Diagnostic accuracy of frozen section tests for surgical diseases

Precisão diagnóstica das doenças cirúrgicas nos exames por congelação

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A B S T R A C T

Objective: To evaluate the accuracy of frozen section tests at different anatomical sites performed in an academic department of pathology. **Methods**: We conducted a retrospective study from a computerized database of all frozen section tests. These diagnoses were compared to definite paraffin, used as controls. The tests were divided into three groups: inconclusive, consistent and inconsistent, the latter being subdivided into false positives and false negatives. The main indications for examinations and anatomical sites involved with diagnostic disagreements were also analyzed. **Results**: Four hundred and thirty-three specimens were frozen tested, and the main indication was diagnostic (75.75%). In 404 tests (93.30%) diagnoses of biopsies in paraffin and frozen section were consistent. In 20 cases (4.62%) the results of frozen section biopsy were inconclusive and in 9 (2.08%) they were false negative. There were no false positive results. The most commonly assessed organ was the thyroid (25.64%). In the overall analysis, the body region most related with inconclusive diagnoses was the thyroid (seven cases) and in relation to specific sites it was the lungs/pleura/mediastinum (13.33%). Skin was the organ that showed more discordant diagnoses between frozen biopsies and paraffin. **Conclusion**: The global accuracy of frozen section was 93.30%; for specific anatomical sites, diagnostic accuracy ranged from 86.67% to 100%.

Key words: Biopsy. Freezing. Pathology, surgical. Diagnostic techniques and procedures. Quality control.

INTRODUCTION

In 1905, Louis B. Wilson began a new era in intraoperative diagnosis by verifying the need for a technique to evaluate the tissue removed in operations and develop new pathological methods of cutting and coloration. He froze the pieces in cold air environment, blushed with methylene blue, washed in saline and, using a mixture of glucose, mounted them on glass slides. From these early efforts emerged microscopic images with the colors purple and blue, in contrast to the brown and pink viewed with the traditional fixation. With the implementation of a microtome it became possible to provide surgeons with pathological diagnosis in five minutes[1]. Since then, pathologists began to play a critical role in many operations, assisting in guidance and determination of the best approach during surgery[1-5].

The classic indication for frozen section examination is the need for an immediate decision during a surgical procedure in differentiating between benign and malignant neoplasms[2,6-9].

The rate of accuracy in current series in different services reach high levels[3,9,10]. The most frequent discordance of results when comparing frozen sections with the final paraffin results are caused by false-negative diagnoses[6,11-13]. False diagnoses may generate consequences for patients, especially considering the situations of false positive results[14]. Thus, the analysis of the accuracy of such diagnostic method (frozen biopsy) it is extremely important in order to minimize unnecessary or inadequate surgical procedures[4,6,10,11,13,15].

The accuracy of frozen section exams varies according to the specific anatomical site examined[11,12,16,17], which ends up interfering directly in the global diagnostic accuracy of a service. Despite the importance of the issue, the national (Brazilian) literature is scarce. Most national studies evaluate only one anatomical site[18,19].

This study aims to assess the degree of diagnostic accuracy of frozen section exams in various anatomical sites.

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METHODS

We conducted a retrospective study from a computer database of all frozen section examinations performed between May 2002 and February 2009, at the Laboratory of Pathology, Benevolent Association University Hospital (ABHU), University of Marilia, São Paulo, Brazil. Through the use of a specific tool to filter the database, frozen section exams and subsequent definitive results of biopsies in paraffin of each specimen were selected for comparison.

The frozen tests followed this technique: tissues without fixation were received after they were harvested during surgery, were frozen in tetrafluorethane and cut with a ANCAP® manual microtome in five-mm-thick slices with disposable razors. The samples were "caught" on glass slides with frosted edges, identified, and stained by thionin. The so prepared slides were examined under a Nikon® YS-100 light microscope by pathologists. The frozen test results were printed and delivered in the operating room during the procedures. The results were also introduced into the computerized database of the service.

The remaining tissues were then fixed in formalin for the examinations after routine paraffin embedding. The materials were processed in histotechnical Lupe® and embedded in paraffin. The paraffin blocks were cut with a manual microtome. The samples were placed on slides with frosted edges, identified and stained with hematoxylin-eosin. The slides were viewed by pathologists, new reports issued and the results also filed on the same database where the data from the frozen biopsies were previously inserted.

The cases in this study were selected from the results of frozen section exams. The frozen section diagnoses were compared with the definitive diagnoses in paraffin, used as controls. The test results of frozen section biopsies were then divided into three groups after comparing the results of biopsies in paraffin: inconclusive, consistent and inconsistent, or discordant, which were subdivided into false-positives and false-negatives.

All frozen examinations that showed the report "await paraffin" and had no description of the suspected diagnosis were considered inconclusive. The examinations were considered concordant when the final diagnosis in paraffin biopsy result was the same as suggested by the frozen biopsy.

The main indications for performing the tests and the anatomical sites involved with diagnostic disagreements were analyzed. All frozen examinations followed the methodology described above and therefore were part of the study.

RESULTS

A total of 22,601 pathological exams were performed from different surgical specimens received in the Laboratory of Pathology, ABHU / UNIMAR. From those, 433 specimens were submitted to prior frozen biopsy, and the main indication was the diagnosis of the lesion (75.75%) (Table 1).

In 404 (93.30%) cases, the frozen tests provided diagnoses that were confirmed by subsequent paraffin cuts (consistent). In 20 (4.62%) exams the results were inconclusive and in nine (2.08%) they were false-negatives. There were no false-positive results in this period.

The primary tumor site assessed was the thyroid, with 111 (25.64%) samples, followed by breast, with 62 (14.32%) and ovary/adnexa, with 60 (13.86%) specimens studied. The region of the body most associated with overall inconclusive frozen diagnoses was the thyroid (seven cases), and, as for a specific site, lungs/pleura/mediastinum (13.33%). Upon global and specific anatomical site analysis, the skin was the organ that showed more discordant diagnoses between frozen biopsies and paraffin, with three (7.89%) cases (Table 2).

After assessing the final diagnoses in paraffin and globally analyzing the determinants of diagnostic differences, it was found that all false-negative cases were generated from malignancies and in 14 (70%) cases of inconclusive

Table 1 – Main particulars of frozen section exams distributed by anatomical sites (N = 433).

Anatomical sites	Diagnosis of lesion N° (%)	Evaluation of margins N° (%)
Thyroid	111 (25.64)	-
Ovaries and adnexa	60 (13.86)	-
Lungs/Pleural Cavity/Mediastinum	41 (9.47)	04 (0.92)
Breast	20 (4.62)	42 (9.70)
Lymph Nodes	32 (7.39)	-
Gastrointestinal tract	12 (2.77)	01 (0.23)
Skin	07 (1.61)	31 (7.16)
Other	45 (10.39)	27 (6.24)
Sub-total	328 (75.75)	105 (24.25)
Total	433 (100)	

biopsies the cause was also neoplastic, whereas 11 (78.57%) lesions were malignant.

Final diagnosis in paraffin tests for determining the discordant and inconclusive frozen exam according to specific anatomical sites are shown in table 3.

DISCUSSION

Frozen biopsy is a well established procedure for the rapid diagnosis of intraoperative samples, which allows the surgeon the diagnosis of an injury and determines the extent of resection, thus helping in making therapeutic decisions. Its accuracy should be high so that the surgeon can have confidence in the approach to be used[11].

How the storage and shipping of the pathological reports of the frozen exams are performed is little discussed and specified[3,17,20,21]. The processing of data for these tests in digital computer systems facilitates the review of cases and retrospective studies, and provides solid support for medical-legal issues[21].

In this study, 328 (75.75%) frozen examinations were performed for obtaining the diagnosis during surgery. In other studies this percentage varies from 61.3 to 82.3%%[10,11].

The accuracy rate of frozen section pathological examinations in the service in question (93.30%) is high. However, other studies show even higher levels, ranging from 98.3% to 98.9%[3,9,10]. This difference may be explained, at least in part, by different methods of analysis. If it were used, for example, the methodology of two other works, who disregarded inconclusive tests, it would render the same diagnostic accuracy as Cerski *et al.* (97.70%)[12], which would be above the observed by Ahmad et al. (97.08%)[18].

Moreover, in different series the diagnostic accuracy of frozen section examination is variable according to the anatomic site studied[11,12,18,19]. The most examined organ in this study was the thyroid, with 111 (25.64%) samples, and this is, as a rule, an important cause of inconclusive exams[10,22]. Inconclusive examinations lead to decreased accuracy when combined in the overall analysis. When we evaluate the specific anatomical sites in the present series, the accuracy of frozen section biopsy ranged from 86.67% in the lungs/pleura/mediastinum to 100.00% in the gastrointestinal tract.

Upon comparative analysis of this study with other works in the literature, it appears that this percentage of inconclusive examinations may be framed within the acceptable. However, other studies have reported lower values, ranging from 0.35% to 2.8%[11,14,17]. This can be explained by the fact that the organ most often studied in this work is the thyroid[10,22], and also because the lung / pleura / mediastinum render a large number of inconclusive diagnoses[9,10,16,20].

False-negative results are often associated with diagnostic discrepancies, ranging from 0.4% to 2.56%[6,11-13]. As for false-positive results in this study, there was none, as observed by other authors[17,20,21], although they may vary from 0.14% to 1.46%[6,11,13,16]. Prevalence of certain diagnostic discrepancies are almost inevitable and may be explained by the distribution of several focal lesions – which requires many cuts in paraffin for detection of lesions –, by their absence in the fragment sent to the pathologist, or even because the lesions are deeply situated in the fragments sent for examination, thus going unnoticed. Problems and implicit technical limitations, insufficient material and lack of clinical information also contribute to discordant results[2,4,9,19,23]. The lesions that most often lead to diagnostic disagreements are well differentiated malignant tumors that can be confused with proliferative conditions, poorly differentiated benign tumors and malignant lesions with associated inflammatory processes[7]. In this study all injuries that led to diagnostic discrepancies corresponded to malignant neoplasms.

Unlike most of the series appraised, in this service no case of false-positive was observed. Rosen[23] said that when there is any uncertainty about the diagnosis, it is best to postpone it. He recommended that surgeons would accept the reports of inconclusive examinations instead of pressuring the pathologists to take an imprecise decision,

Table 2 - Diagnostic Accuracy by anatomical sites evaluated (N = 433).

Anatomical sites	Nº cases Nº (%)	Inconclusive Nº (%)	False - Nº (%)	False + Nº (%)	Accuracy (%)
Thyroid	111 (25.64)	07 (6.30)	02 (1.80)	-	91.90
Breast	62 (14.32)	03 (4.84)	-	-	95.16
Ovaries/adnexa	60 (13.86)	01 (1.67)	-	-	98.33
Lungs/Pleural Cavity/Mediastinum	45 (10.39)	06 (13.33)	-	-	86.67
Skin	38 (8.77)	-	03 (7.89)	-	92.11
Lymph Nodes	32 (7.39)	02 (6.25)	01 (3.12)	-	90.63
Gastrointestinal tract	13 (3.00)	-	-	-	100.00
Other	72 (16.63)	01 (1.39)	03 (4.16)	-	94.45
Total	433 (100)	20 (4.62)	09 (2.08)	-	93.3

+ = positive; - = negative.

Table 3 - Final diagnoses in paraffin determinants of dissenting and inconclusive frozen section exams distributed according to anatomical sites (N = 51).

Final diagnosis in paraffin	False+	False-	Inconclusive
Thyroid			
Colloid goiter with cystic degeneration	-	-	01
Adenomatous multinodular goiter	-	-	01
Follicular Adenoma	-	-	01
Papillary Carcinoma	-	-	03
Follicular Carcinoma	-	01	01
Papillary Microcarcinoma	-	01	-
Ovaries/Adnexa			
Endometriosis	-	-	01
Breast			
Invasive ductal Carcinoma	-	-	02
Invasive lobular Carcinoma	-	-	01
Skin			
Margin compromised with melanoma	-	01	-
Malignant neoplasm of small cell	-	02	-
Lung/Pleural Cavity/Mediastinum			
Chronic granulomatous inflammatory process	-	-	02
Usual interstitial Pneumonia	-	-	01
Typical Central Carcinoid Tumor	-	-	01
Poorly differentiated malignant neoplasm	-	-	01
Hemangioma	-	-	01
Lymph Node			
Chronic granulomatous inflammation	-	-	01
Lymphoma, Hodking	-	-	01
Metastasis of Papillary Carcinoma	-	01	-
Other			
Margin compromised with adenoid cystic carcinoma	-	01	-
Margin compromised with fibrohistiocitoma	-	01	-
High-grade Sarcoma	-	01	-
Lymphoma	-	-	01
Total	-	09	20

+ = positive; - = negative.

and concluded that to minimize the frequency of false-positive results, the option of delaying diagnosis is appropriate. Another group[6] suggested that pathologists and surgeons should not draw any conclusions from inconclusive interpretations and should proceed as if the tests were not performed.

The main sites of diagnostic discordance in a study of the College of American Pathologists[9] involving 461 institutions that assessed more than 90,000 frozen section exams were: skin (17.1%), breast (16.7%), female genital system (10.2%), lymph nodes (10.1%), thyroid / parathyroid (6.1%), lung / pleura (5.3%) and gastrointestinal tract (5.2%).

As noted in this series, the gastrointestinal tract was the "site" that was associated with less diagnostic discrepancies in other series[9,10]. The skin, on its turn, was the specific anatomical site that was mostly associated with false-negative tests (7.89%). Another study on the skin[24] showed that, in most cases, the frozen section tests are used for evaluation of surgical margins, and that in those situations the accuracy rates range from 90% to 95%. This observation is similar to the one of this research (92.11%).

We observed another anatomic site that was associated with two (1.08%) false-negative cases and seven (6.30%) inconclusive exams: the thyroid. About this organ, a previous study[8] showed that 54% of lesions diagnosed as papillary microcarcinomas were false-negative and that the inability to diagnose them was the main factor determining the low sensitivity of frozen section exams. The diagnostic sensitivity of intraoperative surveys depends on the type of carcinoma.

In this study, a number of thyroid nodules submitted for evaluation by frozen section was diagnosed

as colloid goiter, which was confirmed by subsequent cuts in paraffin. This examination was considered concordant. However, in other areas of the specimen sent after the operation, papillary microcarcinoma was detected.

In our findings, the lung / pleura / mediastinum were the sites with lower accuracy (86.67%). In the literature there are reports of 5.3%[9] to 8.7%[10] diagnostic discrepancies. The frozen section diagnosis of pulmonary nodules can be difficult, especially in inflammatory and fibrotic tissue, which can be mistaken for malignant lesions[20].

By globally assessing the pathological frozen section exams and comparing them with subsequent examination of paraffin, we found a diagnostic accuracy of 93.30%. When analyzed by specific anatomic site, diagnostic accuracy ranged from 86.67% to 100.00% and therefore it can be considered similar to the ranges reported by other authors[11-13,16,17,21].

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.

R E S U M O

Objetivo: *Avaliar o grau de precisão diagnóstica dos exames por congelação em diferentes sítios anatômicos realizados em um serviço universitário de patologia.* ***Métodos:*** *Foi realizado estudo retrospectivo a partir de banco de dados informatizado de todos os exames por congelação. Estes diagnósticos foram comparados com os definitivos em parafina, utilizados como controles. Os exames foram distribuídos em três grupos: inconclusivos, concordantes e não concordantes, sendo este último subdivido em falsos positivos e falsos negativos. As principais indicações dos exames e os sítios anatômicos envolvidos com as divergências diagnósticas também foram analisados.* ***Resultados:*** *Quatrocentas e trinta e três peças cirúrgicas foram submetidas a exames por congelação, sendo a principal indicação o diagnóstico da lesão (75,75%). Em 404 exames (93,30%) os diagnósticos das biópsias por congelação e em parafina foram concordantes. Em 20 (4,62%) casos os resultados das biópsias por congelação foram inconclusivos e em nove (2,08%) ocorreram falsos negativos. Não houve resultados falsos positivos. O principal órgão avaliado foi a tireoide (25,64%). Na análise global, a região do corpo mais relacionada com os diagnósticos inconclusivos por congelação foi a tireoide (sete casos) e em relação aos sítios específicos foram os pulmões/pleura/mediastino (13,33%). Pele foi o órgão que mais apresentou diagnósticos discordantes entre biópsias por congelação e em parafina.* ***Conclusão:*** *A acurácia da congelação de forma global foi de 93,30%; por sítios anatômicos específicos, a precisão diagnóstica variou de 86,67% a 100%.*

Descritores: *Biópsia. Congelamento. Patologia cirúrgica. Técnicas de diagnóstico e procedimentos. Controle de qualidade.*

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