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Frozen section in thyroid gland follicular neoplasms: It's high time to abandon it!☆

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ABSTRACT

Thyroid nodules are a very common clinical condition. The 2015 American Thyroid Association (ATA) guidelines recommend surgical excision for Bethesda IV nodules. The use of intraoperative frozen section (FS) has been recommended as a strategy to tailor the extent of the initial surgery. We critically evaluated the literature that discusses the utility and cost-effectiveness of FS to make an intraoperative decision in patients with thyroid nodules classified as follicular neoplasm. FS should not be recommended as a routine intraoperative test to assess for malignancy in thyroid follicular patterned lesions due to its low performance; the high number of deferred results; the inability to adequately assess histologically defining features; the improvements in risk stratification guiding total thyroidectomy; and the low cost-effectiveness of FS.

1. Introduction

Thyroid nodules are a very common clinical condition. Ultrasound and fine needle aspiration biopsy (FNAB) are the main diagnostic tests used to risk stratify nodules and guide treatment planning [1]. In 2009, the Bethesda System for Reporting Thyroid Cytopathology was established as a standardized, category-based reporting system for thyroid FNAB specimens based on the expected risk of malignancy [2], updated in 2017 [3]. The classification uses six categories that describes a spectrum of changes that ranges from very low risk of malignancy (benign, category II)] to high risk (malignant, category VI). In the middle are categories III, IV and V: category III including *atypia of undetermined significance (AUS)* or *follicular lesion of undetermined significance (FLUS)*; category IV: *follicular neoplasm or suspicious for a follicular neoplasm;* and category V: *suspicious for malignancy*; these categories are associated with a moderate probability of malignancy. The 2015 American Thyroid Association (ATA) guidelines [1] recommend surgical excision (usually a thyroid lobectomy) for Bethesda IV nodules,

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although a total thyroidectomy could also be recommended depending on several characteristics, such as size, ultrasound pattern, bilateral disease, patient preference and genetic molecular testing [4].

Over the last 40 years, the use of intraoperative frozen section (FS) has been recommended as a strategy to obtain a definitive histologic diagnosis of a preoperatively indeterminate thyroid nodule classified as follicular neoplasia during surgery and to tailor the extent of the initial surgery accordingly [5]. However, its use provokes intense discussion regarding its utility and cost-effectiveness due to the discrepancies in reported results.

The aim of this review is to critically evaluate the literature that discusses the utility and cost-effectiveness of FS to make an intraoperative decision in cases of patients with thyroid nodules classified as follicular neoplasm and to critically assess its utility.

2. Diagnostic performance of frozen section in follicular thyroid nodules

The first formal description of utilizing FS to make an intraoperative decision was reported by De Reimer from The Netherlands in 1818, with Welch in 1891, at Johns Hopkins in Baltimore, Maryland, was the first to apply it to clinical material, examining a breast cancer operated on by Halsted [6]. Later, in 1905, Wilson from Mayo Clinic in Rochester, Minnesota, published his systematic experience [7]. Since that time, FS has been widely used for separating benign from malignant lesions, and to define the margin status after tumor resections. For thyroid nodules, it has been used since the middle of the 20th century [7]. A PubMed search with the terms "*frozen section*" and "*thyroid nodules*" made in March 2020, retrieved more than 9500 articles. The subject has been widely discussed in the literature and by the end of the 20th century, an editorial published in the American Journal of Clinical Pathology titled "Frozen Section of Thyroid? Just Say No", discussed its current use in thyroid gland pathology [8].

In thyroid nodules, the main diagnostic objective is to define if they are malignant in order to offer appropriate surgical treatment. The wide use of FNAB, with its high sensitivity and specificity, helps to define the nature of nodules and to select the most appropriate therapeutic approach [3]. For categories with a high risk of malignancy, such as Bethesda VI, above the therapeutic threshold [9], a surgical procedure without further diagnostic tests is the most cost-effective treatment. At the other end of the spectrum, nodules classified as Bethesda II, which are located below the diagnostic threshold, have a low risk of malignancy, and thus clinical and ultrasonographic surveillance is the recommended strategy (Fig. 1). Therefore, in these two extremes, the use of FS is not only useless, but it increases intraoperative risks and the cost of treatment. Older studies evaluating FS reported a high accuracy (70%–95%), but most of these studies included a number of nodules located at both ends of the diagnostic spectrum [10–13]. Depending on the number of low- or high-risk nodules included, the predictive values of the FS can be artificially increased, which is known as "*spectrum bias*" or the "*spectrum effect*" that explains the "*variation in diagnostic test performance according to the prevalence and distribution of a disease in a population*" [14]. Peng et al. [15], clearly demonstrated this bias for the FS in thyroid lesions, when the positive predictive value changed from 86% in studies that included mostly follicular neoplasms to 98% when including all types of thyroid nodules. Although this phenomenon is widely recognized, recent studies still include nodules from these categories and report overestimated results that further contribute to confusion [16, 17].

In contrast, nodules classified as follicular neoplasms are in the middle of the risk spectrum, i.e. between the diagnostic and therapeutic thresholds, where diagnostic tests such as FS or genetic molecular testing must prove their utility to offer useful information because a positive result will move the risk over the therapeutic threshold, while a negative result will move the risk below the diagnostic threshold (Fig. 1). In a meta-analysis conducted in 2008, Peng et al. [15], reported 23 studies that evaluated the FS performance in follicular neoplasia and found a sensitivity of 21% and a specificity of 99%. Although they proposed not to use FS as a diagnostic tool in follicular neoplasms, many additional studies were published later where the use of FS was evaluated in the same scenario [18–28]. In 2019, Grisales and Sanabria [29] updated this meta-analysis and found a low sensitivity of 43% and a specificity of 100%. The final conclusion based on results of FS diagnostic performance was that its routine use should be avoided. The determination of malignancy in a follicular patterned nodule relies mainly on the presence of invasion, which is a matter of tissue sampling and therefore it is difficult to differentiate benign from malignant based on a FS. FS in nearly all cases will not be able to confirm follicular cancer, as it is based on sometimes very focal and potentially easily missed capsular and lymphatic or vascular invasion; if the FS diagnosis is papillary thyroid carcinoma (PTC), in the vast majority of cases, nothing assessed of the primary tumor by the frozen section would lead you to convert a lobectomy to a total thyroidectomy.

3. Reasons against frozen section for follicular lesions/neoplasms: primary studies

Other reasons which limit the adoption of FS in follicular lesions include those related to the primary studies themselves, and to the practical application of FS in clinical practice. When examining the literature, there is significant and mounting evidence that frozen section for follicular lesions/neoplasms is either not efficacious, not cost-effective, or both.

The first reason is the limited sample size in the primary studies [29]. In a meta-analysis that assessed FS in follicular neoplasms, only a few studies (11/46) included more than 100 patients. It is generally accepted

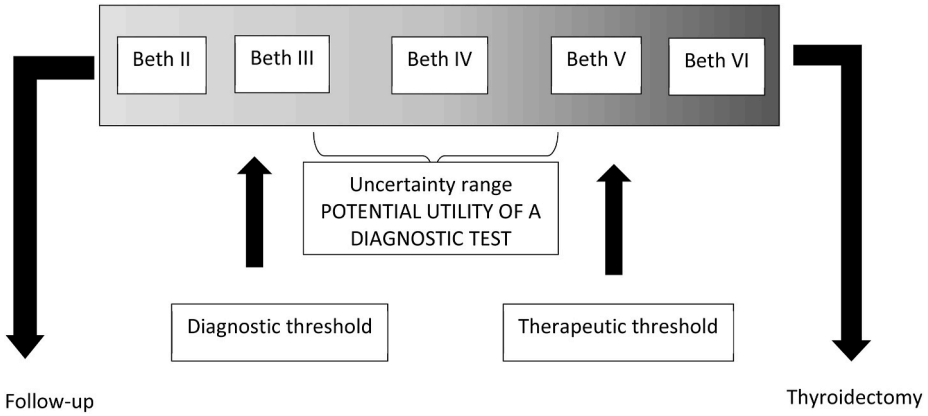

Fig. 1. Risk spectrum and thresholds in thyroid nodules according to Bethesda classification.

that specialized training in pathology is an important factor that improves interpretation of FNAB and FS [30,31]. Moreover, reference centers, where higher numbers of FS are performed, acquire experience and improve technical processing factors (tissue folding, tangential sectioning, architectural findings, nuclear size and shape, contour irregularities and chromatin staining or distribution), which can modify the pathologist's interpretation in the final pathology report [32–34]. Therefore, if a center performs FS for follicular lesions, it is reasonable to assume that with the low sensitivity of FS, the number of FSs for follicular neoplasms will decrease. As the number of samples declines, so does the technical and professional experience, further reducing diagnostic performance, creating a negative spiral that eliminates the routine use of FS.

A second reason is the high rate of deferred results. The rates reported in the meta-analysis varied from 0 to 97%, and 58% of the studies reported deferred results; a high rate of deferred results was related to better performance of the FS [29]. There is no information about the acceptable percentage of deferred results, but high percentages could be a proxy of sampling difficulties. A deferred result will falsely increase the performance of the test due to *information or diagnostic review bias* that occurs when the interpretation of the reference test is not independent of the index test [35,36]. In studies with high rates of deferred results, the pathologist interprets the final sample knowing clinical data and surgical findings without intraoperative time limitations, which does not occur when an immediate result is offered without deferring. The frequency of deferred cases depends on several other factors, such as sample conditions, type of characteristics to be evaluated and the pathologist's experience. As mentioned previously, experience increases with the evaluation of a high number of samples in a short period of time, which is not easily acquired in contemporary circumstances. Additionally, for thyroid follicular neoplasms, the physical conditions of the sample play an important role in the evaluation. It has been previously reported that freezing artifacts can confound the interpretation of the samples [32,33] and that training and dedication in the management of the samples by specialized technicians are important factors to avoid this problem. If there are limited personnel and fewer samples, experience will be hard to acquire. Finally, the characteristics evaluated to separate follicular adenoma from follicular thyroid carcinoma (FTC) (capsule and/or lymphovascular invasion) are elusive when only a few tumor sections are examined or a limited number of tissue sections are histologically reviewed. All these situations will increase the number of deferred results, which will increase the operative time and cost without a significant change in the rate of total thyroidectomies.

Third, performance of a diagnostic test depends on the prevalence of the condition. According to Cibas et al. [3], the current rate of malignancy in follicular neoplasms ranges from 10 to 40%, with a mean of approximately 25%. Therefore, predictive values of FS vary depending where the study is performed. In a reference center, the expected number of malignant cases will be higher than those in community hospitals, with a consequent difference in predictive values and differential effect in intraoperative decisions. As diagnostic performance is lower in settings with a low prevalence of malignancy, FS use will produce more diagnostic misclassification, and it can be inferred FS use will decrease with time (Fig. 2). Ultimately, a lower number of FSs will be performed, as previously reported in several hospitals in Japan by Osamura et al. [37].

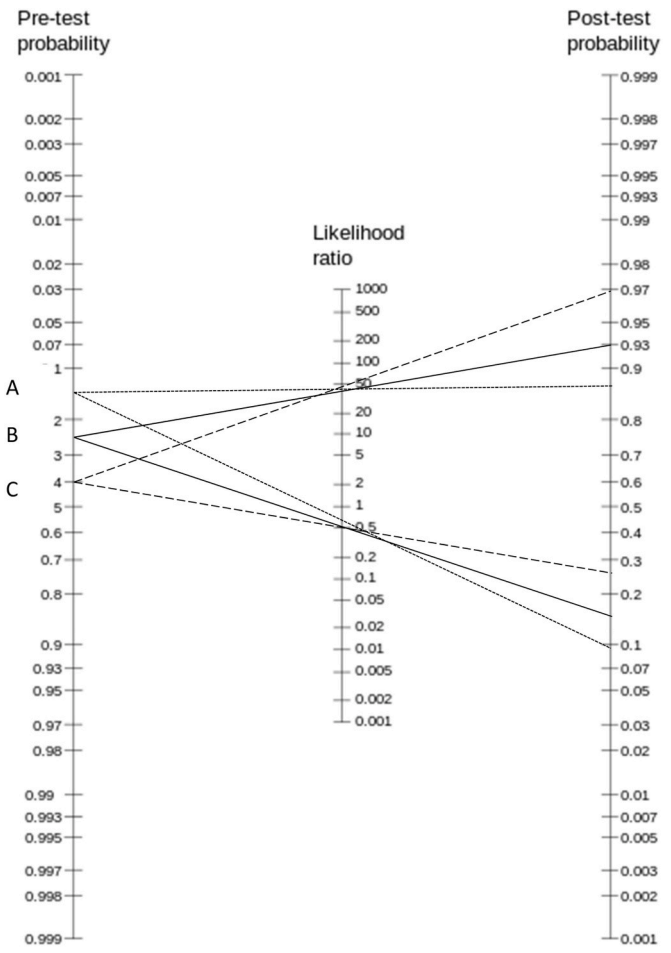

Fig. 2. Effect of prevalence in results of FS in follicular neoplasm. As can be seen, when the prevalence (pre-test probability) of FTC is high as 40% (line C), a negative result of FS, will decrease the post-test probability to 26%, which left the situation unsolved. When the prevalence is low, 15% (line A), a negative result of FS will move the post-test probability to 10%, that does not solve the situation. Between both, the standard values show the poor performance of FS.

4. Reasons against frozen section for follicular lesions/ neoplasms: practical usage

In addition to arguments against the routine use of frozen section for follicular lesions/neoplasms from primary studies in the literature, there are a number of practical concerns related to frozen section with indeterminate thyroid nodules.

First, the pathologist's opinion about the utility of FS in determining a definitive diagnosis of follicular thyroid carcinoma is not optimal because capsular and/or lymphovascular invasion cannot be adequately assessed [8,38]. A complete sampling of the parenchyma-to capsule-to tumor interface is necessary to exclude capsular and/or lymphovascular invasion, which cannot be achieved by FS due to the low number of slices commonly obtained, unless the tumor is microscopic (≤1 cm in greatest dimension). Fig. 3. It has been calculated that at least nine paraffin-embedded tissue blocks are necessary for the histologic identification of lymphovascular invasion in minimally invasive follicular thyroid carcinoma, depending on the tumor size [39]. Moreover, the impossibility of sampling the entire capsule and the artifacts in FS obscure the nuclear details that are necessary to distinguish this lesion from other conditions, such as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [32,39]. Fig. 4. If the predicted number of NIFTP tumors is approximately 20% of all follicular-patterned neoplasms, the FS will be useless in these cases. Moreover, there are concerns about wasting tissue in small nodules that can suffer permanent frozen section artifacts, compromising the definitive diagnosis [33]. However, in spite of clear cut reasons, most pathologists do not exert active opposition against frozen sections on thyroid nodules [38,40–42].

Second, the most important concern initially regarding follicular neoplasms was the possibility of missing a FTC which had a worse prognosis in comparison with PTC. However, the original follicular thyroid carcinoma rate of 20–30% has been significantly reduced by the

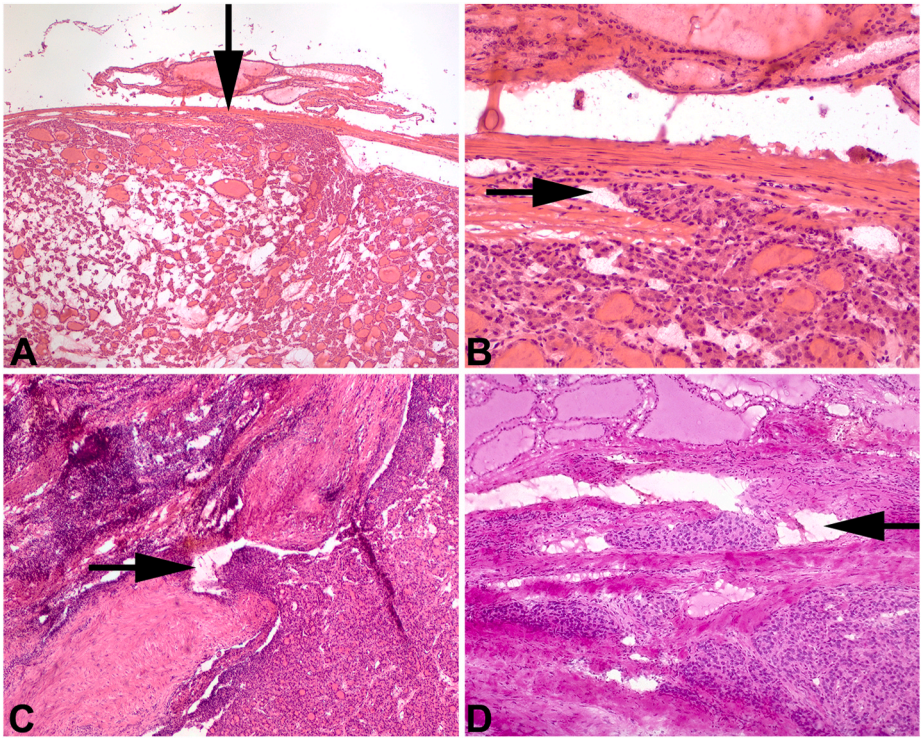

Fig. 3. Thyroid frozen section difficulties in evaluating capsular and vascular invasion. A) and B) demonstrate an area of capsule invasion, captured on frozen section, but only recognized as invasion on the permanent sections. C) An area of capsular penetration is seen here on the frozen section material, but it was interpreted as a fold in the tissue and thus was not called. D) A small rounded tumor embolus is noted within this lymphatic channel on the frozen section material, but again due to the nature of the specimen was not recognized until the permanent section was reviewed. Therefore, even though features of invasion may be present on frozen sections they are often too difficult to identify and state with certainty that they represent invasion.

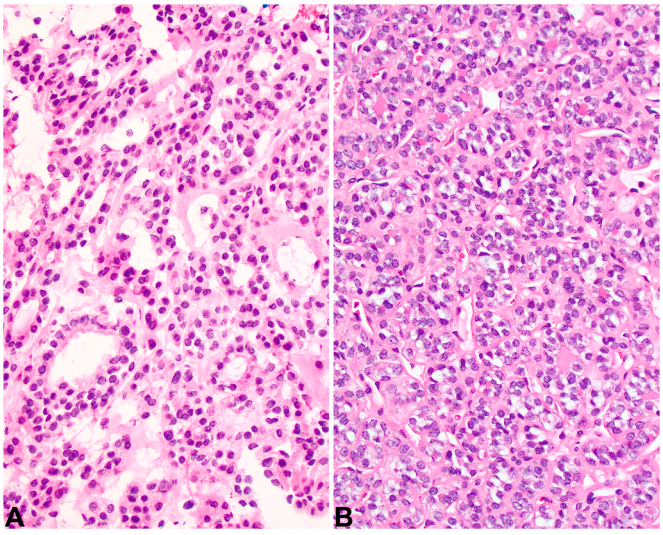

Fig. 4. Thyroid frozen section difficulties in evaluating nuclear cell characteristics. A) The frozen section shows round and regular nuclei with a follicular architecture. B) Permanent sections demonstrate the same follicular architecture, but the nuclei are enlarged, irregularly placed, with grooves, folds and irregular contours. There is delicate and fine, even nuclear chromatin.

reclassification to follicular variant of PTC or NIFTP, both of which have a significantly better prognosis [43,44]. Today, the rate of "true" FTC in larger datasets is approximately 7% [45,46]. Therefore, because FTC is less frequent, the potential utility of FS is even lower.

Third, the recommended extent of surgery for low-risk well-differentiated thyroid carcinoma has changed in the last two decades. Prior to 2009, most cases of thyroid carcinoma, independent of size and other factors, were treated with total thyroidectomy; thus, FS played an important role in the intraoperative decision to remove the contralateral lobe. When ATA recommendations changed, the threshold for a total thyroidectomy was modified progressively, first to tumors larger than 1 cm [47] and later to tumors larger than 4 cm [1]. Further, most nodules classified as follicular neoplasms are smaller than 4 cm; therefore, the utility of FS to decide on a contralateral lobectomy is limited. Tumors that previously were considered an absolute indication for total thyroidectomy, such as minimally invasive FTCs are now treated with lobectomy [48,49]. Currently, the decision is based on size (>4 cm), adverse features (number of foci of lymphatic and/or vascular invasion and degree of capsular invasion), contralateral lobe findings on US and patient preference. None of these can be assessed using FS.

Fourth, there is an unfounded belief in the diagnostic performance of FS to accurately classify follicular neoplasms that is deeply rooted in the surgical community. In some services, surgeons confidence in cytological results is low due to the lack of experienced thyroid cytologists or FS is part of the tradition and institutional routine, and is performed in all patients without regard to any preoperative findings or to decrease the possibility of a second surgical procedure [50]. If the follicular neoplasm is smaller than 4 cm with benign ultrasonographic findings, the use of FS should not change the preoperative decision to perform a lobectomy. Some surgeons demand immediate information or want to satisfy their curiosity without the delay of a definitive histopathological examination, without realizing that the diagnostic performance of FS for follicular patterns lesions is poor [40,41].

Fifth, it is expected that the progressive use and adoption of genetic classification tests will decrease even more the number of nodules candidates for FS and will make it even more outdated.

Finally, 6 of 8 economic studies demonstrated that FS was not cost-effective for follicular neoplasms. FS increases the costs due to the increased operative time, increased burden on pathology personnel (pathologist, technician, operating room transportation), and the need for pathological processing, which results in a negligible effect on the rate of delayed completion thyroidectomy.

5. Conclusions

Although the use of FS in high volume, tertiary institutions is decreasing progressively, many studies are still published, usually from non-academic centers, which helps to perpetuates its use. In conclusion,

based on its low diagnostic performance, FS should not be recommended as a routine intraoperative test to assess for malignancy in thyroid follicular patterned lesions with the aim of defining the extent of initial surgery. Arguments against the practice include the low quantity of FSs performed which makes it difficult for pathologists to gain enough experience in a short time; the high number of deferred results, which cannot help in making an intraoperative decision; the inability of FS to adequately assess histologically defining features; follicular patterned tumors require cytological evaluation that cannot be reliably achieved with the artifacts of FS; the improvements in risk stratification guiding total thyroidectomy; and the low cost-effectiveness of FS. Therefore, a thorough clinical history and examination, combined with high definition ultrasound assessment and FNAB (with judicious molecular testing), should be the cornerstone of pre-operative decision making in all cases of suspected thyroid cancer. By considering these factors, the peri-operative findings and the patient's preferences in relation to management, the need for completion thyroidectomy can be minimized without relying on a test with poor diagnostic performance with negligible impact on case management.

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Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

Author contributions

A.S., L.P.K; I.N: Conceptualization, methodology, formal analysis, investigation, data curation, writing—original draft, writing—review and editing; M.Z; L. T; J. H; A.S; J.P.R; A.M.; V.V.P; C.S.; P.Z.; A.R;, A.F.: Conceptualization, validation, writing—original draft, writing—review and editing, supervision. All authors have read and agreed to the published version of the manuscript.

References

[1] B.R. Haugen, E.K. Alexander, K.C. Bible, G.M. Doherty, S.J. Mandel, Y.E. Nikiforov, F. Pacini, G.W. Randolph, A.M. Sawka, M. Schlumberger, K.G. Schuff, S.I. Sherman, J.A. Sosa, D.L. Steward, R.M. Tuttle, L. Wartofsky, American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer, Thyroid 26 (2016) (2015) 1–133, https://doi.org/10.1089/thy.2015.0020.

[2] E.S. Cibas, S.Z. Ali, NCI Thyroid FNA State of the Science Conference, The Bethesda system for reporting thyroid cytopathology, Am. J. Clin. Pathol. 132 (2009) 658–665, https://doi.org/10.1309/AJCPPHLWMI3JV4LA.

[3] E.S. Cibas, S.Z. Ali, The 2017 Bethesda system for reporting thyroid cytopathology, Thyroid 27 (2017) 1341–1346, https://doi.org/10.1089/thy.2017.0500.

[4] M. Zafereo, B. McIver, S. Vargas-Salas, J.M. Dominguez, D.L. Steward, F. C. Holsinger, E. Kandil, M. Williams, F. Cruz, S. Loyola, A. Solar, J.C. Roa, A. Leon, N. Droppelman, M. Lobos, T. Arias, C.S. Kong, N. Busaidy, E.G. Grubbs, P. Graham, J. Stewart, A. Tang, J. Wang, L. Orloff, M. Henriquez, M. Lagos, M. Osorio, D. Schachter, C. Franco, F. Medina, N. Wohllk, R.E. Diaz, J. Veliz, E. Horvath, H. Tala, P. Pineda, P. Arroyo, F. Vasquez, E. Traipe, L. Marin, G. Miranda, E. Bruce, M. Bracamonte, N. Mena, H.E. Gonzalez, A thyroid genetic classifier correctly predicts benign nodules with indeterminate cytology: two independent, multicenter, prospective validation trials, Thyroid (2020), https://doi.org/10.1089/thy.2019.0490.

[5] I.J. Nixon, A.R. Shaha, S.G. Patel, Surgical diagnosis: frozen section and the extent of surgery, Otolaryngol. Clin. 47 (2014) 519–528, https://doi.org/10.1016/j.otc.2014.04.006.

[6] C.R. McHenry, I.B. Rosen, P.G. Walfish, Y. Bedard, Influence of fine-needle aspiration biopsy and frozen section examination on the management of thyroid cancer, Am. J. Surg. 166 (1993) 353–356.

[7] A.A. Gal, P.T. Cagle, The 100-year anniversary of the description of the frozen section procedure, J. Am. Med. Assoc. 294 (2005) 3135–3137, https://doi.org/10.1001/jama.294.24.3135.

[8] R.M. DeMay, Frozen section of thyroid? Just say no, Am. J. Clin. Pathol. 110 (1998) 423–424.

[9] S.G. Pauker, J.P. Kassirer, The threshold approach to clinical decision making, N. Engl. J. Med. 302 (1980) 1109–1117, https://doi.org/10.1056/NEJM198005153022003.

[10] M.S. Sabel, E.D. Staren, L.M. Gianakakis, S. Dwarakanathan, R.A. Prinz, User of fine-needle aspiration biopsy and frozen section in the management of the solitary thyroid nodule, Surgery 122 (1997) 1021–1026, discussion 1026-7.

[11] H.Y. Chang, J.D. Lin, J.F. Chen, B.Y. Huang, C. Hsueh, L.B. Jeng, J.S. Tsai, Correlation of fine needle aspiration cytology and frozen section biopsies in the diagnosis of thyroid nodules, J. Clin. Pathol. 50 (1997) 1005–1009.

[12] M.M. Mulcahy, J.I. Cohen, P.E. Anderson, J. Ditamasso, W. Schmidt, Relative accuracy of fine-needle aspiration and frozen section in the diagnosis of well-differentiated thyroid cancer, Laryngoscope 108 (1998) 494–496.

[13] L.A. Boyd, R.C. Earnhardt, J.T. Dunn, H.F. Frierson, J.B. Hanks, Preoperative evaluation and predictive value of fine-needle aspiration and frozen section of thyroid nodules, J. Am. Coll. Surg. 187 (1998) 494–502.

[14] J.A. Usher-Smith, S.J. Sharp, S.J. Griffin, The spectrum effect in tests for risk prediction, screening, and diagnosis, BMJ 353 (2016) i3139, https://doi.org/10.1136/bmj.i3139.

[15] Y. Peng, H.H. Wang, A meta-analysis of comparing fine-needle aspiration and frozen section for evaluating thyroid nodules, Diagn. Cytopathol. 36 (2008) 916–920, https://doi.org/10.1002/dc.20943.

[16] Q. Ye, Q. Zhao, P. Wang, P. Huang, L. Chen, Y. Ying, S.E. Yang, X. Li, J. Rao, Fine needle aspiration versus frozen section in the evaluation of malignant thyroid nodules: a comparative review within a single institution in China, Journal of the American Society of Cytopathology 4 (2015) S3.

[17] J. Huang, J. Luo, J. Chen, Y. Sun, C. Zhang, K. Xu, Q. Ye, P. Huang, Intraoperative frozen section can be reduced in thyroid nodules classified as Bethesda categories V and VI, Sci. Rep. 7 (2017) 5244, https://doi.org/10.1038/s41598-017-05459-x.

[18] J.P. Almeida, S.D. Couto Netto, R.P. Rocha, E.G. Pfuetzenreiter Jr., R.A. Dedivitis, The role of intraoperative frozen sections for thyroid nodules, Braz J Otorhinolaryngol 75 (2009) 256–260.

[19] F. Lumachi, S. Borsato, A. Tregnaghi, F. Marino, F. Polistina, S.M. Basso, H. Koussis, U. Basso, A. Fassina, FNA cytology and frozen section examination in patients with follicular lesions of the thyroid gland, Anticancer Res. 29 (2009) 5255–5257.

[20] V.J.F. Araujo Filho, L.G. Brandão, C.R. Cernea, C.I. Ronchi, V.J.F. Araujo Neto, Congelação intra-operatória em tireoidectomias, Rev. bras. cir. cabeça pescoço (Impr.) 39 (2010).

[21] F.H. Liu, M.J. Liou, C. Hsueh, T.C. Chao, J.D. Lin, Thyroid follicular neoplasm: analysis by fine needle aspiration cytology, frozen section, and histopathology, Diagn. Cytopathol. 38 (2010) 801–805, https://doi.org/10.1002/dc.21294.

[22] D. Arumugam, C.A. Macias, R.L. Sanders, S. Lu, M. Deen, M. May, R. Artymyshyn, N.J. Barnard, T. Davidov, S.Z. Trooskin, Intraoperative frozen section may reduce the need for reoperative thyroid surgery in patients with follicular neoplasm, Thyroid 23 (2013) A32–A33, https://doi.org/10.1089/thy.2013.2310.abs.

[23] R. Kahmke, W.T. Lee, L. Puscas, R.L. Scher, M.J. Shealy, W.M. Burch, R. M. Esclamado, Utility of intraoperative frozen sections during thyroid surgery, Int J Otolaryngol 2013 (2013) 496138, https://doi.org/10.1155/2013/496138.

[24] J.H. Yoon, E.K. Kim, J.H. Youk, H.J. Moon, J.Y. Kwak, Better understanding in the differentiation of thyroid follicular adenoma, follicular carcinoma, and follicular variant of papillary carcinoma: a retrospective study, Internet J. Endocrinol. 2014 (2014) 321595, https://doi.org/10.1155/2014/321595.

[25] M.A. Cohen, K.R. Patel, J. Gromis, D.I. Kutler, W.I. Kuhel, B.J. Stater, A. Schulman, R.S. Hoda, T. Scognamiglio, Retrospective evaluation of frozen section use for thyroid nodules with a prior fine needle aspiration diagnosis of Bethesda II-VI: the Weill Cornell Medical College experience, World Journal of Otorhinolaryngology - Head and Neck Surgery 1 (2015) 5–10, https://doi.org/10.1016/j.wjorl.2015.09.002.

[26] T.M. Cotton, J. Xin, J. Sandyhya, R. Lirov, B.S. Miller, M.S. Cohen, P.G. Gauger, D. T. Hughes, Frozen section analysis in the post-Bethesda era, J. Surg. Res. 205 (2016) 393–397, https://doi.org/10.1016/j.jss.2016.06.072.

[27] S. Roychoudhury, F. Souza, C. Gimenez, R. Glass, R. Cocker, K. Chau, N. Kohn, K. Das, Utility of intraoperative frozen sections for thyroid nodules with prior fine needle aspiration cytology diagnosis, Diagn. Cytopathol. 45 (2017) 789–794, https://doi.org/10.1002/dc.23765.

[28] S.J. Trosman, R. Bhargavan, B.L. Prendes, B.B. Burkey, J. Scharpf, The contemporary utility of intraoperative frozen sections in thyroid surgery, Am. J. Otolaryngol. 38 (2017) 614–617, https://doi.org/10.1016/j.amjoto.2017.07.003.

[29] J. Grisales, A. Sanabria, Utility of routine frozen section of thyroid nodules classified as follicular neoplasm, Am. J. Clin. Pathol. (2019), https://doi.org/10.1093/ajcp/aqz152.

[30] J.Y. Seok, J. An, H.Y. Cho, Improvement of diagnostic performance of pathologists by reducing the number of pathologists responsible for thyroid fine needle aspiration cytology: an institutional experience, Diagn. Cytopathol. 46 (2018) 561–567, https://doi.org/10.1002/dc.23893.

[31] S.S. Raab, D.M. Grzybicki, J.E. Janosky, R.J. Zarbo, F.A. Meier, C. Jensen, S. J. Geyer, Clinical impact and frequency of anatomic pathology errors in cancer diagnoses, Cancer 104 (2005) 2205–2213, https://doi.org/10.1002/cncr.21431.

[32] A.T. Turk, B.M. Wenig, Thyroid tumors with follicular architecture, Ann. Diagn. Pathol. 38 (2019) 51–58, https://doi.org/10.1016/j.anndiagpath.2018.10.007.

[33] J.B. Taxy, Frozen section and the surgical pathologist: a point of view, Arch. Pathol. Lab Med. 133 (2009) 1135–1138, https://doi.org/10.1043/1543-2165-133.7.1135.

[34] Z.W. Baloch, V.A. LiVolsi, Cytologic and architectural mimics of papillary thyroid carcinoma. Diagnostic challenges in fine-needle aspiration and surgical pathology specimens, Am. J. Clin. Pathol. 125 (Suppl) (2006) S135–S144.

[35] R.L. Schmidt, Verification bias is common in cytopathology studies on diagnostic accuracy, CytoJournal 11 (2014) 13, https://doi.org/10.4103/1742-6413.132994.
[36] R.L. Schmidt, R.E. Factor, Understanding sources of bias in diagnostic accuracy studies, Arch. Pathol. Lab Med. 137 (2013) 558–565, https://doi.org/10.5858/arpa.2012-0198-RA.
[37] R.Y. Osamura, J.L. Hunt, Current practices in performing frozen sections for thyroid and parathyroid pathology, Virchows Arch. 453 (2008) 433–440, https://doi.org/10.1007/s00428-008-0674-x.
[38] H. Jaafar, Intra-operative frozen section consultation: concepts, applications and limitations, Malays. J. Med. Sci. 13 (2006) 4–12.
[39] E. Leteurtre, X. Leroy, F. Pattou, A. Wacrenier, B. Carnaille, C. Proye, M. Lecomte-Houcke, Why do frozen sections have limited value in encapsulated or minimally invasive follicular carcinoma of the thyroid? Am. J. Clin. Pathol. 115 (2001) 370–374, https://doi.org/10.1309/feu2-t1vt-gv5p-9rch.
[40] D.L. Page, G.F. Gray Jr., Intraoperative consultations by pathologists at the Mayo Clinic: a unique experience, Mayo Clin. Proc. 70 (1995) 1222–1223, https://doi.org/10.1016/S0025-6196(11)63454-X.
[41] M.R. Wick, Intraoperative consultations in pathology. A current perspective, Am. J. Clin. Pathol. 104 (1995) 239–242.
[42] V.A. LiVolsi, Z.W. Baloch, Use and abuse of frozen section in the diagnosis of follicular thyroid lesions, Endocr. Pathol. 16 (2005) 285–293.
[43] N.A. Cipriani, S. Nagar, S.P. Kaplan, M.G. White, T. Antic, P.M. Sadow, B. Aschebrook-Kilfoy, P. Angelos, E.L. Kaplan, R.H. Grogan, Follicular thyroid carcinoma: how have histologic diagnoses changed in the last half-century and what are the prognostic implications? Thyroid 25 (2015) 1209–1216, https://doi.org/10.1089/thy.2015.0297.
[44] V.A. LiVolsi, S.L. Asa, The demise of follicular carcinoma of the thyroid gland, Thyroid 4 (1994) 233–236, https://doi.org/10.1089/thy.1994.4.233.
[45] K.J. Otto, J.S. Lam, C. MacMillan, J.L. Freeman, Diminishing diagnosis of follicular thyroid carcinoma, Head Neck 32 (2010) 1629–1634, https://doi.org/10.1002/hed.21373.
[46] M. Sobrinho-Simoes, C. Eloy, J. Magalhaes, C. Lobo, T. Amaro, Follicular thyroid carcinoma, Mod. Pathol. 24 (Suppl 2) (2011) S10–S18, https://doi.org/10.1038/modpathol.2010.133.
[47] Thyroid Association Guidelines Taskforce on Thyroid N. American, C. Differentiated Thyroid, D.S. Cooper, G.M. Doherty, B.R. Haugen, R.T. Kloos, S. L. Lee, S.J. Mandel, E.L. Mazzaferri, B. McIver, F. Pacini, M. Schlumberger, S. I. Sherman, D.L. Steward, R.M. Tuttle, Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer, Thyroid 19 (2009) 1167–1214, https://doi.org/10.1089/thy.2009.0110.
[48] A. Robinson, D. Schneider, R. Sippel, H. Chen, Minimally invasive follicular thyroid cancer: treat as a benign or malignant lesion? J. Surg. Res. 207 (2017) 235–240, https://doi.org/10.1016/j.jss.2016.08.052.
[49] G. Dionigi, J.L. Kraimps, K.W. Schmid, M. Hermann, S.Y. Sheu-Grabellus, P. De Wailly, A. Beaulieu, M.L. Tanda, F. Sessa, Minimally invasive follicular thyroid cancer (MIFTC)–a consensus report of the European Society of Endocrine Surgeons (ESES), Langenbeck's Arch. Surg. 399 (2014) 165–184, https://doi.org/10.1007/s00423-013-1140-z.
[50] E.R. McIntosh, S. Harada, J. Drwiega, M.S. Brandwein-Gensler, J. Gordetsky, Frozen section: guiding the hands of surgeons? Ann. Diagn. Pathol. 19 (2015) 326–329, https://doi.org/10.1016/j.anndiagpath.2015.07.004.