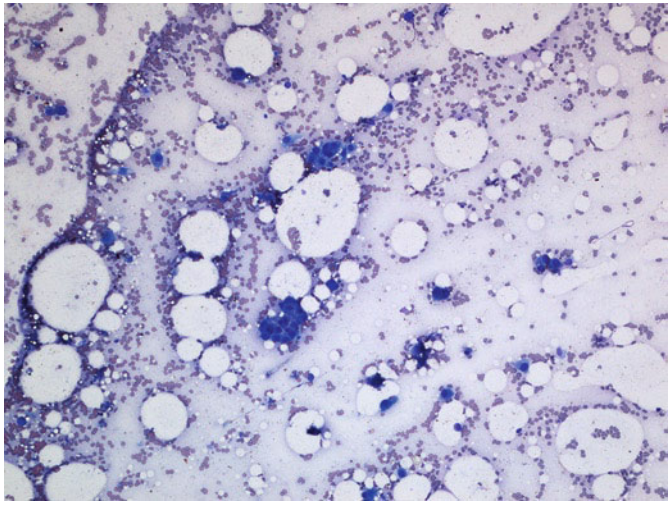


FIGURE 2.16 Rare tumor cells on touch imprint. This touch imprint shows blood in the background with relatively few single and small clusters of malignant epithelial cells. Careful screening of such preparations is needed in order to reach the correct diagnosis.

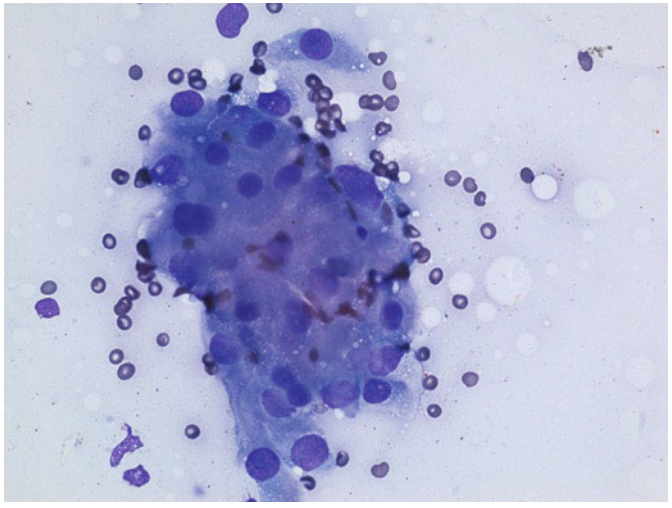


FIGURE 2.17 Positive imprint from surgical margin. This high power view shows a cluster of epithelial cells with malignant cytologic features, e.g., enlarged cells, nucleomegaly, high NC ratio and nucleolus. There is some cellular dyscohesion.

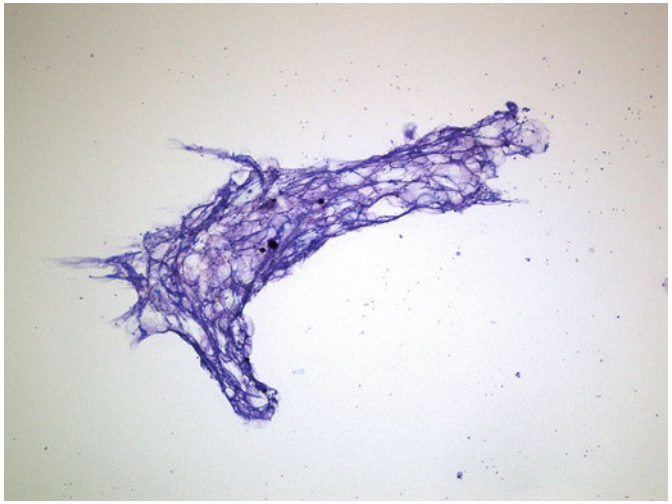


FIGURE 2.18 Negative margins on diff-quik stained imprint. This air-dried imprint from a surgical margin shows a piece of benign adipose tissue. No epithelial cells are present, consistent with negative margin.

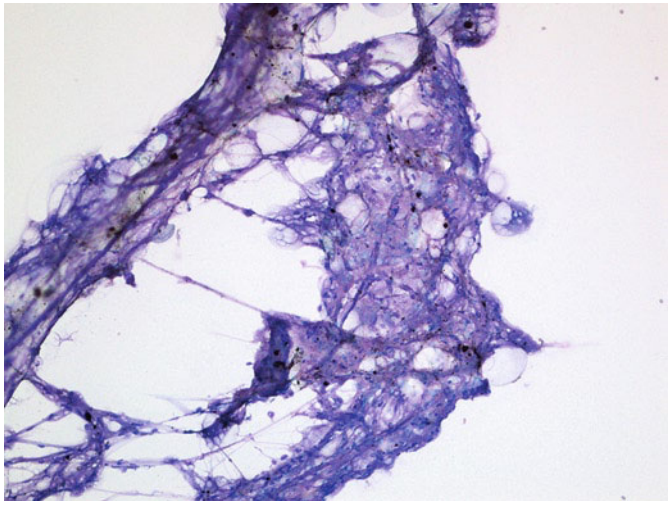


FIGURE 2.19 Typical appearance of imprint from a negative margin. There is a large piece of adipose tissue in a clean background. This is a fairly typical appearance of touch imprints in case of a negative margin.

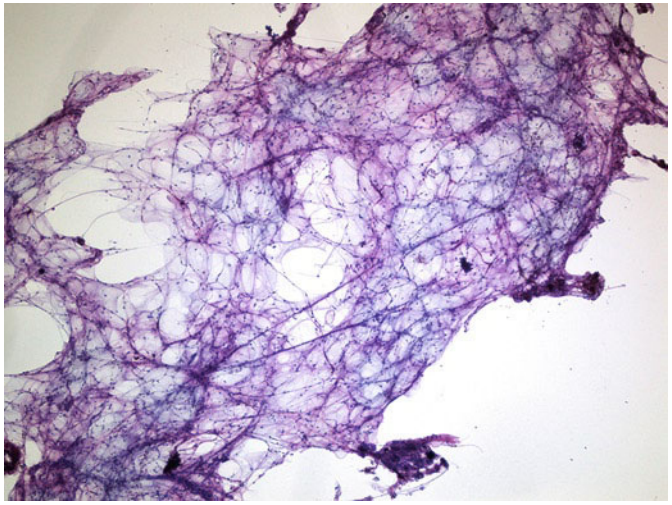


FIGURE 2.20 Touch imprint from normal breast tissue at margin. This slide shows a clean background with a large fragment of adipose tissue. There are a few possible clusters of epithelial cells, which need more evaluation.

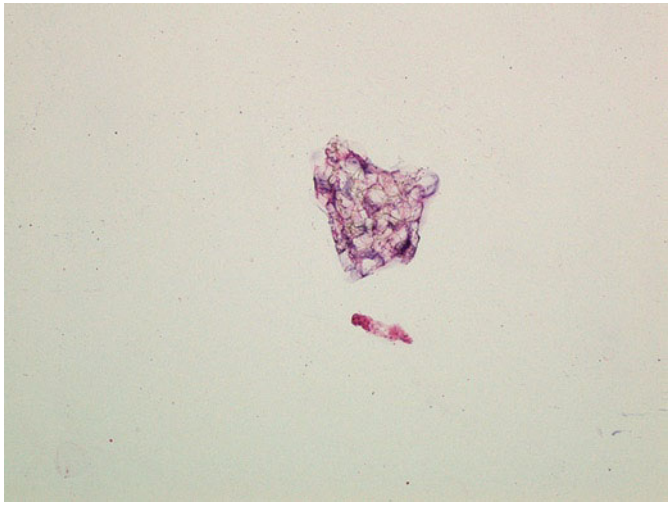


FIGURE 2.21 Alcohol-fixed touch imprint for surgical margin evaluation. This touch imprint for margin is fixed in alcohol and a rapid H&E stain is done. The background is clear and there is only a small amount of fat on the slide, consistent with a negative margin.

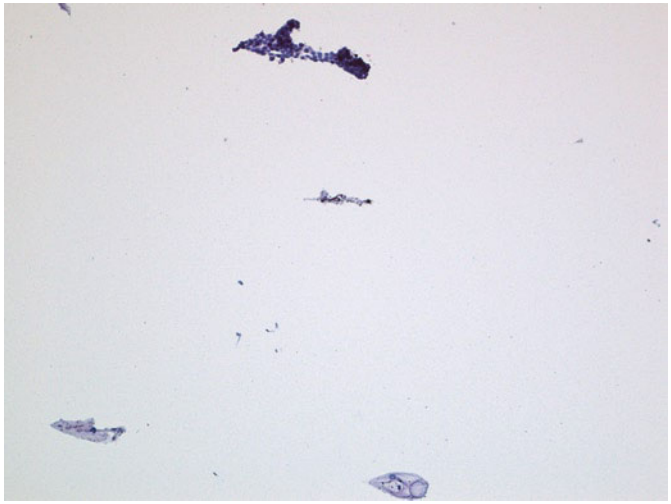


FIGURE 2.22 Typical features of touch imprint from a negative margin. Intermediate power view of an alcohol-fixed touch imprint. Besides clear background and small amount of fat, there is a small group of epithelial cells. They are arranged in monolayer and have uniform nuclei, typical of benign breast ductal epithelium. The interpretation is negative margin.

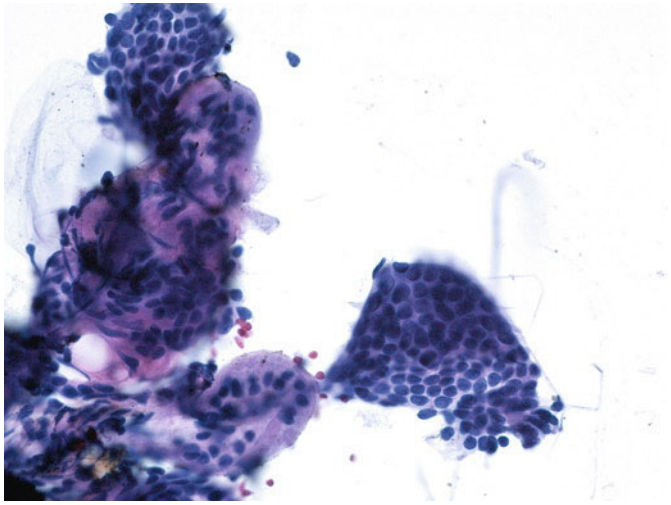


FIGURE 2.23 Evaluation of epithelial structures from touch imprints. High power view of the epithelial group seen in Fig. 2.24. Note the flat sheet-like arrangement, uniform nuclear size, and slightly branched architecture of normal ductal epithelium.

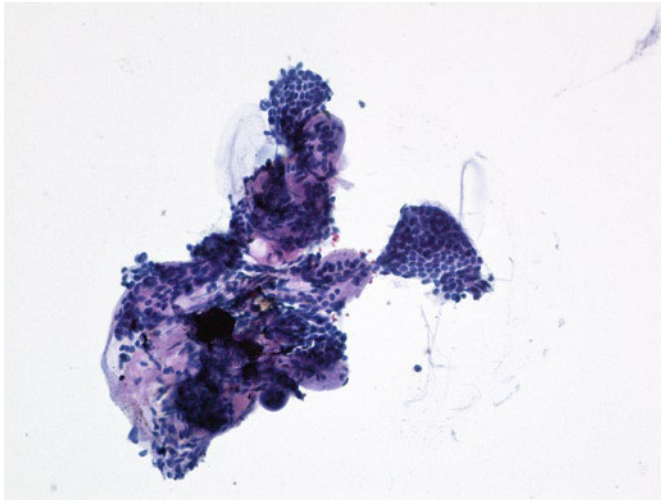


FIGURE 2.24 Evaluation of epithelial structures from touch imprints. Intermediate power view of normal breast epithelial component in a touch imprint. The overall architecture recapitulates a terminal duct lobular unit.

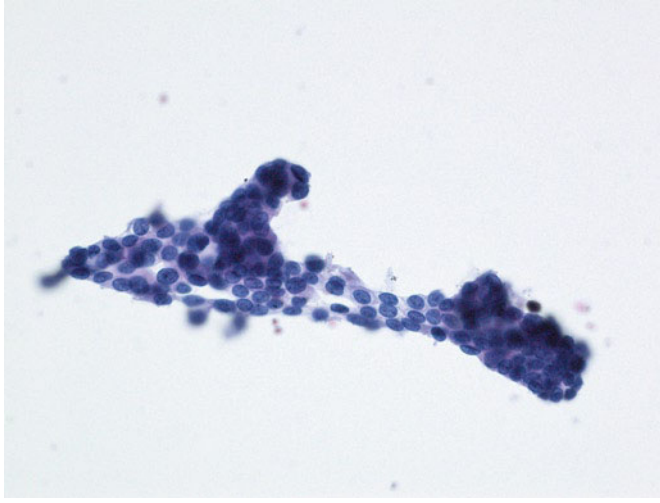


FIGURE 2.25 Normal breast epithelium on touch imprint of surgical margin. High power view of normal breast epithelial component (seen in Fig. 2.22), sometimes seen on touch imprints of negative margins.

TABLE 2.4 List of studies evaluating the usefulness of touch imprint method of surgical margin assessment.

Authors	No.	Sensitivity (%)	Specificity (%)
Klimberg et al.	428	100	100
D'Halluin et al.	400	89	92
Cox et al.	114	100	97
Saarela et al.	55	38	–
Valdes et al.[a]	12	8	98

[a] Invasive lobular carcinoma only

of median follow-up. Therefore, TI for margin assessment for breast specimens can be safe, rapid, and in experienced hands a relatively reliable method. Some reports state that touch imprint can be successful in the assessment of margin during second surgery to obtain clear margins. However, it is important to exercise caution in interpreting either TI or FS in this setting, since the changes after the initial surgery can mimic malignancy.

Some studies have specifically evaluated a combination of different methods in reducing the re-excision rates for positive margin at the time of the first surgery. Weber et al. compared the benefits of specimen radiography and FS in assessing surgical margins in 115 lesions. FS assessment of surgical margins rendered 27.5% cases as margin-negative versus 14.3% by specimen radiography only. In a series of 264 patients with stage 0–III breast cancers, Cabioglu et al. reported that with the use of intraoperative margin assessment, about 25% of this population was rendered margin-negative. They verified this approach by reporting the 5-year recurrence-free survival rate of 99% for invasive and 100% for DCIS after addition of radiation therapy to BCS. In another study of DCIS, using the same methodology, a significant number of patients were spared a second surgery to obtain negative margins. These studies demonstrate the benefit of intraoperative surgical margin assessment.

OTHER INDICATIONS FOR FROZEN SECTION

FS of breast specimens can be used in the assessment of skin margins in skin-sparing mastectomies. In addition, a FS may be used to rule out DCIS or invasive cancer in cases of nipple-sparing mastectomy. Usually a section from subareolar area is submitted for FS evaluation (Figs. 2.26–2.33). Unlike the FS for soft tissue margins for palpable or nonpalpable cancers, FS are technically

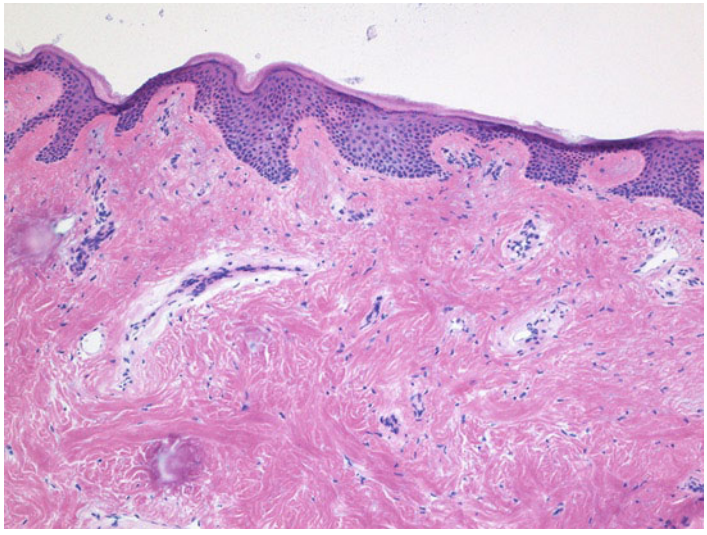


FIGURE 2.26 Frozen sections of skin margins in locally advanced cancer. They are easy to prepare and evaluate, unlike fatty breast tissue. Detailed histologic examination is possible. In this case, the margin is negative.

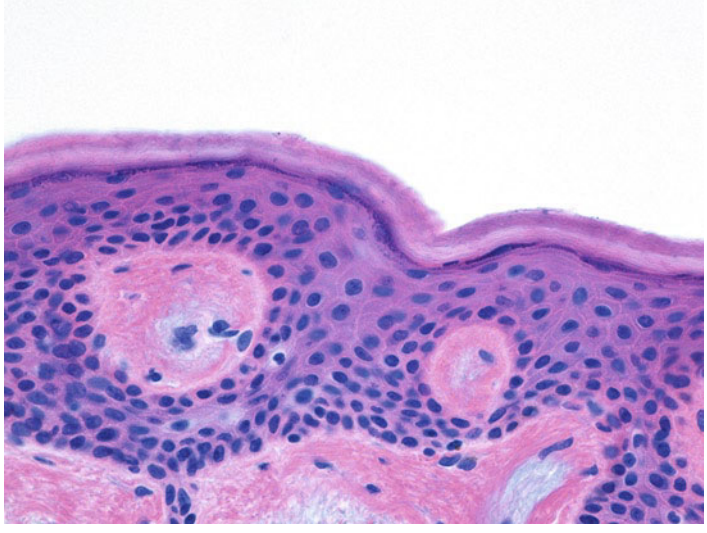


FIGURE 2.27 Skin margin for Paget's disease. Skin margin by frozen section. Another example of good microscopic details in the epidermis to rule out Paget's disease.

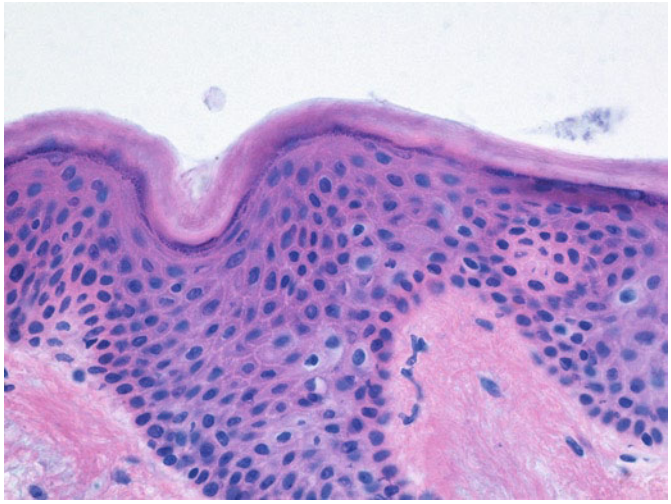


FIGURE 2.28 Skin margin for Paget's disease. High power view of skin margin for a case with Paget's disease. These sections are easy to cut and show enough details to easily rule out malignant cells in the epidermis.

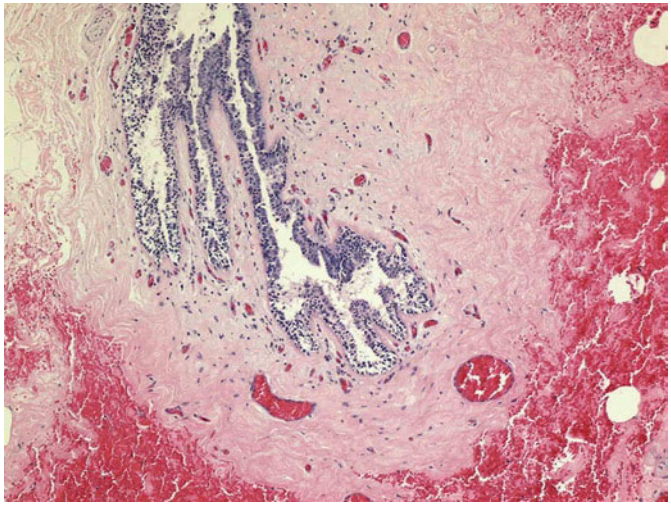


FIGURE 2.29 Frozen section of the subareolar area with a normal duct. There is some hemorrhage and the surgeon was concerned about biopsy site and thus tumor extending too close to nipple to prevent nipple-sparing mastectomy.

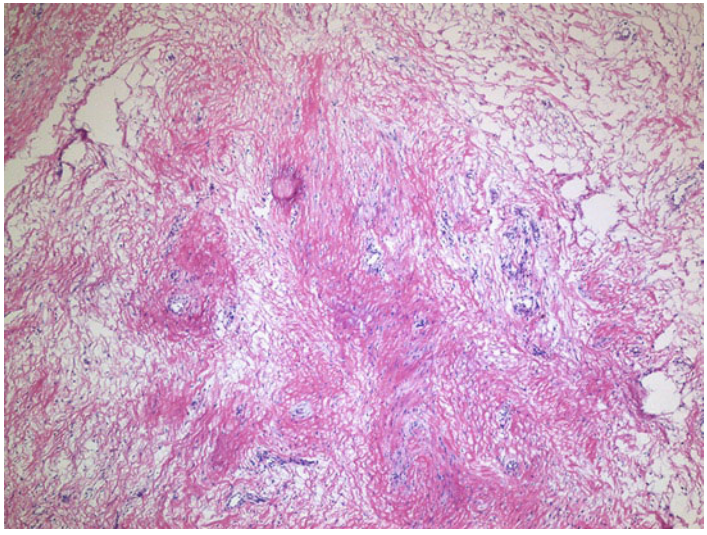


FIGURE 2.30 Frozen section to rule out DCIS extending into the nipple area. No large ducts are seen and the stroma appears benign.

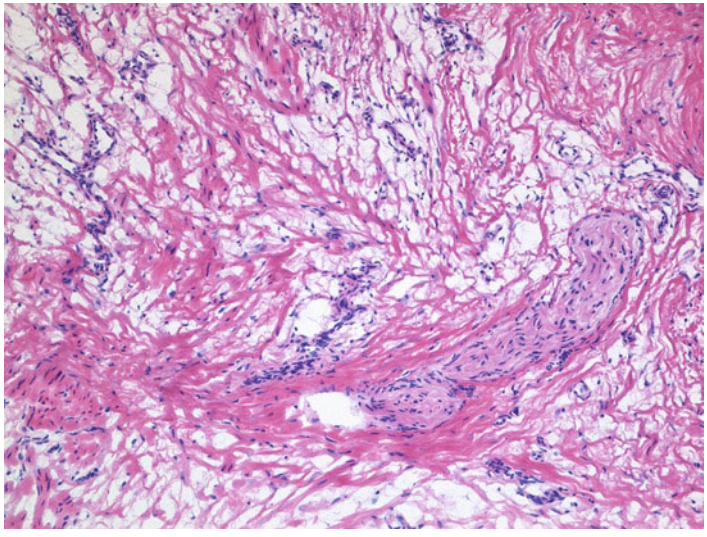


FIGURE 2.31 Frozen section of nipple area. A good quality frozen section allows for detailed examination of benign structures. A nerve and a few blood vessels are identified. No epithelial structures are seen.

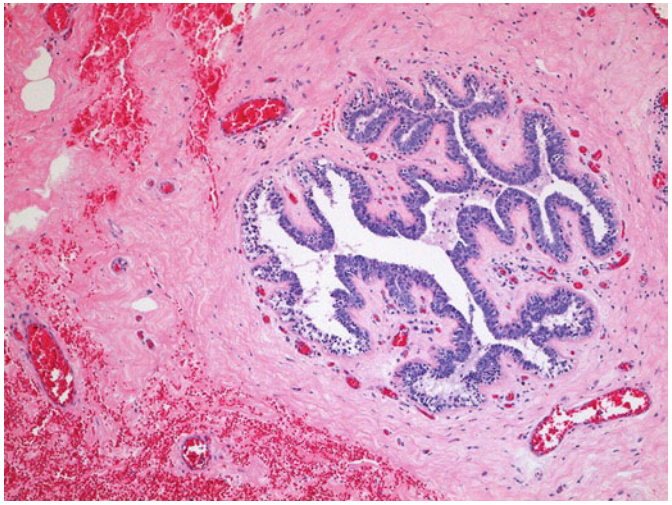


FIGURE 2.32 Frozen section of anterior margin for a centrally located tumor. A benign duct is seen in cross-section. No epithelial proliferation is noted.

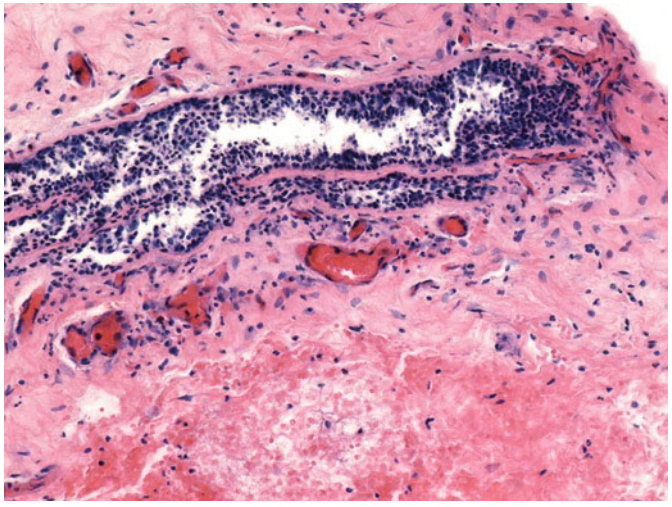


FIGURE 2.33 Frozen section of the subareolar tissue in nipple-sparing mastectomy. A segmental duct is cut longitudinally but shows the two layers without atypia.

easy to perform for evaluation of skin and nipple margins. In such cases, the FS evaluation is primarily used for the diagnosis of malignancy, i.e., DCIS or invasive cancer, particularly in nipple-sparing mastectomy. Certain benign lesions, such as radial sclerosing lesions, intraductal papillomas, sclerosing adenosis, and subareolar sclerosing duct hyperplasia can mimic either in situ or invasive carcinoma. Similarly, a small invasive lobular or tubular carcinoma in this location can be difficult to diagnose. FS artifacts can further enhance the difficulty in making a reliable diagnosis of benignity in these situations. In general, a conservative approach should be used.

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