

Validity of Intra-Operative Frozen: Results from A Single Tertiary Center

Intra-Operative Frozen'ın Geçerliliği: Tek Bir Üçüncül Merkezden Alınan Sonuçlar

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ABSTRACT

Objectives: Frozen Section (Fs) Is Mainly Performed To Decide If The Sampled Tissue In Surgery Is Benign Or Malignant. The Accuracy Of Fs Exams Varies Based On The Specific Anatomical Site. False Diagnoses May Cause Consequences For Surgeons And Patients, Considering The Circumstances Of False Positive Reports. In This Study, We Aimed To Evaluate The Accuracy Of This Method (Frozen Biopsy) In Surgeries.

Materials and Methods: In This Retrospective Study, Frozen Sections Of The Pathology Department Of Taleghani Hospital Have Been Reviewed And Compared With The Permanent Section Results As Gold Standard To Evaluate The Sensitivity And Specificity Of The Test. In Cases Where The Results Were Dissonant, We Investigated The Causes Of This Discordance.

Results: A Total Of 1016 Samples From 557 Patients Were Studied. The Mean Age Of The Patients Was 52.15 ± 16.94. In The Study Of Frozen Sections, 778 Sections (76.6%) Were Benign, 192 Sections (18.9%) Were Malignant, 38 Sections (3.7%) Were Suspected, And In 8 Sections (0.8%) The Samples Could Not Be Identified Due To The Inappropriate Specimen. In All, 95 Cases (9.35%) Were Deferred, And Of The Remaining, 19 Cases (2.06%) Were Discordant. Out Of 19 Discordant Cases, 13 Cases (68.4%) Were Due To Pathologist Interpretation Error. Sensitivity, Specificity, Positive Predictive Value, And Negative Predictive Value Of All Samples Were 93.37%, 99.32%, 97.13%, And 98.38%, respectively.

Conclusion: Frozen section is a valid test for intra-operative consultation and ongoing monitoring in pathology departments should be performed to improve FS accuracy.

Keywords: Frozen sections, Histology, Sensitivity and Specificity, Neoplasm.

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ÖZET

Amaç: Dondurulmuş Kesit (Fs) Esas olarak Ameliyatta Örneklenen Dokunun Benign veya Malign Olup Olmadığına Karar Vermek İçin Yapılır. Fs Sınavlarının Doğruluğu Spesifik Anatomi Bölgeye Göre Değişir. Yanlış Teşhisler, Yanlış Pozitif Rapor Koşulları Dikkate Alındığında Cerrahlar ve Hastalar İçin Sonuçlara Neden Olabilir. Bu Çalışmamızda Bu Yöntemin (Frozen Biopsi) Ameliyatlarda Doğruluğunu Değerlendirmeyi Amaçladık.

Gereç ve Yöntemler: Bu Retrospektif Çalışmada, Testin Duyarlılığını ve Özgüllüğünü Değerlendirmek İçin Taleghani Hastanesi Patoloji Bölümü'nün Dondurulmuş Kesitleri İncelenmiş ve Altın Standart Olarak Kalıcı Kesit Sonuçları ile Karşılaştırılmıştır. Sonuçların Uyumsuz Olduğu Durumlarda Bu Uyumsuzluğun Nedenlerini Araştırdık.

Sonuçlar: 557 Hastadan Toplam 1016 Örnek İncelendi. Hastaların Yaş Ortalaması 52.15 ± 16.94 idi. Dondurulmuş Kesitler Çalışmasında 778 Bölüm (%76,6) Benign, 192 Bölüm (%18,9) Malign, 38 Bölüm (%3,7) Şüpheli ve 8 Bölümde (%0,8) Numuneler Nedeniyle Tanımlanamadı. Uyumsuz Numune. Toplamda 95 Vaka (%9,35) Ertelendi ve Kalan 19 Vaka (%2,06) Uyumsuzdu. 19 Uyumsuz Olgudan 13'ü (%68,4) Patolog Yorum Hatasından Kaynaklanmıştı. Tüm Örneklerin Duyarlılık, Özgüllük, Pozitif Tahmin Değeri ve Negatif Tahmin Değeri sırasıyla %93.37, %99.32, %97.13 ve %98.38'dir.

Sonuç: Donmuş kesit intraoperatif konsültasyon için geçerli bir testtir ve FS doğruluğunu artırmak için patoloji bölümlerinde sürekli izleme yapılmalıdır.

Anahtar Sözcükler: Donmuş kesitler, Histoloji, Duyarlılık ve Özgüllük, Neoplazm

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INTRODUCTION

History of using frozen section as an intra-operative consultation goes back to 1891, when William H Welch at John Hopkins Hospital, firstly used the frozen section. Then, Wilson and McCarty promoted it in 1905 at Mayo Clinic. Finally, after the development of Cryostat In 1959, the frozen section method reaches a high quality in which pathology departments are performing(1, 2).

On some occasions, surgeons need specimen's pathologic results quickly, so they ask a pathologist for an intra-operative consultation about the specimen. When the pathologist evaluates the specimen, the patient is in the operating room and under anesthesia. The pathologist conveys Frozen section results to the surgeon as soon as possible, enabling him/her to make a more appropriate intra-operational decision(3). Since then, pathologists play a valuable role in many operations, helping to determine the best approach during surgery (4-7).

The main impetus to perform FS is to develop a speedy diagnosis to assist in intra-operative patient management. FS is indicated for recognition of tissue, tumor margins evaluation, finding lymph node metastasis, confirmation of the adequacy of specimen for paraffin section technique, and lesion's nature determination. It is mainly conducted to decide if the sampled tissue by the surgeon is benign or malignant. It shouldn't be requested to compensate for inappropriate preoperative work-up, to convey diagnosis faster to the patient or patient's family, or just for surgeon's curiosity satisfaction (3, 4, 8).

The accuracy of frozen section studies varies based on the specific anatomical site examined (9). The rates of accuracy in current studies in different lesions reach high levels. False-negative diagnoses are responsible for the most discordance results between permanent sections and frozen sections (4, 7, 10). False diagnoses may cause consequences for surgeons and patients, considering the circumstances of false-positive reports (11). Thus, controlling the quality and accuracy of such diagnostic methods (frozen biopsy) is crucial to decrease unnecessary or inadequate surgical procedures (4, 10).

Therefore, we decided to compare the results of frozen sections in the Taleghani Hospital with the final results from the Permanent Section as the Gold Standard. Also, the indication of the test and the causes of the discordance of the two methods were rooted.

MATERIALS and METHODS

After obtaining institutional review board (IRB) approval, we reviewed all consecutive frozen sections performed at Taleghani Hospital, Tehran, Iran, between 2013 and 2017 retrospectively. All frozen sections with documented permanent section results were included in our evaluation. The exclusion criterion was defined as: lacking documented permanent results. Test results and demographic data were extracted from patients' files to be analyzed. Patients' informed consent was taken.

Pathology department technicians embed specimens with a specific gel and keep it in the Tissue-Tech Cryo 3 (Sakura) to be frozen and ready to be sliced by the microtome. Slices are transformed on slides and are stained with Hematoxylin and Eosin (H&E) to be ready for analysis by the pathologist. The remaining specimens are fixed in formalin and embedded with paraffin for 3-7 days and then were stained with H&E. Hospital's experienced pathologists examine specimens under light microscopes and report the results.

Frozen section results were compared with permanent section results as the Gold standard to evaluate the accuracy, sensitivity, and specificity of the test. Also, in cases where the results were dissonant, we have investigated the causes of this discordance. Moreover, Data were grouped based on anatomical sites for intergroup comparisons.

Concordant cases are true diagnoses, comprising of true positives (cases that are diagnosed malignant in both frozen section and permanent section), and true negatives (cases that are diagnosed benign in both frozen section and permanent section). Discordant cases are false diagnoses (those diagnoses in which frozen section and permanent section results differ). Discordant cases are false diagnoses, comprising of false positives (cases that are malignant in the frozen section and benign in permanent section analysis), and false negatives (cases that are benign in the frozen section and malignant in permanent section analysis). Sometimes the pathologist couldn't reach a final diagnosis by frozen section.

The final diagnosis is postponed until the permanent section results were ready; these were defined as deferred cases and were excluded in calculating accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Sensitivity equals: TP divided into the sum of TP and FN ($TP/(TP+FN)$). Specificity equals TN divided into the sum of TN and FP ($TN/(TN+FP)$). PPV equals TP divided into the sum of TP and FP ($TP/(TP+FP)$). NPV equals TN, divided into the sum of TN and FN ($TN/(TN+FN)$). The data were analyzed by using the IBM SPSS Statistics 24 (Illinois, United States), and sensitivity and specificity were calculated using MedCalc (New York, United States) software. Categorical data were reported as percentages. This study was approved by Shahid Beheshti University of Medical Sciences School of Public Health and Neuroscience research center ethics committee (Approval ID: IR.SBMU.PHNS.REC.1397.084).

RESULTS

A group of 1016 samples from 557 patients in the pathology department of Taleghani Hospital were studied. The smallest patient was 11 and the oldest was 88 years old and the mean age of the patients was 52.15 ± 16.94 (Figure 1). 341 patients were female (61.22%) and 216 were male (38.78%). The indications of frozen sections were as follows: assessment of margins for 658 cases (64.8%), definite diagnosis for 268 cases (26.4%), ruling out malignancy for 44 cases (4.3%), and diagnosis of tissue type for 45 cases (4.4%).

In the study of frozen sections, 778 sections (76.6%) were benign, 192 sections (18.9%) were malignant, 38 sections (3.7%) were suspicious, and in 8 sections (0.8%) the samples could not be identified due to the inappropriate specimen. In the study of the permanent sections, 796 sections (78.4%) were benign and 219 sections (21.6%) were malignant. The final result was postponed to the Permanent Section evaluation (Deferred) in 95 cases (9.35%), remaining specimens' results (921 cases) were concordant in 902 cases (97.94%), discordant in 19 cases (2.06%) (table I). According to the re-examination of discordant samples, 13 cases (68.4%) were due to pathologists' error in diagnosis of specimens, 5 cases due to tissue preparation errors caused by surgeon (26.3%) and 1 case due to problems with tissue preparation equipment (5.2%). The tissues from which samples were taken listed as below: head and neck 500 cases (49.2%), ovaries 83 cases (8.2%), thyroid 80 cases (9.9%), Pancreas 62 cases (6.1%), liver and biliary ducts 62 cases (6.1%), parathyroid 46 cases (4.5%), skin 45 cases (4.4%), lymph node 41 cases (4 %), uterus and adnexa 39 cases (3.8%), breast 14 cases (1.4%), other tissues 44 cases (4.3%), Skeletal system (13 cases) stomach and intestine, and appendixes (9 cases), and perineum and pelvis (4 cases).

Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of all samples were 93.37% (CI 95%: 88.71% to 96.53%), 99.32% (CI 95%: 98.43% to 99.78%), 97.13% (CI 95%: 93.42% to 99.06%), 98.38% (CI 95%: 97.20% to 99.17%) and 97.93% respectively (table II).

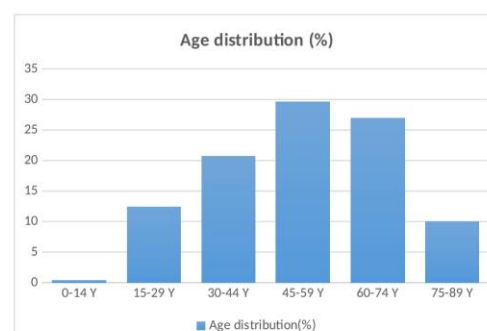


Figure1: Age distribution of patients.

Table I: Final status of results separated by groups.

		Concordance			Total
		Concordant	Discordant	Defer (%)	
Group	Head& Neck	462	8	30 (6%)	500
	Thyroid	75	2	3 (3.75%)	80
	Ovary	60	2	21 (25.3%)	83
	Parathyroid	42	0	4 (8.69%)	46
	Lymph nodes	38	0	3 (7.31%)	41
	Pancreas	58	1	3 (4.83%)	62
	Uterus& adnexa	31	1	7 (17.94%)	39
	Breast	11	0	3 (21.42%)	14
	Liver & Biliary system	54	2	6 (9.67%)	62
	Skin	35	3	7 (15.5%)	45
	Others	36	0	8 (18.18%)	44
Total		902	19	95 (9.35%)	1016

Table II : Sensitivity, Specificity, Positive predictive value and Negative predictive value results separated by groups.

Tissue	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Head & Neck	90.76	99.50	96.72	98.53	98.29
Thyroid	100	95.23	94.59	100	97.4
Ovary	66.66	100	100	96.55	96.77
Parathyroid	100	100	100	100	100
Lymph Node	100	100	100	100	100
Pancreas	100	98.03	88.88	100	98.3
Uterus	100	96.42	75	100	96.87
Breast	100	100	100	100	100
Liver& biliary	92.30	100	100	97.67	96.42
skin	82.35	100	100	87.5	92.1
Others	100	100	100	100	100
Total	93.37	99.32	97.13	98.38	97.96

Table III: Diagnostic value of frozen section in different studies.

Author	Sensitivity	Specificity	PPV	NPV	Accuracy
This study	93.37	99.32	97.13	98.38	97.94
Previous study at this center	92.95	99.55	98.50	97.80	97.96
Chbani et al.	95.02	NC*	98.02	NC	95
Alam et al.	87.2	87.5	NC	NC	86
Preeti et al.	75	97.54	90.9	94	94.2
Z Huang et al	92.7	NC	87.6	NC	81.9
P Patil et al.	97.42	96.30	98.59	92.86	96.96
Abbasi et al	93.1	97.6	96	95	95.9
Farah et al.	84.6	99.8	98.2	97.8	97.5
Khoo et al.	97.98	97.16	NC	NC	97.56
Zubair Ahmad et al	98.52	NC	98.52	NC	97.08

* NC: not calculated

DISCUSSION

Intra-operative consultation is one of the most challenging parts of a pathologist career; their diagnosis on the sampled tissue is determinative in the procedure; whether the surgery begins again unnecessary or ends scanty when they make false diagnoses. So it is fundamental to diminish false diagnoses considerably (12).

In this retrospective study, a total of 1016 frozen sections in the pathology department of Taleghani Hospital were compared with the final results of the Permanent section which is a relatively large sample for this type of study. Also, in cases where there was a discrepancy between the results, by reviewing the samples, we investigated the cause of this heterogeneity. Finding the reasons for the errors and promoting them, decreases unwanted burdens due to false diagnoses by increasing the diagnostic accuracy of the test (13).

Studies showed that more representative slides for specimens and more experienced pathologist and surgeon in sampling tissues prevents misdiagnosis(14). In the previous study in this center, 3.59% of cases were deferred, 2.03% of the remaining cases were discordant, and 97.96% of them were concordant. The effects of the pathologists' error in the misinterpretation of the heterogeneous samples remained nearly constant, 68.4% compared to 66.6%. All of these improvements in accuracy of the test can be attributed to the quality assessment of the center, reducing the errors identified by the previous study and promoting pitfalls (15). In past studies with the same subject around the world, the discordancy of the results varied from 1.4 to 12.5% (16-23) compared to our results of 1.89%. The most frequent reasons for discordance results between frozen sections and permanent sections are interpretation error by pathologists or inaccurate and inadequate sampling by surgeon and/or pathologist (22, 23). In our Evaluation, similar to most of other centers, the most prevalent reason for the discrepancy between results was still misinterpretation by pathologists, it reaches 68.4% of cases compared with 66.6% in the previous study; sampling error was the second cause for misinterpretation by a prevalence of 26.3% of all discordant cases compared to 33.3% of cases in the previous evaluation.

Comparing the results of the frozen sections with Permanent sections, sensitivity, specificity, positive predictive value and negative predictive value of all samples were calculated 92.95%, 99.55%, 98.50%, and 97.80%, respectively; these indicate that frozen section results are reliable in this center in intra-operative consultations. Comparing the results of two studies conducted at this center shows that sensitivity raised from 92.95% to 93.37%. Although the test specificity has dropped from 99.55% to 99.32%. Overall sensitivity and specificity of the frozen section test in our study are compared with other studies in table III. (3, 9, 15, 16, 19, 24-28).

The proportion of deferred cases in our center (9.35%) is higher than other studies ranging from 0.04% to 4.62% of cases (3, 4, 9, 15, 26, 29). This could be attributed to the reason for requesting intra-operative consultation by surgeons; in many cases, they need to know whether the sampled tissue is benign or malignant, and not the exact diagnosis, to decide about surgery. Another probable reason for high rates of deferred cases in this center may be due to more circumspect pathologists; because of legal issues, they don't risk reporting exact diagnosis for even low suspicious samples leading to higher rates for deferred cases and also high accuracy for the test, since deferred cases are excluded while calculating diagnostic accuracy. The proportion of deferred cases should be considered when talking about and comparing accuracy, Sensitivity, and specificity of frozen sections; for instance, in Uterus and adnexa group of our study, accuracy, Sensitivity, specificity, PPV, and NPV calculated 96.87%, 100%, 100%, 100%, and 100% respectively, but about 18% of this group's results are deferred. It means in 18% of referred cases frozen sections may not be helpful in making decisions for surgeons; even though, diagnostic accuracy, sensitivity, and specificity rates are high enough, knowing that frozen section's help is the motive for requesting it.

In conclusion, this study reinforces the importance of integration between the professional activities of surgeons and pathologists, through confidence in the test results provided by frozen sections, tested by systematic and periodic evaluation of its accuracy in the service. In suspected patients for malignancy, the pathologist should perform more sections to reduce false diagnosis, and deferred cases.

Conflict of interest

No conflict of interest was declared by the authors.

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