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Original article

Role of frozen section analysis in nodular thyroid pathology

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ABSTRACT

Introduction: Frozen section (FS) analysis used to be the principal examination guiding surgical strategy. The development and recent standardization of fine-needle aspiration cytology (FNAC) challenges it as a systematic attitude. The present study assessed the current contribution of FS, comparing it with FNAC as a diagnostic tool guiding surgery.
Material and methods: A retrospective diagnostic study analyzed 1515 thyroid samples over a 6-year period. Two hundred and fifty-two of the patients had undergone both FNAC (analyzed in our unit) and FS, revealing 69 cancers.
Results: The sensitivity and specificity of FS and FNAC were 75.36% and 100% versus 31.88% and 100%, respectively. In case of malignancy on FNAC (22 patients), FS did not influence indications for surgery. In case of non-malignant FNAC findings, FS diagnosed cancer in 13% of cases (30/230). In the subgroup of follicular lesions (Bethesda 3 and 4), FS modified surgical strategy in only 6.2% of cases (6/97), but diagnosed 13 of the 16 cancers (81.25%) in case of Bethesda 5 on FNAC (21 cases) and in 9 of the 13 cancers (69%) associated with non-diagnostic FNAC results (Bethesda 1: 70 cases).
Conclusion: Although its contribution is small, FS optimizes surgery in certain cases. Systematic implementation may be economically justified, especially in follicular lesions diagnosed on FNAC, improving interpretation of a difficult and operator-dependent test, as is essential in certain FNAC results.

1. Introduction

Despite the numerous good practice guidelines in thyroid nodule pathology, certain issues such as frozen section (FS) analysis remain controversial [1–6]. FS is a quick intraoperative micro- and/or macroscopic examination involving freezing of a surgical tissue fragment, and is classically the prime guide to surgical extension [7]. It thus first serves to confirm diagnosis and its efficacy can be assessed in terms of the elimination of false positives so as to avoid "over-treatment" (unnecessarily extensive surgery) and of false negatives, to limit the risk of "under-treatment" (failure to perform neck dissection, or 2-step thyroidectomy).

Systematic FS has been challenged for poor cost-effectiveness as compared to the widespread use of increasingly effective cytology techniques for indication in thyroid surgery. Fine-needle aspiration cytology (FNAC) is non-invasive, simple, reproducible, inexpensive, well tolerated and more or less free of complications. It has the great advantage over imaging of enabling direct intraoperative morphologic assessment of thyroid tissue. It has become systematic in the management of nodules, and standardization on the Bethesda classification has improved the quality of analysis. Papillary cancer is thus frequently diagnosed preoperatively; and in other cases, notably of follicular-type FNAC findings, FS is often found wanting.

FS, however, is not only an intraoperative examination: it could be the keystone in a novel concept of integrative pathology [8–10]; fresh thyroid specimens can serve not only for FS analysis but also for biobanking [11–13].

Fresh thyroid specimens sampled for FS analysis can thus provide short-term benefit by "real-time" adaptation of surgery, and also a longer term contribution from molecular biology analysis based on a biobank.

In the context of this new integrative approach, the present study compared FS and FNAC as diagnostic tests guiding surgery.

2. Materials and methods

A retrospective experimental diagnostic study included all thyroid specimens sampled for FS analysis and included in the center's biobank between September 1st, 2004 and December 31st, 2010.

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Table 1
Cytology-histology equivalences.

Bethesda terminology	Number of cases n (%)	Malignant FS n (%)	Malignancy on definitive histology n (%)	Malignancy rate in literature (%) [15]
Bethesda 1 (non-diagnostic)	70(27.8)	9(69)	13(18.6)	1–4
Bethesda 2 (benign)	42(16.7)	2(4.7)	2(4.7)	0–3
Bethesda 3 (follicular lesion of indeterminate significance)	14(5.6)	0(0)	2(14.3)	5–15
Bethesda 4 (follicular neoplasm or suspicious for Hürthle-cell neoplasm)	83(32.9)	6(42.9)	14(16.9)	15–30
Bethesda 5 (suspicious for malignancy)	21(8.3)	13(81.3)	16(76.2)	60–75
Bethesda 6 (malignant)	22(8.7)	100(100)	22(100)	97–99

2.1. Selection for surgery

Our patient selection criteria were based on the national and international guidelines available at the time [1], and the team's own experience [14]. A single surgical strategy founded on clearly codified indications could thus be implemented as of 2004. Three groups of indications were distinguished: mechanical complications (head and neck axis compression), hyperthyroidism (isolated nodule or multinodular goiter) and suspected cancer (or "nodule at risk of cancer").

The third group comprised of asymptomatic patients for whom the risk of cancer associated with a nodule or nodules was to be assessed. Since 2006, our diagnostic strategy was standardized, dividing this group between mandatory and theoretic indications for surgery. Mandatory indications were ranked according to 3 factors: biological results with elevated calcitoninemia (> 10 ng/l) suggestive of thyroid medullary carcinoma, cytology with malignant or suspect FNAC samples, and clinical with hard nodule or suspect cervical adenopathy on palpation. In theoretic indications, there were no elements making surgery obligatory and few if any factors of malignancy; surveillance including FNAC was proposed and the risk/benefit ratio was discussed in consultation with the patient and in multidisciplinary team meeting.

Factors of malignancy were based on the classical literature data: predisposition involving age < 25 years, male gender, immunosuppression, and history of cervical irradiation or familial history of thyroid cancer. Ultrasound findings were also taken into account: full hypoechogenic nodule, irregular contours, microcalcifications, absence of nodular halo, signs of extracapsular invasion and nodular vascularization.

Prior to the 2008 NCI/Bethesda cytopathology system [15], a four-fold classification was used: benign, non-diagnostic, follicular and suspect. When cytology suggested a follicular lesion, surgery was frequently proposed on theoretic grounds, weighted by other clinical and ultrasonographic findings.

After 2008 and the routine adoption of the NCI/Bethesda system [15], our therapeutic attitude was adapted to the consensual guidelines. In "follicular lesions of indeterminate significance" (Bethesda 3), FNAC was repeated under ultrasound guidance at 3–6 months, with surgery indicated in case of a second indeterminate result. In "follicular neoplasm or suspicious for Hürthle-cell neoplasm" (Bethesda 4), surgery was systematically proposed.

2.2. Frozen section analysis

The FS arrived by the pneumatic tube transport system between the operating theater and the laboratory macroscopy room. The physician performed timely macroscopic examination and entered the results (specimen quality, anatomic location, size, weight, and location of principal and associated lesions) on standardized macroscopy forms. Macroscopically suspect regions were placed on a support covered with Cryomatrix^{TM} resin, and cut into 5 μm slices after freezing in a cryostat (LEILA CM 1950). Rapid staining (carbolic toluidine blue and differentiation in water) was performed for microscopic examination. Imprint cytology was also performed at the pathologist's discretion. Results were communicated orally to the surgeon and also entered on a dedicated FS form faxed to theater: patient ID, date and time of specimen arrival, ordering department, type of sample, number of samples and of imprints, FS analysis findings, contact with theater receiving the result, name of pathologist. Results were of 3 types: benign lesion, malignant lesion or diagnosis pending. Histologic tumor type was specified whenever possible. After thawing and fixation in 10% formaldehyde, the specimen and the non-frozen part of the specimen were included in paraffin for definitive diagnosis on HES staining.

2.3. Freezing of fresh thyroid tissue

Following FS analysis, the pathologist decided whether to conserve the specimens by freezing. Sample region topography, weight and time to freezing were entered on standardized forms with 2 mirror-image samples of lesion and perilesional tissue. The clinical and pathology data were stored in a database (Cresalys Software; Alphelys, Paris, France), a part of which was put on-line on the biobank website (www.biobank06.com).

2.4. Thyroid FNAC samples

From 2004 to 2009, a number of thyroid samples were taken by fine-needle aspiration. Cytology samples from before 2008 were reclassified on the new NCI/Bethesda system [15], based on cytology reports or re-reading of slides by the original pathologists who had recorded the initial results. Data were collected using Clinicom Siemens Health Services and Apix software, used for patient databases in our center.

All data were entered under Excel: ID number, date of birth, gender, sample type, FS result, definitive histologic diagnosis, pathologist's name and results of thyroid FNAC performed in the center.

FS and FNAC data were compared as follows. FS analysis was considered positive only in case of malignancy; benign and postponed diagnoses were both counted as negative, as surgery was in both cases suspended awaiting definitive histologic diagnosis. Likewise, malignant FNAC results were considered positive only when they indicated extensive surgery; all others were counted as negative. Histologically indeterminate tumors were counted as