

## Audit of breast frozen sections

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**F**rozen section consultation for breast lesions is rapid and accurate, especially when dealing with small non-palpable lesions. However, violation of the specimen is possible and this can affect the final decision on the permanent section.<sup>1,2</sup> The most important indications for frozen section are 1) to confirm the diagnosis of carcinoma if fine needle aspiration cytology (FNAC), or core needle biopsies are inconclusive prior to major radical surgery, and 2) to provide an assessment of resection margins in carcinoma.<sup>3,4</sup> There are many issues to consider. If the tumor is close to one margin upon gross examination, then frozen section of that margin is indicated.<sup>1,2</sup> However, there is little role for frozen section evaluation of resection margins that are grossly free of tumor because of the fatty nature of the margins, and the number of sections necessary for a thorough study extend the time the patient is exposed to general anesthesia. In addition, sampling error may occur. Therefore, the evaluation of all margins is best performed on permanent sections.<sup>2</sup> A third and rare indication for frozen section, as maintained by H.A. Oberman, is to assist in the management of the highly anxious patient who insists on an expedited decision.<sup>1</sup> A fourth indication is to obtain fresh material from malignant lesions for measurement of estrogen and progesterone receptors, flow cytometry and other proliferative markers.<sup>5</sup> In the latter situation, a frozen section is not an absolute indication if transfer of the specimen to the laboratory can be accomplished within two hours of excision, so as to perform these tests on a fresh sample.

The size of the lesions is very important in determining whether frozen section is considered. If the suspicious lesion is less than one centimeter, or by gross examination is suspicious for invasive carcinoma but less than one centimeter, then a frozen section is contraindicated because it will have enough frozen artifacts to render the permanent section suboptimal or useless for diagnosis.<sup>4,8</sup> A frozen section can be deferred when the lesion is suspicious for papillary neoplasm,<sup>9,10</sup> or frozen section diagnosis can be deferred to a permanent section if dealing with ductal or lobular borderline lesions or a stromal or vascular lesion.<sup>9-11</sup>

The prevalence of frozen sections is variable in different institutions depending on their experience with frozen section. However, the frequency of performing breast frozen sections is 20% to 35% at M.D. Anderson in Houston, Texas, USA, where they have averaged 70 diagnostic frozen sections per day.<sup>1,11</sup> In current practice, a frozen section of the breast is performed for diagnosis of both palpable masses, and/or for handling specimens of non-palpable masses for

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permanent section with needle localization for abnormal mammogram or calcification. The first scenario would be a breast mass that is clinically and pathologically suspicious for invasive cancer and that measures more than one centimeter; in that case, a frozen section can be done to confirm the diagnosis and to obtain tissue for estrogen and progesterone receptors or other ancillary studies. However, if the lesion is suspicious and measures less than one centimeter, then frozen section is not mandatory and is contraindicated. The second scenario is a clinically non-palpable mass with an abnormal mammogram or identifiable calcification. Needle localization is required prior to surgery, followed by excision of the tissue with the needle. The specimen should be x-rayed immediately after excision. The x-ray will determine if the area that was suspicious in the mammogram is also present in the specimen radiogram. The x-ray will also delineate the relationship of the tip of the needle to the suspicious area. The pathologist paints the specimen and slices it into the thinnest possible sections (no more than one centimeter thick). The pieces are then subjected to a second x-ray. The x-ray of these thin pieces of tissue will clearly localize microcalcification or any area of increased density, indicating the important area to submit for microscopic examination.<sup>12-14</sup> Once the calcification or suspicious area is detected by a second x-ray, then the question of submitting it for frozen section examination arises. Some centers will postpone freezing to save the tissue and the whole piece will be processed for permanent section. Others will evaluate the suspicious area grossly if there is a mass suspicious for malignancy and there is enough tissue for permanent section, i.e. the lesion is more than one centimeter. In that case, the frozen section will be deferred to save the tissue for permanent section for final diagnosis, and another operation will be required.<sup>14-17</sup> Therefore surgical management of breast lesions could involve only one diagnostic step and operation if the mass

is sizable, or two diagnostic steps and therapeutic surgery if the mass is very small or detected radiographically.

Some surgeons still prefer the one-step surgical procedure for the treatment of carcinoma of the breast by frozen section confirmation, rather than the more well-known two-step procedure, that is, obtaining a diagnostic biopsy studied with permanent histological sections, and then discussing therapeutic alternatives with the patient before contemplating definitive treatment.<sup>18</sup> FNAC prior to surgical excision of both big and small masses will help in diminishing the frequency of the two-step surgical procedure and can even help, in the same manner, on mammographically detected breast lesions if a radiologically guided FNAC procedure is performed.

Frozen section is a vital technique used in breast diagnostics. It is costly and time consuming, and requires the immediate availability of a consultant pathologist and one or more technicians to accomplish the job in shortest possible time. These requirements increase the cost (range, 1000-2000 Saudi Riyals per procedure). Frozen section diagnosis of a palpable breast mass is performed as a guide in determining the course of action of the surgeon in the operating room. This study was prepared at King Abdul Aziz University Hospital to evaluate the usefulness and limitations of frozen section diagnosis of palpable masses of the breast (effectiveness vs. reliability) and to assess the utilization of FNAC as an equivalent accurate and cost effective technique in breast diagnostics prior to frozen section. The usefulness of the frozen section procedure in diagnosis is compared with the new, less costly technique of fine needle aspiration biopsy of breast tissue, which is highly accurate.

**Material and Methods**

All the intra-operative diagnostic frozen sections (n=203) performed at King Abdul Aziz University Hospitals during a period of 17 years, from 1985 to September 2002 are reviewed. All biopsies that required frozen section were

examined by the same technique, with minor variations. The gross specimens of the tumors were examined, painted and cut into thin slices. Abnormal and suspected lesions were immediately frozen at -30°C in a cryostat. A few specimens were grossly reported to be benign after thorough examination of thin slices of the mass.<sup>2</sup> Frozen tissues were stained by routine technique, after fixing in 95% alcohol, as described in the Manual of Histologic Staining Methods of the Armed Forces Institute of Pathology.<sup>19</sup> When we receive an oriented specimen and clinically there was a suspicious mass, we paint the specimen and slice the tissue into thin slices less than 1.0 centimeter. A section will be taken from the mass and submitted for frozen section. If the tumor was close to the resection margin, we performed frozen sections of that specific margin. If all the margins appeared to be clear of tumor, we discussed this finding with the surgeon for further action. Microscopic findings were reported to the surgeon in the operating room. The frozen section diagnosis was recorded immediately. Remainders of the frozen tissue on the block and unfrozen tissue of the mass were fixed in 10% neutral formaldehyde solution, and the operating room sent the material to the laboratory receiving area with any additional material excised. Permanent paraffin sections were obtained from the mass and routinely stained by hematoxylin and eosin technique. Permanent histological sections of the frozen material were obtained and compared with the frozen sections. The final diagnosis was based upon the permanent paraffin sections recorded the next day, in addition to the frozen section diagnosis.

**Results**

The results of the study are summarized in Table 1. The frequency of malignant lesions was 72.4% (147 cases), while the frequency of benign lesions was 27.6% (56 cases). The mean age of the patients with a palpable mass in the breast was 50 with a range of 19 to 89 years. The mean age of the patients with benign disease was 52 years, with a range of 19 to 69 years. Twenty-eight (13.7%) were diagnosed on

**Table 1.** Breast lesion diagnoses by age range from frozen sections performed during 1985 to 2002.

Age Range	Infiltrating ductal cancer	Adenocarcinoma	Medullary cancer	Fibroadenoma	Fibrocystic change	Hamartoma	Adenosis	Mastitis	Apocrine metaplasia	TOTAL
<19	8			1						9
20-29	10			3	1				1	15
30-39	29	1		4	4		1	1		40
40-49	41			14	5		2			62
50-59	36			1	8			1		46
60-69	10		2	5	1	1		1		20
70-79	5						1			6
80-89	5									5
TOTAL (%)	144 (70.9)	1 (0.5)	2 (0.9)	28 (13.7)	19 (9.3)	1 (0.5)	4 (1.9)	3 (1.5)	1 (0.5)	203 (100)

**Table 2.** Discrepant cases (false negatives) (n=4).

Frozen section diagnosis	Permanent section diagnosis
1. Fibroadenoma	Infiltrating ductal carcinoma
2. No tumor deposits	Positive for malignant cells
3. Fibrosis No malignancy	Secondary Adeno CA
4. All margins examined free of malignancy	Infiltrating ductal and intraductal papillary CA

**Table 3.** Diagnosis by fine needle aspiration cytology prior to frozen section.

FNAC diagnosis (n=56)	Number of cases
Benign	10
Fibroadenoma	5
Granulomatous mastitis	1
No malignant cells	4
Malignant	17
Inadequate	14
Total	41

frozen section as fibroadenoma, 19 (9.3%) as fibrocystic change. Among malignant cases, 144 (70.9%) were diagnosed on frozen section as infiltrating ductal carcinoma and 2 (0.9%) as medullary carcinoma. There were 4 cases that showed discrepancy in frozen section, resulting in an uncertain diagnosis (false negative cases) (Table 2). The frozen section accuracy rate was 98% (calculated after exclusion of discrepant cases,  $203-4/203 \times 100$ ). According to the quality control sheet in the frozen section laboratory, in 48.2% of the cases the surgeon changed the final surgical procedure (most of them were lumpectomy for surgical margins) and in 51.8% of the cases there was no change in the final surgical procedure. The number of tissue specimens provided during frozen sections by the surgeons for analysis were 1 in 103 (50.7%) cases, 2 in 61 (30%) cases, 3 in 19 (9.35%) cases, 4 in 13 (6.4%) cases and 5 in 4 (1.97%), 6 in 2 (0.98%) cases and 9 in 1 case (0.49%). The total number of deferred cases at frozen section were 10.

Of 203 frozen section breast biopsies, 41 cases had FNAC prior to operation. The FNAC rate prior to frozen section in breast diseases was 20%. For the benign frozen section diagnoses (n=56), 10 had FNAC with benign diagnosis (Table 3). For the malignant cases (n=147), 17 had FNAC and were positive for malignancy, yet frozen sections was carried out to confirm the FNAC diagnosis. Fourteen FNAC were not adequate, and therefore a frozen section was carried out to reach a diagnosis and to treat the patient accordingly.

## Discussion

As described in the literature, 20% to 35% of all frozen sections are from the breast. The percentage of false positive frozen section diagnoses of breast lesions vary from 0.05% to 0.1% and false negative diagnoses varies from 0.5% to 1%. Frozen section diagnosis is deferred in 0.5% to 3% of all breast biopsies.<sup>10</sup>

The main indication for frozen section is for diagnosis and therapeutic decision-making. However, frozen section is increasingly being replaced by preoperative FNAC and/or core biopsy of the lesion. In cases where margin assessment is critical in management, selected margins should be identified by the surgeon for freezing, rather than submitting all six margins, which takes more time. In this study we noticed that two of the four discrepant cases showed negative margin on frozen section, but on permanent section were invasive and an in situ component appeared at those margins. This finding is supportive of the surgeon selecting margins for frozen section, rather than having the pathologist take all the margins.<sup>1,2,19,20</sup> The status of the margins does not prevent local recurrence. Weber et al found that approximately 5% of patients had local recurrence of their tumor after lumpectomies and all the margins were free of tumor invasion.<sup>21</sup> The management of cases with positive margins after lumpectomies is by irradiation or chemotherapy, especially when the tumor is less than one centimeter in maximum diameter.<sup>22,23</sup> In our institution frozen section was commonly done to confirm the diagnosis of malignancy if the lesion was suspicious for malignancy on FNAC or core biopsy. Secondly, we did frozen sections to reach a diagnosis if the lesion was clinically or radiologically suspicious of malignancy and there was no previous core biopsy or FNAC, or if the FNAC was not adequate. Thirdly, frozen section is indicated if previous lumpectomy with carcinoma in situ or invasive carcinoma at the painted margins and frozen section is done to complete excision of the involved margin. Finally, recently, we infrequently performed a frozen section on cases that had a suspicious mammogram with needle localization, where freezing of the tissue at the tip of the needle took place. (Although this later situation is not a true indication for frozen section in the literature).<sup>4,5</sup>

The accuracy rate of frozen section in our institution is 98%. We had four cases (0.02%) with a discrepancy between frozen section diagnosis and permanent diagnosis that were considered false negatives. This rate of discrepancy is much less than that reported by the M.D. Anderson group (0.5-1%) and by others in the literature (3.5-3.9%)<sup>10,24</sup> This lower rate could be due to the tendency of our pathologist to defer the suspicious cases rather than providing a false negative diagnosis. Our deferred rate (4.9%) is higher than that of the M.D. Anderson group 0.5-3%, and by others in the literature (0.1-3.5%)<sup>10,24</sup> A false-positive diagnosis at frozen section can lead to an unnecessarily radical surgical procedure; e.g., a modified radical mastectomy with axillary clearance for benign

**Table 4.** Histologic reasons for postponing diagnosis at the time of frozen section.

- All papillary lesions including:
  - atypical intraductal papilloma, benign
  - early intraductal carcinoma in situ
  - subareolar papillomatosis
- Sclerosing adenosis with pseudoproliferative pattern
- Florid adenosis and blind duct adenosis
- Duct hyperplasia, atypical
- Fat necrosis
- In situ carcinoma

lesions. This will cause disfigurement and serious psychological trauma to the patient, and in such cases deferring frozen section diagnosis is advisable. No means have been devised for replacing the resected breast. Although our study shows no false positive cases, it is well recognized in the literature that certain benign lesions of the breast mimic carcinoma histologically and have to be examined carefully.<sup>4,25</sup> The histologic reasons for postponing diagnosis at the time of frozen section, in our study, are listed in Table 4.

In those instances in which doubt is entertained, frozen section diagnosis should be deferred for thorough sampling. Although this study show a slightly higher rate of deferred

cases (4.9%), they were cases that needed to be deferred, according to the literature. Five lesions were of papillary pattern and there were two instances of sclerosing adenosis with a pseudo-invasive pattern, which resulted in 7 of the 10 deferred diagnoses. Delay in diagnosis should not be considered an error on the part of the pathologist. It is also wise to wait for permanent sections if a lesion is too small because such a minute lesions or a rather small sample may be lost permanently during the cutting of the blocks of frozen tissue.

Use of frozen section on benign lesions (27%) can be decreased if FNAC is performed routinely on these cases, and frozen sections can be limited to cases that have inconclusive FNAC. Furthermore, this study reveals that our surgeons are not using the FNAC effectively prior to final surgical management. This could be related to the experience of both surgeons and pathologists. However, this technique should be encouraged and established in an effective fashion in order to minimize the unnecessary use of frozen section, and as a first line of diagnosis during operations for therapeutic decision-making. Frozen section service is highly accurate in diagnosing breast diseases, but its use needs more refinement. Furthermore, FNAC is under utilized prior to frozen section and should be encouraged to minimize unnecessary frozen sections.

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