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Diagnostic Accuracy and Discrepancies of Frozen Section Analysis in a Colombian Intermediate Care Center

Precisión diagnóstica y discrepancia diagnóstica en el análisis de congelaciones en un centro de mediana complejidad en Colombia

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ABSTRACT

Introduction: Frozen section procedure is an intraoperative diagnostic method widely used and useful for surgical decision making; which minimizes costs and optimizes staging. **Objectives**: This research assesses the diagnostic accuracy of frozen section in an intermediate care center, analyzes the factors that may be involved in misdiagnosis and compares the results of the original study with other studies. **Materials and methods:** This is a cross-sectional study in which the diagnostic accuracy was evaluated and a univariate analysis was performed in a sample of 417 cases in which a frozen section was used. The characteristics of the samples were registered along with the concordance or discordance between the frozen section and the final diagnosis. In addition, a systematic review was made using the Pubmed database in order to compare results with previous studies. **Results:** The sample included predominantly females with a mean age of 50 years. The sensitivity and specificity of malignancies was 89% and 100% respectively and the sensitivity for borderline tumors was lower (73%). Specimens equal or larger than 10cm and patients with age ≥ 50 years showed association to misdiagnosis when using frozen sections. For example, the analysis of 300 ovary specimens showed association to misdiagnosis in borderline, epithelial and stromal tumors. **Conclusions:** Frozen sections continue to be the best tool for quick intraoperative diagnosis, and even with some diagnostic inaccuracies, this does not impair clinical and surgical practice.

Keywords
frozen sections; diagnostic errors; neoplasms; ovary; sensitivity and specificity.

RESUMEN

Introducción: La biopsia por congelación es un método de diagnóstico intraoperatorio ampliamente usado, vigente y útil para la toma de decisiones quirúrgicas, que minimiza el costo y optimiza el estadiaje de malignidades. **Objetivos:** Determinar la precisión diagnóstica de la biopsia

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por congelación en un centro de nivel intermedio, analizar factores que pueden influir en los errores diagnósticos de la biopsia por congelación y comparar los resultados del estudio original con otros estudios similares. **Materiales y métodos**: Este es un estudio transversal en el cual se evaluó la precisión diagnóstica y se realizó un análisis univariado de una muestra de 417 casos de biopsia por congelación donde se registraron sus características y la concordancia o discrepancia entre la biopsia por congelación y el diagnóstico definitivo (fijado en parafina); además, se realizó una revisión sistemática en la base de datos Pubmed, con el fin de comparar los resultados de otros estudios. **Resultados**: La muestra era predominantemente femenina con una edad media de 50 años; para malignidad se presentó una sensibilidad del 89 % y una especificidad del 100 %. La sensibilidad para tumores con malignidad limítrofe fue menor (73 %), especímenes mayores o iguales a 10 cm y pacientes con edad mayor o igual a 50 años presentaron asociación con errores en el diagnóstico por congelación. En el análisis de 300 especímenes de ovario se encontró asociación con el diagnóstico erróneo en tumores de malignidad limítrofe, epiteliales y estromales. **Conclusiones**: Las secciones congeladas continúan siendo la mejor herramienta para un diagnóstico intraoperatorio rápido, e incluso con algunas inexactitudes en el diagnóstico, esto no perjudica la práctica clínica y quirúrgica.

Palabras clave
biopsia por congelación; errores diagnósticos; neoplasias; ovario; sensibilidad y especificidad.

Introduction

Intraoperative frozen section consultation has become an essential tool for making surgical decisions about treatment options, understanding whether a lesion is malignant or benign, ensuring the absence of tumor cells in the excision margins and identifying specific tissues (1). Intraoperative consultations must be done quickly in order to be useful for the surgeon's decision process and to avoid unnecessary surgical procedures. Hence, it is recommended to send only samples that are representative for the frozen section (2).

Frozen section diagnosis is usually compared with the diagnosis of paraffin-embedded tissue, better known as permanent diagnosis, in order to determine diagnostic accuracy, evaluate discrepancies, identify deficiencies and solve associated problems, with the ultimate purpose of improving the quality of the intraoperative biopsy and diagnostic accuracy (3).

Many studies have reported the accuracy of biopsies from intraoperative consultation. However, in intermediate care institutions from medium-sized Colombian cities, there were no reports of this kind in our search; one study from Colombia was found, but it belonged to a tertiary care center (4). The objective of this study is to compare the accuracy of frozen section diagnosis in this institution with the results of other studies in the world and analyze the possible causes of discrepancy.

Materials and methods

The purpose and methodology of this study were approved by the Local Ethical Committee supported by the investigation program in genetic analysis of human diseases of the University of Tolima. All procedures and data collection were conducted in accordance with the Declaration of Helsinki.

A total of 417 cases in which frozen section was used between January of 2015 and November of 2019 in an intermediate care center were included in this retrospective study. From them, the following data were recollected: age of the patient, anatomic site, specimen size, histological results of the frozen section and the final report. The cases were classified in two categories: concordant and discordant. In addition, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. Univariate analysis was performed in order to identify predictor factors for misdiagnosis in the general sample and in the ovary specimens. The data distribution was valued with X^2 and Fischer's exact test. All the calculi were made with Vassarstats online software.

The literature search was performed in Pubmed using the criteria "frozen section" and "concordance", and 277 articles were found. The search was confined to the last five years (89 articles), then filtered by "humans" and in English with full text available (54 articles). After reading the abstract, it was reduced to 9

articles that could be compared to this study, including the results of sensitivity and specificity for malignancies in different anatomical sites.

Results

From the 417 cases, 395 were female and 22 were male; the most frequent anatomical site of extraction was ovary with 300 cases, the median age of the sample was 50 years, and 276 of the total specimens were less than 10 cm in size; the clinical accuracy values are shown in Table 1. There were no false positives for malignancy, giving a 100% in specificity; borderline tumors had the worst accuracy (sensitivity: 72.7%; PPV: 61.5%); benign tumors did not present false negatives. Sensitivity for malignant neoplasm was 88.9% in our study.

Table 1

Diagnostic accuracy of frozen section

Value	Benign	Borderline	Malignant
TP	296	16	88
FP	7	10	0
TN	114	385	318
FN	0	6	11
Sen (%)	100	72.73	88.89
Spe (%)	94.21	97.47	100
PPV (%)	97.68	61.54	100
NPV (%)	100	98.46	96.66

TP: true positives; FP: false positives; TN: true negatives; FN: false negatives; Sen: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value

The attributes of the 17 discordant cases are shown in the Table 2. All of the discordant cases were female, the anatomical site for 15 of these cases was ovary and the specimen size was greater or equal to 10 cm in 12 of the cases.

Table 2

Attributes of the discordant cases

Age	Organ/site	Frozen section diagnosis	Definitive (paraffine) diagnosis	Specimen size (cm)
55	Ovary	Papilar serous borderline tumor	Serous adenocarcinoma	≥10
21	Ovary	Cystic mucinous borderline tumor	Clear cell carcinoma	≥10
51	Ovary	Mucinous cystadenoma	Mucinous borderline tumor	≥10
39	Ovary	Papilar serous borderline tumor	Serous cystoadenocarcinoma	≥10
54	Ovary	Cystic mucinous borderline tumor	Mucinous tumor with intraepithelial carcinoma	≥10
67	Ovary	Papilar serous borderline tumor	Serous cystoadenocarcinoma	<10
61	Ovary	Papilar serous borderline tumor	Serous tumor with intraepithelial carcinoma	<10
40	Skin	Scamous hiperplasia	Low grade scamous lesion	<10
72	Ovary	Papilar serous borderline tumor	Granulosa cell tumor	≥10
73	Ovary	Mucinous cystadenoma	Mucinous borderline tumor	≥10
48	Ovary	Leiomyoma	STUMP	≥10
41	Ovary	Papilar serous borderline tumor	Papilar cystoadenocarcinoma	≥10
50	Ovary	mucinous borderline tumor	Low grade mucinous tumor	≥10
47	Lymph node	Negative	Metastatic compromise	<10
32	Ovary	Serous borderline cystadenoma	Low grade serous carcinoma	≥10
66	Ovary	mucinous benign tumor	Mucinous mixt borderline cystoadenoma	≥10
65	Ovary	Papilar serous cystadenoma	Serous borderline cystoadenoma	<10

The univariate analysis for the general sample is shown in Table 3; it shows an association to misdiagnosis in age ≥ 50 years (OR = 1.21) and specimen size ≥ 10 cm (OR = 5.04). The specimen size showed more statistical significance ($p = 0.001$). In addition, the analysis showed a correlation with the anatomical size such as ovary (OR = 1.16) but with low statistical significance ($p = 1$). Table 4 shows the univariate analysis for the 300 ovary specimens. It revealed association to misdiagnosis in individuals 50 years or older (OR = 2.12; $p = 0.15$), size ≥10 cm (OR = 5.83; $p = 0.003$), borderline tumors (OR = 1.37; $p < 0.001$), and stromal epithelial histology (OR = 2.28 and 3.79; $p = 0.6$).

Table 3

Univariate analysis for the general sample

	Total	Concordant	Discordant	Odds	OR	p
Age						0.708
<50 years	215	207	8	0.04	0.83	
≥50 years	202	193	9	0.05	1.21	
Tumor size						0.001
<10 cm	276	271	5	0.02	0.20	
≥10 cm	141	129	12	0.09	5.04	
Organ						1
Ovary	300	285	15	0.05	1.16	
Thyroid	37	37	0	0.00		
Uterus	17	17	0	0.00		
Pleura	19	19	0	0.00		
Lymph nodes	20	19	1	0.05	1.02	
Others	26	25	1	0.04	0.76	

Table 4

Univariate analysis for ovary (n = 300)

	Concordant	Discordant	Odds	OR	p
Age					0.15
<50 years	167	6	0.04	0.47	
≥ 50 years	118	9	0.08	2.12	
Tumor size					0.003
<10 cm	169	3	0.02	0.17	
≥10 cm	116	12	0.10	5.83	
Malignancy					<0.001
Benign	228	0	0.00		
Borderline	15	5	0.33	1.37	
Malignant	42	10	0.24	0.73	
Type					0.6
Epitelial	180	13	0.07	3.79	
Stromal	18	2	0.11	2.28	
Germinal	45	0	0.00		
Non tumoral	42	0	0		

Possible biases include selection bias because ovary tumors are the most frequent cause of intraoperatory consultation in our center. There

might be a bias due to the small sample size in the measurement of sensitivity and specificity.

Discussion

Frozen section is a commonly used tool for immediate diagnosis in multiple organs, but it has a particular widespread application in ovarian tumors, as shown in this study with a vast majority of cases with an ovarian origin. Therefore, the sample for this study was mainly female. The results of this study were compared with the results of other nine studies. The selected studies for comparison are shown in Table 5. The sensitivity for malignancy in this study varied from 99.7 to 72.5% (5,6). Interestingly, in four of the other studies, the main organ sampled was ovary (6-9). In one of these, the specificity and PPV was 100%, giving equal results as this study. One study did not present true positive cases for malignancy because its main focus was borderline tumors. Another study with low sensitivity was performed by Park et al. with a sensitivity of 72.5%. However, it only included mucinous tumors (6). The diagnostic accuracy of frozen section in this study had high values for malignant and benign lesions presenting flaws in borderline lesions, causing 10 cases of under-diagnosis, the sensitivity for malignancy is similar to the mean sensitivity in the studies listed in Table 5.

Table 5

Clinical accuracy for malignance between studies

Study	Country	Organ/region	n	TP	FP	TN	FN	Sen (%)	Spe (%)	PPV (%)	NPV (%)
Alanu et al., 2019	India	Orbital, ocular adnexa	51	30	2	14	5	87.2	87.5	93.7	73.7
Hashmi et al., 2019	Bangladesh	Ovary	136	27	0	108	1	96.4	100	100	99.1
Hatami et al., 2015	Iran	head, neck, thyroid, ovary, lymph nodes	295	66	1	223	5	93.0	99.6	98.5	97.8
Huang et al., 2018	China	Ovary	155	0	3	137	15	0.0	97.9	0.0	90.1
Layfield et al., 2018	USA	Head & neck	1796	278	20	1463	35	88.8	98.6	93.3	97.6
Mokhles et al., 2019	Iran	Ovary & Uterus	188	26	9	109	4	86.5	99.4	96.3	97.5
Ouaiss et al., 2015	USA	Skin	288	187	23	77	1	99.7	77.0	89.0	98.7
Park et al., 2019	South Korea	Ovary (mucinous only)	1032	71	11	923	27	72.5	98.8	86.6	97.1
Preeti et al., 2016	India	Lymph nodes, breast, oral, ovary, abdominal nodules	224	30	4	178	10	75.0	97.5	90.9	94.0
This study	Colombia	Ovary, thyroid, uterus, pleura, lymph nodes	417	88	0	318	11	88.89	100	100	96.66

There are different factors that can be correlated with misdiagnosis in frozen section. This study showed an association with patient's age ≥50 years and misdiagnosis with medium statistical significance. On the other hand, a larger specimen size (≥10 cm) correlates with misdiagnosis in addition to high statistical significance for both the general sample and the ovary cases. This agrees with previous studies (8). The anatomical site of extraction of the samples was not significant in this study. The tumor type in ovary as stromal or epithelial tumor were associated with misdiagnosis in a medium statistical significance. Other studies have shown that some histological types of tumors are more likely to be misdiagnosed. For example, ovarian clear cell carcinoma may be confused in first instance with borderline serous tumor (10). One of the discordant cases in this study had this characteristic. Mucinous tumors are the most frequently misdiagnosed type of tumor. (6). The misdiagnosis in stromal ovarian tumors has also been reported to be frequent (11). Another tumor characteristic related to misdiagnosis is borderline malignancy, with a high statistical value. Many studies also confirm this to be an important factor leading to discordances between frozen section and definitive diagnosis (12-14).

The importance of intraoperative consultation using frozen section comes from the fact that some tumors can only be diagnosed through surgery, mainly ovarian neoplasms (15). Thus, frozen section diagnosis becomes a guide for the surgeon, and studies report that it is an accurate modality for this purpose (16). Although the most common discrepancies occur between borderline tumors and real malignancy, fortunately this issue does not affect its usefulness as a guide in the choice of surgery, since to a large extent intraoperative treatment in borderline and malignant ovarian tumors includes bilateral salpingo-ophorectomy and appendectomy, and fertility preservation procedures are not performed in any of these tumors (15).

In conclusion, pathological diagnosis by frozen section has been and will continue to be the best tool for rapid diagnosis in intraoperative consultation, even though it may have its flaws in specimens that are too large or have specific characteristics for certain tumors and patients. The results of this study showed concordance with previous findings, in which the inaccuracy tend to be about diagnosis details more than in general diagnosis of malignancy, an event that

does not usually impair surgical practice and the prognosis of the disease.

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Conflict of interests

The authors declare none.

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References

1. Espinoza M de los A, Barahona O. Biopsias transoperatorias por congelación. Rev Med Hondur [Internet]. 1992;60:129–33. Available from: http://cidbimena.desastres.hn/RMH/pdf/1992/pdf/Vol60-3-1992-4.pdf

2. McIntosh ER, Harada S, Drwiega J, Brandwein-Gensler MS, Gordetsky J. Frozen section: guiding the hands of surgeons? Ann Diagn Pathol. 2015;19(5):326–9. https://doi.org/10.1016/j.anndiagpath.2015.07.004

3. Hatami A. The diagnostic accuracy of frozen section compared to permanent section: single center study. Kathmandu Univ Med J. 2019;17(67):229–33.

4. Suarez-Zamora DA, Barrera-Herrera LE, Palau-Lazaro MA, Torres-Franco F, Orozco-Plazas A, Barreto-Hauzeur L, Rodríguez Urrego PA. Accuracy and interobserver agreement of retroareolar frozen sections in nipple sparing mastectomies. Ann Diagn Pathol. 2017;29:46–51. https://doi.org/10.1016/j.anndiagpath.2017.05.001

5. Onajin O, Wetter DA, Roenigk RK, Gibson LE, Weaver AL, Comfere NI. Frozen section diagnosis for non-melanoma skin cancers: Correlation with permanent section diagnosis. J Cutan Pathol. 2015;42(7):459–64.

6. Park JY, Lee SH, Kim KR, Kim YT, Nam JH. Accuracy of frozen section diagnosis and factors associated with final pathological diagnosis upgrade of mucinous ovarian tumors. J Gynecol Oncol. 2019;30(6):1–10.

7. Hashmi AA, Naz S, Edhi MM, Faridi N, Hussain SD, Mumtaz S, et al. Accuracy of intraoperative frozen section for the evaluation of ovarian neoplasms: An institutional experience. World J Surg Oncol. 2016;14(1):1–5. https://doi.org/10.1186/s12957-016-0849-x

8. Huang Z, Li L, Li CC, Ngaujah S, Yao S, Chu R, et al. Diagnostic accuracy of frozen section analysis of borderline ovarian tumors: A meta-analysis with emphasis on misdiagnosis factors. J Cancer. 2018;9(16):2817–24. https://doi.org/10.7150/jca.25883

9. Mokhles P, Ahmadi A, Rahehagh R, Soofizadeh N, Ghaderi E. Compatibility of the frozen section method in histopathological specimens for female pelvic masses with results for pathology and tumor markers. Med J Islam Repub Iran. 2019 May 15;33:42. https://doi.org/10.34171/mjiri.33.42

10. Buza N. Frozen section diagnosis of ovarian epithelial tumors. Arch Pathol Lab Med. 2019;143(1):47–64. https://doi.org/10.5858/arpa.2018-0289-RA

11. Genç M, Solak A, Genç B, Sivrikoz ON, Kurtulmuş S, Turan A, Sahin N, Gür EB. A diagnostic dilemma for solid ovarian masses: the clinical and radiological aspects with differential

diagnosis of 23 cases. Eur J Gynaecol Oncol. 2015;36(2):186-91.

12. Zhang W, Jia S, Xiang Y, Yang J, Jia C, Leng J. Factors associated with misdiagnosis of frozen section of mucinous borderline ovarian tumor. J Int Med Res. 2019 Jan;47(1):96-104. https://doi.org/10.1177/0300060518795582

13. Bozdag H, Guzin K, Gocmen A, Kabaca S, Usta A, Akdeniz Duran E. The diagnostic value of frozen section for borderline ovarian tumours. J Obstet Gynaecol (Lahore). 2016;36(5):626–30.

14. Morice P, Uzan C, Fauvet R, Gouy S, Duvillard P, Darai E. Borderline ovarian tumour: Pathological diagnostic dilemma and risk factors for invasive or lethal recurrence. Lancet Oncol. 2012;13(3):18–21. https://doi.org/10.1016/S1470-2045(11)70288-1

15. Salcedo-Hernández RA, Cantú-de-León DF, Pérez-Montiel D, García-Pérez L, Lino-Silva LS, Zepeda-Najar C, et al. The usefulness of intraoperative consultation for the diagnosis of borderline ovarian tumors. Ann Transl Med. 2021;9(3):261. https://doi.org/10.21037/atm-20-3932

16. Palakkan S, Augestine T, Valsan M, Vahab K, Nair L. Role of frozen section in surgical management of ovarian neoplasm. Gynecol Minim Invasive Ther. 2020;9(1):13–7. https://doi.org/10.4103/GMIT.GMIT_2_19