

Validity of Frozen Section in the diagnosis of Breast Lumps: 5 years experience at the Aga Khan University Hospital

Nuzhat Sultana, Naila Kayani

Department of Pathology, The Aga Khan University Hospital, Karachi.

Abstract

Objective: To determine the accuracy of frozen section in the diagnosis of breast lump.

Methods: Frozen section diagnosis given in consecutive breast biopsies performed in 5 years in our laboratory was evaluated against the final pathology report of permanent sections.

Results: The Aga Khan University Hospital Lab receives more than 400 cases per year for frozen section. Three hundred and nineteen consecutive frozen sections of breast lumps examined from 1999-2003 were considered for analysis. Age of patients ranged between 22 and 90 years (mean age 49 years). In 316 cases (99%) there was no difference between the frozen section diagnosis and the final diagnosis. Three cases (0.94%) were incorrect; 2 cases (0.62%) were false positive. One case was false negative (0.31%). In 7 cases (2.19%), frozen section diagnosis was deferred to permanent sections. Frozen section diagnostic accuracy was 99%. Sensitivity and specificity was 99.3% and 93% respectively. Positive predictive value and negative predictive values of frozen section were 96.6% and 99.3% respectively.

Conclusion: High accuracy of the frozen-section diagnosis in the breast lumps was confirmed in our study (JPMA 55;533:2005).

Introduction

Frozen section (FS) is a vital technique used in breast diagnostics. The frozen section technique was first performed by Welch in 1891 and developed for intraoperative pathological diagnosis by Wilson in 1905. Following the introduction of the cryostat in 1960, the intraoperative frozen section examination was established as a highly reliable procedure for the rapid histological evaluation of tissue specimens during surgery.¹ Traditionally, if the clinical diagnosis is cancer, fresh tissue is submitted for frozen section examination before immediate mastectomy.¹

The use of frozen section for breast biopsies followed by immediate radical mastectomy was not employed on a wide scale until the 1930s. Until then, surgeons made their own gross diagnosis at the time of breast biopsies and decided whether a tumor was malignant. Radical mastectomy was immediately carried out if the lesion was judged to be malignant. With growing number of surgical pathologists trained in the 1930s and 1940s; the diagnosis of frozen sections increasingly fell into their domain. Until 1970s, breast biopsies were performed because of palpable mass clinically suspicious for carcinoma.

Frozen section may be applied to open biopsy or needle core biopsy specimen.

In either case, the false negative rate is less than that experienced with needle aspiration and additional information is obtained regarding the histological characteristics of the neoplasm. Although a positive result may be considered

diagnostic, a negative report is always tenuous and should not lead to definitive therapy. Although other methods have been developed to reach a preoperative diagnosis (such as imprint and smear cytology, fine needle aspiration and intraoperative cytology), frozen section still plays an important role in aiding the surgeon to choose the best therapeutic approach. In surgical oncology and particularly in breast pathology, frozen section allows the surgeons to take an immediate therapeutic decision, possibly sparing the patient a second operation and reducing hospitalization costs. Frozen section of palpable breast biopsies can be performed with a high degree of accuracy (varying between 94% and 98%).¹

The most important indications for frozen section are to confirm the diagnosis of carcinoma if the fine needle aspiration cytology or core needle biopsies are inconclusive prior to major radical surgery and to provide an assessment of resection margins in carcinoma.²

Technical skill and diagnostic expertise are essential for frozen diagnosis. Because the diagnoses made by the pathologist from frozen section have consequences for the treatment, high degree of accuracy is mandatory and quality control is important. We suggest that an accuracy survey of frozen section should be periodically performed, in every pathology department as part of its quality assurance program.³

Materials and Methods

All intra-operative frozen section of breast lumps performed at Aga Khan University Hospital during a

period of 5 years from 1999 to 2003 are reviewed. All biopsies that required frozen section were examined by the same technique. The gross specimens of the tumors were examined, painted and cut into thin slices from abnormal and suspected areas, or from the firm lesion a section was taken placed in a mounting medium, frozen immediately to -20°C, sectioned at 4 to 5 microns and stained in hematoxylin and eosin. Nominated consultants were responsible at all time for the service. The trainee pathologists and technical staff was delegated responsibility according to their experience. Microscopic findings were reported to the surgeon in the operating room and were recorded immediately in a book. After completion, remainders of the frozen tissue on the block and unfrozen tissue were fixed in 10% neutral formaldehyde solution. Permanent histological sections of the frozen material were obtained and compared with frozen section. A frozen section diagnosis of infiltrating neoplasia was reported only if unequivocal evidence was available, whereas in situ carcinoma was assumed as a temporary diagnosis needing confirmation. Whenever any doubt existed, the diagnosis was deferred to paraffin sections and the deferrals were categorized as being due to technical imperfection, the focal nature of the lesion or morphological misinterpretation of the appearances of frozen section. The results and causes of concordant, discordant and deferral cases were obtained on a predesigned Proforma respectively.

Results

The Aga Khan University Hospital Laboratory receives over 400 cases per year for frozen section. Three hundred and nineteen frozen sections of breast lumps examined from 1999-2003 were considered for analysis. Age ranged between 22 and 90 years (mean age 49 years). In 316 cases (99%) there was no difference between the frozen section diagnosis and the final diagnosis. Of the remainder, 2 cases (0.62%) were false positive and one false negative (0.31%). In 7 cases (2.19%) diagnosis was deferred to permanent sections.

Table 1. Discordant cases (n=3).

		Frozen section diagnosis	Permanent section diagnosis
False positive	1	Infiltrating carcinoma	Diffuse large cell Non Hodgkin's Lymphoma of B cell phenotype
	2	Papillary carcinoma	Atypical ductal papilloma
False negative	1	No viable tissue seen	Focus of infiltrating ductal carcinoma seen

Table 2. Deferral cases (n=7).

S.No.	Frozen section diagnosis	Permanent section diagnosis
1	DCIS with no invasion	DCIS with no invasion
2	DCIS invasion cannot be excluded	DCIS with invasion
3	DCIS invasion cannot be excluded	DCIS with invasion
4	DCIS invasion cannot be excluded	DCIS with early focus of invasion
5	DCIS invasion cannot be excluded	DCIS with early focus of invasion
6	Papillary neoplasm invasion cannot be excluded	Papillary carcinoma
7	Marked crushing artifacts malignancy cannot be excluded	Crushing artifacts few atypical cells malignancy cannot be excluded

DCIS ductal carcinoma in situ.

The frequency of malignant lesion was 89.9% (287 cases), while the frequency of benign lesions was 9.09% (29 cases). The mean age of patients with malignant lesion was 53.3 years with a range 24-90 years. The mean age of benign lesions was 43.5 with a range of 22-70 years.

Table 3. Distribution of frozen section diagnosis for 319 breast lesions according to final histological diagnosis.

Frozen Section Diagnosis	Histological Diagnosis		Total
	Benign	Malignant	
Benign	29	1	30
Malignant	2	287	289
Total	31	288	319

Sensitivity = $287/288=99.6\%$, Specificity $29/31=93\%$, Negative predictive value (NPV) = $29/30=96.6\%$ Positive Predictive value (PPV) = $287/289=99.3\%$.

Table 3 shows the degree of accuracy of FS diagnosis. Benign or malignant (grouping in situ and invasive carcinomas). Frozen section diagnostic accuracy was 99%, and sensitivity and specificity 99.6% and 93% respectively.

Discussion

Breast cancer is the most common cancer and second leading cause of cancer related death of women after 30 years of age in USA and western world. In the western world breast cancer accounts for 27% of all female cancers and one out of fourteen women can expect to develop breast cancer in their life time. It is also the most frequent female cancer in Pakistan accounting for almost 26.6%. Moreover, a higher incidence in younger age has been observed in our population.⁴

Breast cancer (ICD C50) was the most frequent cancer of women in Karachi, accounting for one-third of the cancers in the females. The age standardized incidence rates (ASR) being the highest in Asia, except the Jews in Israel.⁵

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 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.²

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 or a rather small sample may be lost permanently.² A frozen section can be deferred when the lesion is suspicious for papillary neoplasm 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.²

In the hands of trained and experienced pathologists frozen section is one of the most accurate diagnostic procedures currently available, and its reliability and high degree of accuracy in palpable breast lesions is well established. If surgery is performed in close cooperation with a pathologist, the interpretation of frozen section allows a definite one stage surgical procedure possibly leading to a reduction in medical costs.⁶

The main indication of frozen section is for diagnosis and therapeutic decision-making. In our institution frozen section was commonly used to confirm the diagnosis of malignancy especially if the lesion was suspected for malignancy on FNAC or core biopsy. Secondly, a frozen sections helped to reach a diagnosis if the lesion was clinically and radiologically suspicious of malignancy and there was no previous core biopsy or FNAC, or if the FNAC was not adequate. In case of a previous lumpectomy with carcinoma in situ or invasive carcinoma at the painted margins, a frozen section is done to complete excision of the involved margins.

Recently changing concepts regarding the surgical treatment of primary breast cancer have resulted in additional recommended uses for rapid frozen section. Needle core biopsy of palpable breast masses is a technique that may be applied to out-patients. In the case of small primary breast cancers where complete axillary dissection is considered optional, Leis has recommended the use of frozen section

for the evaluation of proximal axillary lymph nodes.⁷ The definitive surgical procedure may then be modified depending on the result of this axillary sampling. However, it must be remembered that the aforementioned potential sampling error of frozen section introduces an increased potential for false negative results unless additional time is taken to prepare multiple sections from each lymph node sampled.⁶

Similarly, all cases not allowing differential diagnosis between invasive carcinomas and sclerosing adenosis should also be deferred to permanent sections. Alternatively, whenever the FS histological pattern is not clear cut the pathologist must defer definitive diagnosis to paraffin section.¹ Under diagnosis of malignancy is obviously preferable to over diagnosis, which could result in unnecessary mutilating surgery.

In major published studies of consecutive FS examinations reported in the literature, the breast is always listed as an organ most frequently examined. The relative frequency of breast specimens in these studies ranges from 16% to 62% of all cases. Thus, it seems particularly important to be able to assess the results in the intraoperative examination of specimens from this organ. The prevalence of frozen sections is variable in different institutions depending on their experience with frozen sections.⁸ However, the frequency of performing breast frozen sections is 20% to 30% at M.D. Anderson in Houston, Texas, USA, where they have averaged 70 diagnostic frozen sections per day.^{3,9} In our institute the frequency of performing breast frozen section is 16% which is comparable to these studies.

The accuracy rate of frozen section in our institution is 99%. We had three cases (0.94%) with a discrepancy between frozen section diagnosis and permanent diagnosis. This rate of discrepancy is comparable to that report by the M.D. Anderson in Houston, Texas, USA group (0.5-1%) and is less than others in the literature (3.5-3.9%).⁹ Our deferred rate (2.19%) is comparable to that of the M.D. Anderson group 0.5-3% and that in the literature (0.1-3.5%).⁹

In our study the rate of false negative results (one case; 0.31%), deferred cases (2.19%) are lower than the other studies. However our false positive rates (0.62%) are higher than the other studies. The histologic reasons for postponing diagnosis at the time of frozen section, in our study are ductal carcinoma in situ and papillary lesion in which invasion cannot be excluded.

Among the larger series reporting accuracy of FS diagnosis in the 1960s and early 70s, the results are generally excellent, with false positive rates of 0.2-0.3%, false negative rates between 0.5 and 1.2% and deferred diagnosis rates ranging from 0.5 to 1.6%.¹⁰ With specific reference to breast specimens, Holaday and Assor reported one false positive, eight false negative and six deferred diagnoses among

1,616 breast cases. They specified that most of the deferred diagnoses and false negative diagnoses involved intraductal lesions.¹¹ Lessells and Simpson reported one false positive (a case of fat necrosis) and thirteen false negative diagnoses among 2,197 breast FSs and mentioned that 7 of the 13 false negative diagnoses resulted from sampling error.¹² Nakazawa and colleagues reported one false positive (an atypical fibrous histiocytoma), four false negative, and nine deferred diagnoses among 677 breast FSs.¹³ Rosai and Ackerman recorded no false positive, 0.4% false negative and 0.9% deferred diagnoses among 679 breast lesions in their study.¹⁰

In more recent FS experience, however, as the frequency of noninvasive and other "minimal" breast cancer has increased, there has been a parallel increase in the frequency of false negative and deferred diagnoses. In the study of Rosen, there were no false positive, 1.4% false negative and 5.4% deferred diagnoses among 556 consecutive breast biopsies. It was pointed out that all of the false negative diagnoses involved sampling error and seven of eight cases involved were in situ carcinomas. The deferred diagnoses also primarily involved occult and/or intralobular and intraductal lesions, as well as a single case of infiltrating lobular carcinoma with few malignant cells in the specimen.¹⁴

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 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. Our study shows 2 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.

The essentially high accuracy of the frozen-section behavior in the breast tumor has been mentioned by others and was confirmed in our study. The surgeon and the pathologist must each accept certain responsibilities if the patient

has to receive maximum benefit from the frozen-section procedure. The accuracy of this method must be very high so that the surgeon can have complete confidence in his pathologist. Self-examination through a prospective study, as presented here, prones to both the surgeon and the pathologist the high accuracy of this technique and demonstrates its pitfalls, thus enabling them to handle it more wisely for the ultimate welfare of the patient.

References

1. Bianchi S, Palli D, Ciatto S, Galli M, Galli M, Giorgi D, et al. Accuracy and reliability of frozen section diagnosis in a series of 627 non palpable breast lesions. *Am J Clin Pathol* 1995;103:199-205.
2. Fadwa JA. Audit of breast frozen sections. *Ann Saudi Med* 2004;24:141-4.
3. Wen MC, Chen JT, Ho WL. Frozen section diagnosis in surgical pathology: a quality assurance study. *Kaohsiung J Med Sci* 1997;13:534-9.
4. Ishtiaq ACH, Salma KQ, Shahid R. Incidence of malignancy in females presenting with breast lumps in opd: a study of 277 cases. *Pak J Med Sci* 2003;19:287-94.
5. Census Bulletin-1, Population and Housing Census of Pakistan 1998, (1999), Population Organization Statistics division, Government of Pakistan, July 1998.
6. Bauermeister DE. The role and limitations of frozen section and needle aspiration biopsy in breast cancer diagnosis. *Cancer* 1980;46:947-9.
7. Leis, HP. Jr: Personal communication.
8. Esteban JM, Zaloudek C, Silverberg SG. Intraoperative diagnosis of breast lesions: Comparison of cytologic with frozen section techniques. *Am J Clin Pathol* 1987;88:681-8.
9. Ramsey AD. Errors in histopathology reporting: detection and avoidance (*Histopathology* vol. 34 no. 6. Department of histopathology. Amelia Botnar Laboratories .Great Ormond Street Hospital for Children.London, UK. July 199 report.
10. Rosai J, Ackerman LV: The pathology of tumors. Part II: Diagnostic techniques. *CA* 1979;29:22-3.
11. Holaday WJ, Assor D. Ten thousand consecutive frozen sections: A retrospective study focusing on accuracy and quality control. *Am J Clinical Pathol* 1974;61:769-77.
12. Lessells AM, Simpson JG: A retrospective analysis of the accuracy of immediate frozen section diagnosis in surgical pathology. *Br J Surg* 1976;63:327-9.
13. Nakazawa H, Rosen P, Lane N, Lattes R: Frozen section experience in 3,000 cases: Accuracy, Limitations and value in residency training. *Am J Clinical Pathol* 1968;49:41-51.
14. Rosen PP: Frozen section diagnosis of breast lesions .Recent experience with 556 consecutive biopsies. *Ann Surg* 1978;187:17-9.