

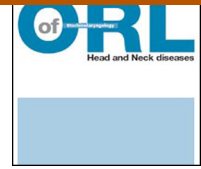


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ORIGINAL ARTICLE

Thyroid nodule surgery: Predictive diagnostic value of fine-needle aspiration cytology and frozen section

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KEYWORDS

Thyroid gland;
Fine-needle
aspiration cytology;
Frozen section;
Thyroid carcinoma

Summary

Objectives: The authors analyse the predictive diagnostic accuracy of fine-needle aspiration cytology (FNAC) and frozen section examination in adult patients operated for thyroid nodules. **Patients and methods:** The same pathologist performed macroscopic and cytological examination, followed by frozen section examination on each operative specimen. FNAC results were classified into three groups: benign, malignant or suspicious of malignancy. Frozen section examination was also classified into three categories: benign, malignant or suspicious of malignancy when not all criteria of malignancy were present.

Results: One hundred and sixty-six (82%) of the 202 patients included in the study were females. Patients had a mean age of 51 years. Thyroid carcinoma was diagnosed on final pathology in 22% of women and 25% of men. FNAC results were benign in 85% of cases, malignant in 9% of cases and atypical or suspicious in 6% of cases, with a specificity of more than 99% and a sensitivity, including and excluding microcarcinomas, of 36% and 48%, respectively. The diagnostic accuracy of FNAC was 84% and 89%, after excluding micro-carcinomas. Frozen section was benign in 85% of cases, malignant in 13% of cases and suspicious in 2% of cases, with a specificity of more than 99% and a sensitivity, including and excluding microcarcinomas, of 56% and 68%, respectively. The diagnostic accuracy of frozen section was 89% and 90%, after excluding microcarcinomas. The diagnostic accuracy of the combination of the two examinations was 94% after excluding microcarcinomas.

Conclusion: FNAC and frozen section have a comparable predictive diagnostic accuracy. Frozen section is requested by the surgeon not only on the basis of preoperative FNAC, especially when it is suspicious, or even indeterminate, but also in the light of the macroscopic surgical findings.

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Introduction

Thyroid nodule surgery is performed for both diagnostic and therapeutic purposes: diagnostic to detect thyroid carcinoma and therapeutic to ensure anatomical and functional control [1,2].

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Although palpable thyroid nodules concern 4 to 7% of the general population, this prevalence can exceed 50% on high-resolution neck ultrasound. Only 10% of these nodules correspond to thyroid carcinoma, which is detected two to four times more frequently in women [3–5]. The annual incidence of thyroid carcinoma is 0.5 to 10 cases per 100,000 inhabitants, corresponding to papillary carcinoma in 70 to 85% of cases, follicular carcinoma in 5 to 10% of cases, medullary carcinoma in 5% of cases, and poorly differentiated or undifferentiated carcinoma in less than 5% of cases [3]. The 10-year relative survival ranges from 98% for papillary carcinoma to 13% for undifferentiated carcinoma. The recurrence rate increases with the size of papillary carcinoma: the 10-year recurrence rate is 7% for 1 to 2 cm tumours, 17% for 4 to 8 cm tumours, but 25% for tumours larger than 8 cm; the 10-year overall survival is significantly poorer only for tumours larger than 4 cm [6]. Classical favourable prognostic factors are: woman under the age of 40, well differentiated papillary carcinoma with a lesion less than 2 cm strictly confined to the thyroid with no metastases [1,3].

Fine-needle aspiration cytology (FNAC), generally ultrasound-guided, is a widely used diagnostic method in patients with thyroid nodules [7]. The main purpose of this technique is to distinguish patients with malignant cytology, therefore requiring surgery, from those with benign cytology, especially cysts and colloid nodules, who require simple surveillance [8].

FNAC can establish a diagnosis of papillary carcinoma, as it is predominantly based on cytological characteristics [3]. However, FNAC is considered to be “uninterpretable” in 10 to 20% of cases or simply “suspicious” in 9 to 38% of cases [4,9,10]. FNAC is also unable to distinguish between adenoma and follicular carcinoma, as analysis of vascular and capsular invasion of the thyroid gland requires a complete histological examination [3]. The two main drawbacks of the technique are false-negative cytology and failure to detect microcarcinomas either due to an error of interpretation or, more often, due to inadequate sampling [1,2]. Finally, excessive repetition of fine-needle aspiration can cause morphological tissue changes [3].

The role of frozen section in the diagnosis of a thyroid nodule has declined with the more widespread use of FNAC. Despite its medico-economic advantages, by allowing one-stage total thyroidectomy, and its diagnostic accuracy for thyroid carcinoma in 78 to 100% of cases, it remains a subject of controversy [3,8].

The objective of this prospective study was to assess the diagnostic accuracy of FNAC and frozen section in adult patients operated for thyroid nodules.

Material and methods

Between October 2008 and December 2010, 202 patients with nodular thyroid disease were included in this study. Surgery was indicated in each case in agreement with the endocrinologist. No patient had been previously operated. Among the cases of multinodular goitre, 45 were considered to be substernal, situated in the anteroposterior mediastinum (>4 cm below the suprasternal notch),

Table 1 Preoperative clinical features.

	<i>n</i>	%
Multinodular goitre	113	56
Isolated nodules	68	34
Graves' disease	14	7
Non-Graves' thyroiditis	8	4
Suspicion of cancer	2	1
Cyst	1	0.5

31 patients were hyperthyroid, 70 goitres were responsible for radiologically documented tracheal deviation and none was associated with recurrent laryngeal nerve paralysis. In contrast, goitres “suspicious of malignancy” were always accompanied by signs of tracheal and/or oesophageal compression, recurrent laryngeal nerve paralysis and/or cervical lymphadenopathy (Table 1).

The same pathologist performed macroscopic examination, cytological examination then frozen section on each operative specimen, preserved and oriented by the surgeon. Final histological examination was performed subsequently.

Macroscopic examination is essential, especially for multinodular goitre, looking for small areas of fibrous or indurated tissue that should preferably be examined by FNAC and frozen section [1,3].

Cytological examination of the operative specimen used 25 to 27 G needles with two to five aspirations per zone to be examined and two slides for each aspiration. Sufficiently abundant cellular material was obtained by gentle aspiration. FNAC results were classified into three groups: formally benign, formally malignant, atypical cells or suspicious of malignancy. Indeterminate cytology was not considered, as the examination was continued until sufficient cellular material was obtained [1,2].

Frozen section of the operative specimen was performed on macroscopically suspicious zones, including the thyroid capsule, allowing examination of the healthy tissue-pathological tissue junction. The sample was frozen in a cryostat and 10 to 20 micron sections were prepared from two or three different depths. Histology results were expressed in three categories: benign lesion leading to termination of the operation in the case of lobectomy with isthmectomy; malignant lesion, leading to recommendation of complementary surgery adapted to the type of tumour; suspicious lesion not presenting all criteria of malignancy, for which the final histological examination was necessary to determine the need for subsequent complementary surgery [1,3].

The diagnostic accuracy of FNAC and frozen section was compared to the final histology results. Papillary microcarcinomas were distinguished on calculations of diagnostic accuracy, as they can only be diagnosed on the final histological examination [3]. Sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy (% of exact results) associated with Youden's index (a negative index corresponds to an inaccurate test; an index closer to 1 indicates a more accurate test) were calculated for FNAC and frozen section for each case.

Table 2 Final histological diagnosis.

	<i>n</i>	%
<i>Benign</i>	153	75.7
Multinodular goitre	92	45.5
Follicular adenoma	43	21.3
Including oncocytic adenoma	5	3
Graves' disease	11	5.4
Non-Graves' thyroiditis	6	3
Cyst	1	0.5
<i>Malignant</i>	49	24.3
Papillary carcinoma	24	11.9
Papillary microcarcinoma	14	6.9
Vesicular/follicular carcinoma	7	3.5
Anaplastic carcinoma	2	1
Medullary carcinoma	1	0.5
Squamous cell carcinoma (metastasis)	1	0.5
<i>Total</i>	202	100

Results

The study population ($n=202$ patients) consisted of 166 women (82% of cases) and 36 men (18%) with a mean age of 51 years (range: 14 to 89 years). Hyperthyroidism was present in 31 patients with multinodular goitre, 14 patients with Graves' disease and 22 patients with isolated nodules. Clinical features are summarized in Table 1.

The final histology results are presented in Table 2. Thyroid carcinoma was demonstrated in 22 patients with multinodular goitre, with unifocal or multifocal microcarcinoma in 12 cases. Carcinoma was detected in 16 isolated nodules, with associated microcarcinoma in two cases. Two patients with thyroiditis presented papillary carcinoma and three of the 14 patients with Graves' disease presented microcarcinoma. Finally, the two patients with clinical suspicion of malignancy presented an undifferentiated carcinoma in one case and vesicular carcinoma with a large oncocytic contingent in the other case. Overall, 22% of women and 25% of men of the study population presented thyroid carcinoma.

FNAC results were classified as benign in 85% of cases, malignant in 9% of cases and suspicious of malignancy in 6% of cases. The specificity of FNAC was higher than 99%,

with a false-positive rate less than 1% and a sensitivity, including and excluding microcarcinomas, of 36% and 48%, respectively. The diagnostic accuracy of FNAC, including and excluding microcarcinomas, was 84% and 89%, respectively (Table 3).

Frozen section results were classified as benign in 85% of cases, malignant in 13% of cases and suspicious of malignancy in 2% of cases, leading to termination of the surgical procedure. The specificity of frozen section was greater than 99% with a sensitivity, including and excluding microcarcinomas, of 56% and 68% respectively. The overall diagnostic accuracy of frozen section was 89% and close to 90% after excluding microcarcinomas (Table 3).

The specificity of the FNAC-frozen section combination (concordant positive results) was 100% eliminating false-positives (Fig. 1) and the sensitivity of the combination, including microcarcinomas, was 44%. The overall diagnostic accuracy of the combination of the two examinations was 89.5% (with a Youden index of 0.44) and 94% after excluding microcarcinomas.

Discussion

Most thyroid nodules observed in clinical practice are benign colloid nodules [2,3]. "Suspicious" thyroid nodules correspond to a broad range of clinical features: de novo nodule or enlargement of a pre-existing nodule, nodule in the context of neck irradiation or a family history of thyroid cancer, nodule in the very young, before the age of 10 years, or in the very old, after the age of 75 years, nodule associated with dysphonia, cervical lymphadenopathy, or even dysphagia or dyspnoea [7]. The presence of these clinical features requires a diagnostic work-up in every case. Although frozen section during surgical exploration was the systematically recommended diagnostic approach for many years [1,2], the development of FNAC, generally ultrasound-guided, has led to a decreased thyroid surgery rate and a less important role for frozen section examination [11].

FNAC is dependent on the operator's experience, whether or not it is ultrasound-guided, the aspiration technique, the cytologist, but also the criteria used to determine the quality of the smear [11,12]. Serious bleeding complications are rare, even in patients treated by anticoagulants or platelet aggregation inhibitors [2]. The specificity of FNAC ranges from 86 to 100%; the false-positive rate is very low, less than 1%. The sensitivity is lower, ranging from 13 to 79%, with a mean of 40%. The

Table 3 Diagnostic accuracy of fine-needle aspiration cytology (FNAC) and frozen section.

	FNAC	Frozen section	FNAC	Frozen section
			Excluding microcarcinoma	Excluding microcarcinoma
Specificity	99.2	99.1	99.1	99.2
Sensitivity	35.7	55.8	48	68
PPV	93.7	95	94	94
NPV	83.3	88.6	89	93
Overall value	84.2	89.4	89.6	93
Youden index	0.35	0.55	0.48	0.67

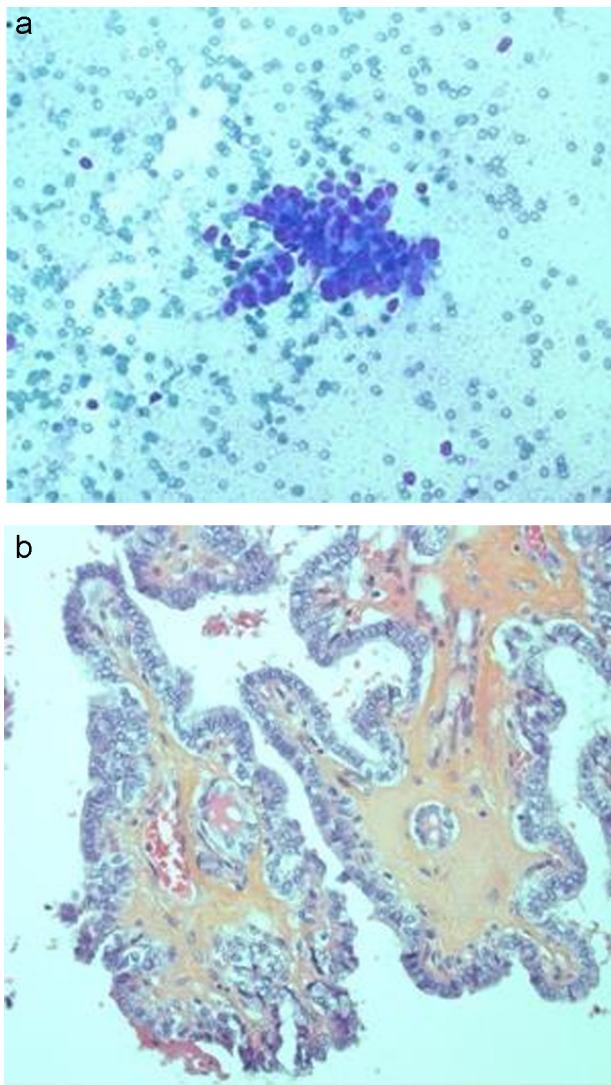


Figure 1 Well differentiated papillary carcinoma: cytology and histology: a: malignant papillary cytology; b: papillary carcinoma.

false-negative rate ranges from 1 to 6%, but is close to 1% after excluding microcarcinomas [13–15]. FNAC results are usually classified into six categories [3,11]: no thyroid follicular cells (Thy 0); presence of an insufficient number of follicular cells (Thy 1); benign thyroid cells (Thy 2); hyperplastic thyroid cells or follicular carcinoma (Thy 3); cells suspicious of malignancy (Thy 4); frankly malignant cells (Thy 5). There are two main limitations to the diagnostic value of FNAC: inadequate cellular material (Thy 0 and Thy 1) and the inability to distinguish between a benign hyperplastic nodule and follicular carcinoma [3]. Ultrasound guidance can improve the adequate material collection rate, which is 95% compared to aspiration guided by simple clinical palpation, which provides adequate material in only 42% of cases [7,8]. Ultrasound can also reveal certain features suggestive of carcinoma, such as irregular nodular margins, increased internal blood supply, and microcalcifications. However, none of these signs are pathognomonic of cancer and FNAC remains the preferred investigation [14,15]. The ultrasound-based TI-RADS suspicious nodule

scoring system was recently proposed, allowing more accurate selection of nodules requiring FNAC [2]. Neck imaging by computed tomography, magnetic resonance imaging or ^{18}F FDG PET-CT may reveal a thyroid incidentaloma. ^{18}F FDG PET-CT can reveal up to 5% of focal nodular lesions, with a carcinoma present in 27% of these lesions, especially those with a SUV_{max} greater than 7. The presence of a thyroid incidentaloma on PET-CT fusion images justifies FNAC to exclude malignancy [16]. However, due to its poor sensitivity and specificity, ^{18}F FDG-PET-CT cannot be recommended for routine assessment of thyroid nodules with indeterminate cytology [17].

No immunohistochemical or molecular biology test is available to formally distinguish benign and malignant lesions on aspiration cytology material, apart from calcitonin immunolabelling for medullary carcinoma [7]. However, the BRAF V600E mutation is associated with papillary thyroid carcinoma in 30% to 80% of cases with a mean of 49% [18]. This mutation is detected in 79% of large-cell variants of papillary carcinoma. The sensitivity of FNAC is 65.5% with conventional morphological methods versus 89.6% with associated detection of BRAF mutations. The diagnostic accuracy also appears to be improved from 91% to 96%, but false-positive results have been described [18].

FNAC is therefore indicated as first-line diagnostic procedure in patients with a thyroid nodule 8 to 30 mm in diameter and low or normal TSH, especially when the nodule is clinically suspicious. Higher false-negative rates are observed for nodules larger than 30 mm or smaller than 8 mm [7,15]. The role of FNAC is more controversial for multinodular goitre when surgery is indicated [1–3].

Malignant cytology (Thy 5) related to probable papillary, follicular or medullary differentiated carcinoma constitutes an indication for total thyroidectomy. The indication for surgery must be carefully evaluated in the presence of lymphoma or anaplastic carcinoma [1,2,11]. Simple surveillance may be sufficient in the case of benign cytology (Thy 3), but FNAC should be repeated 6 to 12 months later due to the 1 to 6% false-negative rate. However, the risk of indeterminate cytology, the cost, and the increased anxiety for patients must be taken into account in this approach [19–21]. Repeated FNAC causes histological changes of the nodule that can interfere with histological examination: follicular cells adjacent to the aspirated zone can be atypical and very large, effraction of the capsule, zones of fibrosis and epidermal metaplasia; a zone of necrosis or papillary endothelial hyperplasia may be observed in the centre of repeatedly aspirated nodules [3]. Surgery is required for the diagnosis of nodules with indeterminate cytology (Thy 3 and Thy 4): the risk of malignancy is estimated to be between 20% and 25% for nodules with “follicular” or “hyperplastic” cytology (Thy 3), but 40% to 50% for true “suspicious” cytology (Thy 4). Lobectomy and isthmectomy with frozen section examination is generally recommended, followed by total thyroidectomy during the same procedure in the case of malignant histology [19–21]. When repeated FNAC remains indeterminate or when the patient refuses repeated FNAC, especially when the nodule is larger than 3 cm, in the case of a recurrent cyst after FNAC or when the nodule is considered to be clinically suspicious, lobectomy and isthmectomy with frozen section should be proposed [20,21].

In the majority of cases, frozen section no longer constitutes the first-line diagnostic examination [1,2,8]. However, it has a specificity of 93% to 100% and a sensitivity of 58% to 94% [21,22]. Similar rates were observed in our population, with a specificity of 99% and a sensitivity of 68% after excluding microcarcinomas.

Frozen section is usually considered in cases with indeterminate cytology (Thy 3 or Thy 4): it can correctly identify carcinoma with excellent specificity, justifying a change of surgical strategy to total thyroidectomy [12,21]. Some authors consider that intraoperative macroscopic examination by an experienced surgeon can have a diagnostic value and that frozen section leads to a change of the surgical strategy in only 5% of cases [23,24]. When FNAC reveals malignant cytology (Thy 5), frozen section confirms the diagnosis and fully justifies total thyroidectomy, possibly combined with lymph node dissection [2,21]. In the present series, the specificity of the FNAC-frozen section combination was 100%, eliminating the rare false-positives of FNAC. The value of frozen section is more questionable in the case of benign cytology when surgery is planned, especially for multinodular goitre. The false-negative results of frozen section correspond to papillary microcarcinoma in 54% of cases or follicular carcinoma in 8% of cases [22,23].

Conclusion

FNAC and frozen section are two diagnostic methods both based on the nuclear appearance of thyroid cells with comparable sensitivity, specificity, accuracy, and positive predictive values. However, frozen section in patients with indeterminate cytology allows improved sampling with direct vision of the nodular lesion. These two examinations are complementary: the surgeon's decision to request frozen section examination depends not only on the results of pre-operative cytology, but also on the surgeon's macroscopic findings.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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