



Role of frozen section in the surgical management of indeterminate thyroid nodules

Haythem Najah¹, Christophe Tresallet^{2,3}

¹Department of Digestive and Endocrine Surgery, CHU de Bordeaux, Groupe Hospitalier Sud, Hôpital Haut-Lévêque, Centre Magellan, 33604 Pessac cedex, Pessac, France; ²Department of Digestive and Endocrine Surgery, Hôpital de la Pitié-Salpêtrière, Assistance Publique des Hôpitaux de Paris, 47-83, boulevard de l'Hôpital, 75651 Paris cedex 13, Sorbonne université (Pierre et Marie curie Paris 6), Paris, France; ³Laboratoire d'imagerie biomédicale (LIB), INSERM U 678, Sorbonne université (Pierre et Marie Curie Paris 6), Paris, France

Contributions: (I) Conception and design: C Tresallet; (II) Administrative support: C Tresallet; (III) Provision of study materials or patients: H Najah; (IV) Collection and assembly of data: H Najah; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Christophe Tresallet, MD, PhD. Department of Digestive and Endocrine Surgery, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Sorbonne University (Paris 6), Paris, France. Email: christophe.tresallet@aphp.fr.

Abstract: Indeterminate thyroid nodules (ITNs) correspond to the categories III (atypia of undetermined significance or follicular lesion of undetermined significance) and IV (follicular neoplasm or suspicious for a follicular neoplasm) of the Bethesda system for reporting thyroid cytopathology. Their malignancy risk is 5–15% and 15–30% respectively, imposing surgical treatment for definitive diagnosis. Thus, they represent a diagnostic and therapeutic challenge given the risk of over or under treatment. Several teams continue to perform systematic intraoperative frozen sections (FS) in order to guide the initial extent of surgery and to avoid a two-stage thyroidectomy. FS have a very high specificity and positive predictive value for the diagnosis of malignancy allowing a one-stage total thyroidectomy if the result is positive. However, this attitude is highly controversial; and this review of the literature demonstrates that FS is of little contribution in this setting, due to low sensitivity and high false-negative rates. In fact, for these lesions, a careful and comprehensive evaluation of the tumor capsule is mandatory in order to visualize a capsular or a vascular invasion permitting to make the diagnosis of malignancy. However, this assessment is only possible on permanent section. Moreover, FS can jeopardize the detection of signs of capsular invasion on final pathologic examination. The recent development of molecular testing results in a better preoperative diagnosis, thus reducing even more the need for intraoperative FS. Contrasting with their limited role in Bethesda III and IV categories, FS are useful in guiding the preoperative management of Bethesda V category nodules, given their high negative and positive predictive values. Intraoperative FS of ITNs are of little use and are not recommended systematically. Their use should be restricted to elderly, high anesthetic risk, or poorly compliant patients for whom an eventual subsequent complementary surgery may be problematic.

Keywords: Thyroid carcinoma; thyroid nodule; fine needle aspiration (FNA); frozen sections (FS)

Submitted Feb 09, 2019. Accepted for publication Apr 08, 2019.

doi: 10.21037/gs.2019.04.07

View this article at: <http://dx.doi.org/10.21037/gs.2019.04.07>

Introduction

Intraoperative frozen section (FS) had been, historically, the main tool to determine the initial histologic diagnosis of a thyroid nodule and therefore to guide the treatment

strategy. Surgery could be limited to a hemi-thyroidectomy in case of a benign nodule, while a malignant FS diagnosis indicates a total thyroidectomy. Since the advent of preoperative fine needle aspiration (FNA), and its

establishment as a mainstay in the preoperative exploration of thyroid nodules, the role of FS in this setting has been widely questioned. The introduction in 2007 of the Bethesda system for reporting thyroid cytopathology (BSRTC) has improved FNA reporting standards and became a standard of practice (1). The widespread use of this system has substantially simplified the cytopathologic diagnosis and subsequent management of thyroid nodules. In fact, in this system, there are six diagnostic categories: Non-diagnostic or unsatisfactory (Bethesda I), benign (Bethesda II), atypia of undetermined significance or follicular lesion of undetermined significance (Bethesda III), follicular neoplasm or suspicious for a follicular neoplasm (Bethesda IV), suspicious for malignancy (Bethesda V), and malignant ((Bethesda VI). Each of these diagnostic categories is linked to an implied risk of malignancy, ranging from 0 to 3% for the benign category to virtually 100% for the malignant category. Naturally, depending on that risk, the treatment could vary from simple surveillance to total thyroidectomy (1).

Difficulties in the management of indeterminate thyroid nodules (ITNs)

However, cytology alone cannot accurately distinguish carcinomas from benign adenomas, and surgery remains the only definitive means for distinguishing cancer from benign nodules. This is particularly true for the ITNs. In the BSRTC, indeterminate follicular lesions are grouped in the categories III and VI. The Bethesda III category comprises follicular lesions of undetermined significance, while the Bethesda IV category comprises follicular neoplasms or suspicious for follicular neoplasms. These two categories represent a significant diagnosis and therapeutic challenge. In fact, the implied risk of malignancy in Bethesda III category and Bethesda IV category is 5–15% and 15–30% respectively (1). Therefore, ITN present a particular risk for over or under-treatment since an initial lobectomy for a cancer greater than 1 cm can be viewed as inadequate treatment, while an initial total thyroidectomy for a benign nodule might be considered excessive or unnecessary from an oncologic standpoint (2). In a retrospective study on 639 patients with ITN, Schneider *et al.* showed 9.3% of oncologically insufficient treatment and 19% of oncologically excessive surgery. The “atypia/follicular lesion of undetermined significance” category (Bethesda III category) proved the most problematic for surgeons to determine the correct amount of initial surgery, with nearly

40% of patients receiving an inappropriate extent of the initial surgery (3).

Contribution of intraoperative FS in the management of ITNs

FS is still considered by several teams as a useful tool to optimize the decision-making for the initial extent of surgery for ITN. In a retrospective study on 662 patients comparing FS and FNA, Chang *et al.* showed that in case of disparity between these two diagnostic tools the accuracy of FS (78.9%) is superior to the accuracy of FNA (21.1%) (4). A positive FS is especially interesting because of the very low false-positive rates of this test, reaching 0% in some reports (5,6). Many other studies have shown FS to have above 90% specificity (7-10).

The high specificity and the low false-positive rates of FS, imply that total thyroidectomy has to be performed if the result is positive. A retrospective series of 122 patients with an “atypia/follicular lesion of undetermined significance” thyroid nodule (Bethesda III Category) found that FS had 100% specificity and 100% positive predictive value (11). In a recent large series, Cotton *et al.* showed that, thanks to FS, reoperation was avoided in 8% of patients with Bethesda IV category and 2.2% of patients with Bethesda III category ITN (12). Avoiding a second neck operation, with the morbidity it carries including the risk of laryngeal nerve damage, is the main argument for the proponents of the systematic realization of intraoperative FS. This is particularly true for elderly, fragile patients having a high anesthetic risk.

Limits and drawbacks of intraoperative FS in the management of ITNs

The real utility of FS for ITN remains, however, controversial. In fact, some histological types, such as follicular and Hurtle cell carcinomas and follicular variant of papillary carcinoma, are easily misdiagnosed by FS (13-15). Unlike papillary carcinomas, the detection of follicular carcinomas depends on a comprehensive analysis of the thyroid nodule in order to visualize a capsular or a vascular invasion permitting to make the diagnosis. Therefore, the capacity of FS to guide surgery in this setting is highly dubious, because of the impossibility to obtain a correct sample of the capsule in order to assess the invasion (15,16). In a retrospective study on 252 patients, Guevara *et al.* reported that FS had a worse sensitivity than FNAC

and did not impact surgical strategy (17). A meta-analysis published in 2008, and analyzing series of the pre-Bethesda era, had already highlighted the high false-negative rate of FS and therefore its low sensitivity (67%). The role of FS in guiding the extent of thyroidectomy seems therefore very limited (18).

Similarly, studies assessing the role of FS in the post-Bethesda era confirm the low sensitivity and negative predictive value rates of this test. Several recent series have found persistently low sensitivity ranging from 22% to 51% (11,19,20). Moreover, FS lead to the prolongation of the operating room time and is source of additional costs (15). These elements should also be taken into account, especially regarding the difficulties of organization and the increasing need of optimization of the operating schedule. In a recently published series, Mallick *et al.* reviewed 236 patients who had thyroidectomy (either partial thyroidectomy or total thyroidectomy) with intraoperative FS. In 95% of the cases, FS didn't have any additional benefit and didn't change the intraoperative management. In eleven patients (4.7%), the initially planned extent of thyroidectomy was modified after the FS diagnosis. But this extent of thyroidectomy was correctly changed only in five cases (2.1%) (21).

Besides, the systematic realization of FS can render the final pathologic diagnosis more difficult and less accurate. In fact, as we've seen previously, a comprehensive assessment of the entire capsule interface of follicular lesions is mandatory in order to demonstrate any capsular or vascular invasion, which is the hallmark of malignancy. FS is realized on a fresh non-fixed thyroid specimen, which is subsequently fixed with formalin and embedded in paraffin for definitive pathologic examination. Hence, the realization of FS results in a more fragmented thyroid specimen, which can lead to difficulties of orientation and section of the specimen after fixation and can jeopardize the detection of signs of capsular invasion. Moreover, the realization of FS can result in an artefactual loss of nuclear features of papillary thyroid carcinoma, which can lead to misdiagnose these tumors especially small ones.

Role of intraoperative FS in the management of Bethesda V category nodules

Contrasting with the conflicting evidence about the merits of the use of FS in ITN, it seems that it may be useful in guiding the peroperative management of Bethesda V nodules.

Even though this category is not truly an indeterminate

category, some authors consider it is. In fact, this category corresponds to the suspicious for malignancy nodules at FNA; its malignancy risk ranges from 45% to 60%, and the usual management is either a lobectomy or a total thyroidectomy. In the recent study of Mallick *et al.*, in six of the eight specimens of Bethesda V category nodules, FS was in concordance with final pathologic examination, and correctly changed the management for three of the lesions (21). In a study carried out in the University of Wisconsin, Haymart *et al.* retrospectively reviewed the data of all patients who underwent thyroid surgery over a period of ten years and specifically studied the role of FS for the suspicious for malignancy nodules subgroup (22). They found that FS led to the optimal operative procedure in 96% of the cases. The positive predictive value of FS was 100% and its negative predictive value was 85%. We believe that for this subgroup (Bethesda V nodules) intraoperative FS still has a role and should be considered in order to determine the optimal surgical intervention.

Intraoperative FS and non-invasive follicular thyroid neoplasm with papillary-like nuclear features

The term "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) is currently used in replacement of the ancient terminology for non-invasive encapsulated follicular variant of papillary thyroid carcinoma. In fact, Nikiforov *et al.* showed in their retrospective study that all the 109 patients with non-invasive encapsulated follicular variant of papillary thyroid carcinoma observed for a period of 10 to 26 years were alive with no evidence of recurrence (23). The international multidisciplinary working group of experts that proposed this new terminology sought to highlight the indolent behavior and the low risk of adverse outcome of this histological subtype of thyroid nodules, and thus excluding it from thyroid malignancies.

Most of the NIFTP nodules yield an indeterminate cytological diagnosis on FNA. In the recently published study of the French speaking Society of Endocrine Surgery, more than half of NIFTP nodules proved to be ITN on FNA (24). In their review of FNA cytology from 96 confirmed NIFTP nodules, Maletta *et al.* showed that the results were in favor of ITN in more than two thirds of the cases (15% of Bethesda Category III and 56% of Bethesda Category IV) (25).

Therefore, the impact of reclassifying non-invasive

encapsulated follicular variant of papillary thyroid carcinoma, now designated as NIFTP, will be necessarily a significant decrease in the risk of malignancy of ITN on FNA; and therefore reduce the role of FS in this setting (1,26). Moreover, like every follicular tumor, a comprehensive examination of the tumor capsule interface is mandatory in order to exclude any invasion before designating a nodule as NIFTP. As we have seen previously, an adequate sampling of the tumor capsule is not possible on FS. Consequently, the diagnosis of NIFTP is only possible on permanent section and final histological examination.

Impact of molecular testing on the need for FS in ITN

In response to the increasing need of improving the diagnostic accuracy of FNA and in order to better guide the surgical management of ITN, we've witnessed this last decade a rapid evolution of molecular testing for thyroid nodules. In fact, thanks to the Cancer Genome Atlas (TCGA) project, all the genetic mutations involved in papillary thyroid carcinoma are currently mapped (27). The mitogen-activated protein kinase (MAPK) pathway is the principal pathway leading to differentiated thyroid carcinoma. The genetic alterations are consisting mainly in mutations of v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) or rat sarcoma (RAS) oncogenes and chromosomal rearrangements of receptor tyrosine kinase (RTK). Recently, several thyroid molecular tests have been evaluated and are currently available, including the Afirma gene classifier (28), the seven gene mutation panel (29), or the new tests using next-generation sequencing (NGS) such as ThyroSeq (30) and ThyGenX/ThyraMIR (31).

As far as ITN are concerned, the excellent specificity (99% and 97% for Bethesda III and IV nodules respectively) and positive predictive value (94% and 86% for Bethesda III and IV nodules respectively) of the molecular testing allow a better preoperative diagnosis and decrease the number of patients requiring a completion thyroidectomy (29). Additionally, the improving sensitivity and positive predictive value will ultimately, in a near future, allow the use of these tests as rule out tests, avoiding unnecessary surgery for benign thyroid nodules.

Consequently, the increasing use of molecular testing will eventually reduce the percentage of ITN, and therefore reduce the need for intraoperative FS.

Conclusions

Finally, in this era of BSRTC, the contribution of routine FS on ITN to guide surgical strategy and decision-making seems to be quite limited. Even though a positive intraoperative FS can be useful and should indicate a total thyroidectomy, false negative rates remain high. Moreover the potential gain to avoid a two-stage surgery should be balanced with the cost of systematic FS. We believe that there is not enough evidence to recommend a systematic use of FS for ITN, and that FS should be restricted to elderly, high anesthetic risk, or poorly compliant patients for whom an eventual subsequent complementary surgery may be problematic.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Cibas ES, Ali SZ, NCI Thyroid FNA State of the Science Conference. The Bethesda System For Reporting Thyroid Cytopathology. *Am J Clin Pathol* 2009;132:658-65.
2. Haugen BR, Alexander EK, Bible KC, et al. 2015 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* 2016;26:1-133.
3. Schneider DF, Cherney Stafford LM, Brys N, et al. Gauging the extent of thyroidectomy for indeterminate thyroid nodules: an oncologic perspective. *Endocr Pract* 2017;23:442-50.
4. Chang HY, Lin JD, Chen JF, et al. Correlation of fine needle aspiration cytology and frozen section biopsies in the diagnosis of thyroid nodules. *J Clin Pathol* 1997;50:1005-9.
5. Mandell DL, Genden EM, Mechanick JI, et al. Diagnostic accuracy of fine-needle aspiration and frozen section in nodular thyroid disease. *Otolaryngol Head Neck Surg* 2001;124:531-6.

6. Kennedy JM, Robinson RA. Thyroid Frozen Sections in Patients With Preoperative FNAs: Review of Surgeons' Preoperative Rationale, Intraoperative Decisions, and Final Outcome. *Am J Clin Pathol* 2016;145:660-5.
7. Huber GF, Dziegielewski P, Matthews TW, et al. Intraoperative frozen-section analysis for thyroid nodules: a step toward clarity or confusion? *Arch Otolaryngol Head Neck Surg* 2007;133:874-81.
8. Basolo F, Ugolini C, Proietti A, et al. Role of frozen section associated with intraoperative cytology in comparison to FNA and FS alone in the management of thyroid nodules. *Eur J Surg Oncol* 2007;33:769-75.
9. Kahmke R, Lee WT, Puscas L, et al. Utility of Intraoperative Frozen Sections during Thyroid Surgery. *Int J Otolaryngol* 2013;2013:496138.
10. Cohen MA, Patel KR, Gromis J, et al. 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 J Otorhinolaryngol Head Neck Surg* 2015;1:5-10.
11. Posillico SE, Wilhelm SM, McHenry CR. The utility of frozen section examination for determining the extent of thyroidectomy in patients with a thyroid nodule and "atypia/follicular lesion of undetermined significance". *Am J Surg* 2015;209:552-6.
12. Cotton TM, Xin J, Sandyhya J, et al. Frozen section analysis in the post-Bethesda era. *J Surg Res* 2016;205:393-7.
13. Antic T, Taxy JB. Thyroid frozen section: supplementary or unnecessary? *Am J Surg Pathol* 2013;37:282-6.
14. Chen H, Nicol TL, Udelsman R. Follicular lesions of the thyroid. Does frozen section evaluation alter operative management? *Ann Surg* 1995;222:101-6.
15. Udelsman R, Westra WH, Donovan PI, et al. Randomized prospective evaluation of frozen-section analysis for follicular neoplasms of the thyroid. *Ann Surg* 2001;233:716-22.
16. Carling T, Udelsman R. Follicular neoplasms of the thyroid: what to recommend. *Thyroid* 2005;15:583-7.
17. Guevara N, Lassalle S, Benaim G, et al. Role of frozen section analysis in nodular thyroid pathology. *Eur Ann Otorhinolaryngol Head Neck Dis* 2015;132:67-70.
18. Peng Y, Wang HH. A meta-analysis of comparing fine-needle aspiration and frozen section for evaluating thyroid nodules. *Diagn Cytopathol* 2008;36:916-20.
19. Berg RW, Yen TW, Evans DB, et al. Analysis of an institutional protocol for thyroid lobectomy: Utility of routine intraoperative frozen section and expedited (overnight) pathology. *Surgery* 2016;159:512-7.
20. Mayoaran N, Waters PS, Kaim Khani TY, et al. FNAC and frozen section correlations with definitive histology in thyroid diseases. *Eur Arch Otorhinolaryngol* 2016;273:2181-4.
21. Mallick R, Stevens TM, Winokur TS, et al. Is Frozen-Section Analysis During Thyroid Operation Useful in the Era of Molecular Testing? *J Am Coll Surg* 2019;228:474-9.
22. Haymart MR, Greenblatt DY, Elson DF, et al. The role of intraoperative frozen section if suspicious for papillary thyroid cancer. *Thyroid* 2008;18:419-23.
23. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors. *JAMA Oncol* 2016;2:1023-9.
24. Chereau N, Greilsamer T, Mirallié E, et al. NIFT-P: Are they indolent tumors? Results of a multi-institutional study. *Surgery* 2019;165:12-6.
25. Maletta F, Massa F, Torregrossa L, et al. Cytological features of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" and their correlation with tumor histology. *Hum Pathol* 2016;54:134-42.
26. Faquin WC, Wong LQ, Afroogheh AH, et al. Impact of reclassifying noninvasive follicular variant of papillary thyroid carcinoma on the risk of malignancy in The Bethesda System for Reporting Thyroid Cytopathology. *Cancer Cytopathol* 2016;124:181-7.
27. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell* 2014;159:676-90.
28. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *N Engl J Med* 2012;367:705-15.
29. Nikiforov YE, Ohori NP, Hodak SP, et al. Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. *J Clin Endocrinol Metab* 2011;96:3390-7.
30. Nikiforov YE, Carty SE, Chiosea SI, et al. Impact of the Multi-Gene ThyroSeq Next-Generation Sequencing Assay on Cancer Diagnosis in Thyroid Nodules with Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance Cytology. *Thyroid*

- 2015;25:1217-23.
31. Labourier E, Shifrin A, Busseniers AE, et al. Molecular Testing for miRNA, mRNA, and DNA on Fine-Needle

Aspiration Improves the Preoperative Diagnosis of Thyroid Nodules With Indeterminate Cytology. *J Clin Endocrinol Metab* 2015;100:2743-50.

Cite this article as: Najah H, Tresallet C. Role of frozen section in the surgical management of indeterminate thyroid nodules. *Gland Surg* 2019;8(Suppl 2):S112-S117. doi: 10.21037/gs.2019.04.07