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Original article

Role of fine-needle aspiration biopsy and frozen-section evaluation in the surgical management of thyroid nodules

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Background: The role of routine frozen section (FS) in the surgical management of thyroid nodules remains uncertain. This study reviewed the role of FS in the presence of an adequate fine-needle aspiration biopsy (FNAB).
Methods: FNAB and FS were evaluated in 206 patients who had surgery for a thyroid nodule. Cytological specimens were classified as benign, malignant or suspicious. The FS diagnoses were benign, malignant or deferred.
Results: A cytological diagnosis was obtained in 93 nodules; the remaining 113 were classified as suspicious, of which 21 were malignant on definitive examination. The overall accuracy of FNAB was 53 per cent. FS evaluation identified 165 lesions as benign; the diagnosis was deferred until definitive histological evaluation in only eight. The overall accuracy, therefore, was 96 per cent. Routine use of FS was cost-effective; lowering the number of reoperations led to an estimated saving of about 40 per cent.
Conclusion: These data suggest that FS remains an important tool in the surgical management of thyroid nodules and can reduce the number of patients requiring reoperation.

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Introduction

Nodular thyroid disease is a common clinical problem, with a prevalence in the general population ranging from 4 to 7 per cent. However, only 5 per cent of thyroid nodules are malignant[1]. Diagnostic procedures to evaluate thyroid nodules include radionuclide scanning and ultrasonography, but fine-needle aspiration biopsy (FNAB) is the most effective test in selecting the patients who require surgery[2]. Routine use of FNAB has decreased the number of patients treated surgically for benign thyroid nodules[3].

A consensus to a specific surgical approach for suspicious thyroid nodules has not yet been reached. In some centres ipsilateral lobectomy is initially performed in patients with a suspect follicular lesion on FNAB; the lesion is then evaluated by paraffin sections, followed by a second operation for completion thyroidectomy if needed. In the authors' unit, the surgical approach involves ipsilateral lobectomy with routine intraoperative frozen section (FS), in order to plan the extent of thyroid resection.

Because of the diagnostic accuracy of FNAB, some authors suggest that intraoperative FS can be avoided, to reduce the duration and cost of operation[4–9]. Others suggest that thyroid surgery can be planned by evaluating known prognostic factors and intraoperative findings[10–13].

The purpose of this study was to review the role of FS in the surgical management of thyroid nodules, in the presence of an adequate FNAB.

Patients and methods

Patients and cytological specimens

Some 206 consecutive patients (173 women and 33 men) who underwent thyroid surgery at the ear, nose and throat unit of San Luigi Hospital, Orbassano, Turin, between January 1995 and December 2000 were evaluated retrospectively. Their ages ranged between 14 and 89 (mean(s.d.) 49(14); median 49) years. All had one or more palpable thyroid nodules with a diameter greater than 1 cm. Some 108 patients (52 per cent) presented clinically with a multinodular goitre (MNG), while 98 (48 per cent) had a solitary palpable thyroid nodule. Initial evaluation included a complete history, physical examination, measurement of serum-free thyroid hormones and thyrotropin, and neck ultrasonography. All patients included in the study were

euthyroid; patients with impaired thyroid function were excluded, even those with suppressed levels of thyroid-stimulating hormone only, to exclude autonomous nodules. Thyroid scintiscan and autoantibody measurements were performed in a few patients only, when clinically advisable.

The indications for operation included a cytological diagnosis of malignancy (14 patients; 7 per cent) or of suspected malignancy (113 cases; 55 per cent). In 79 patients (38 per cent) with benign FNAB diagnosis, surgery was performed for progressive growth, compressive symptoms or at the patient's request.

FNAB and intraoperative FS examination were performed in all patients. The pathologist who reported the FS was blinded to the results of the paraffin sections; the diagnosis of the reported FS was never revised during the retrospective analysis. The cytological specimens from FNAB were classified as: (1) benign, including colloid or hyperplastic nodules, benign cysts and thyroiditis; (2) malignant; or (3) suspicious, including follicular and Hürthle cell lesions.

Frozen-section examination

The FS evaluation was made by the same pathologist. Initially, the specimen was assessed macroscopically (including touch preparation cytology) to select the most significant nodules, to identify widely invasive tumours and to plan the dissection of the surgical sample. The next stage was a histological analysis of between four and ten serial sections. The mean(s.d.) number of sections required to obtain a diagnosis of carcinoma was 6·9(2·1) (median 7). In all cases, ten sections were analysed before concluding that a patient had benign disease. The time required for a careful intraoperative analysis of ten sections was 20–30 min.

Histological criteria of malignancy in follicular and Hürthle cell carcinomas were full-thickness capsular invasion, invasion of vessels located within or immediately outside the capsule, or both. Cytological features were considered in cases of papillary carcinoma[14].

The results of FS were classified as (1) benign, (2) malignant or (3) deferred (inconclusive results).

Table 1 Histological diagnosis in 206 thyroid nodules

	No. of patients
Benign	166 (81)
Nodular goitre	103 (50)
Follicular adenoma	48 (23)
Hürthle cell adenoma	11 (5)
Thyroiditis	4 (2)
Malignant	40 (19)
Papillary carcinoma	14 (7)
Follicular variant of papillary carcinoma	5 (2)
Follicular carcinoma	13 (6)
Hürthle cell carcinoma	8 (4)

Values in parentheses are percentages

Statistical evaluation

The accuracy of FNAB and FS was assessed using definitive histological sections as a reference. Sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated both for FNAB and FS. Statistical evaluation was performed by means of the χ^2 test.

Results

The histological diagnosis was benign in 166 (81 per cent) of lesions and malignant in 40 (19 per cent) (*Table 1*). Papillary carcinoma was the most common malignancy.

Fine-needle aspiration biopsy

A definitive cytological diagnosis (74 benign, 14 malignant) was obtained in 93 patients (45 per cent). The remaining 113 samples (55 per cent) were suspicious of malignancy. Following histological assessment, 21 (19 per cent) of these were confirmed as malignant lesions (13 follicular and eight Hürthle cell carcinomas). Of the 79 samples initially thought benign, 74 (94 per cent) were confirmed as benign on final pathological examination. The remaining five false-negative lesions (6 per cent) were defined histologically as follicular variants of papillary carcinoma. All 14 patients with a malignant FNAB were confirmed to have a papillary carcinoma (*Table 2*). For statistical evaluation of FNAB, the classification of suspicious was included in the malignant group, because of the effect on the surgical decision; therefore, the number of false-positive results was high (92). The sensitivity of FNAB was 88 per cent and specificity 45 per cent with an overall accuracy of 53 per cent, PPV 28 per cent and NPV 94 per cent.

Frozen-section examination

Frozen-section evaluation suggested that 165 lesions were benign; this was confirmed histologically in 161 (98 per cent), while four (2 per cent) were subsequently recognized as Hürthle cell carcinomas and the patients underwent a second operation. In eight patients (4 per cent) the intraoperative diagnosis was deferred to definitive evaluation. In four these proved to be benign lesions (follicular

Table 2 Comparison of histological results in 206 thyroid nodules with preoperative cytology and intraoperative frozen section

	Final paraffin		
	Benign	Malignant	Total
FNAB			
Benign	74	5	79
Suspicious	92	21	113
Malignant	0	14	14
Total	166	40	206
Frozen section			
Benign	161	4	165
Deferred	4	4	8
Malignant	1	32	33
Total	166	40	206

FNAB, fine-needle aspiration biopsy

adenomas) and four were identified as malignant (three follicular carcinomas and one Hürthle cell carcinoma) (*Table 2*). The latter four patients underwent a second operation.

For statistical evaluation of FS, the uncertain samples were classified as false negative (four carcinomas) or true negative (four adenomas). The sensitivity of FS was 80 per cent and the specificity 99 per cent. A single false positive led to inappropriate total thyroidectomy (the intraoperative diagnosis was follicular carcinoma, but the definitive histological diagnosis was Hürthle cell adenoma). The overall accuracy was 96 per cent, PPV 97 per cent and NPV 95 per cent.

Frozen section in follicular lesions

The accuracy of FS examination was evaluated selectively in 113 patients with a cytological diagnosis of suspected malignancy (follicular lesions). In this series, there were six false negatives (three follicular and three Hürthle cell carcinomas), including four deferred diagnoses. The sensitivity was 71 per cent and the specificity 99 per cent. The overall accuracy of FS for follicular lesions was 94 per cent, PPV 94 per cent and NPV 94 per cent.

Frozen section for solitary nodules or multinodular goitre

The results of FS were compared in patients with a clinically palpable solitary nodule (98 patients; 48 per cent) and those with MNG (108; 52 per cent). There were no significant differences in the accuracy of FS (96 *versus* 95 per cent), sensitivity (81 *versus* 79 per cent) or specificity (100 *versus* 99 per cent). There were four inappropriate operations, followed by a second operation in each group. One patient with a MNG had an inappropriate total thyroidectomy at first operation.

Cost analysis

The cost of both surgery and FS was analysed by means of regional refunding fees to the hospitals. The unitary cost of thyroidectomy and FS was estimated at €2065 and €81 respectively.

The value of routine FS was analysed by comparing the number of second operations needed (eight) with the 26 reoperations required if FS was not done. The total cost of FS in 206 operations was €16 686. The routine use of FS led to eight second operations (four initially thought benign and four deferred on the basis of FS), at a total cost of €16 520. Surgical decisions based on FNAB only would have led to 26 reoperations, at a total cost of €53 690. It was estimated that routine use of FS in the present series led to a saving of €20 484 (excluding the patient who had an unnecessary total thyroidectomy).

Discussion

The use of FS is an important adjunct to the operative management of many forms of cancer. However, in the era of FNAB, the routine use of FS in thyroid surgery may be unnecessary. The economic impact of the introduction of routine preoperative FNAB in the management of thyroid malignancy was illustrated by investigators from the Mayo Clinic, who reported that FNAB reduced the number of patients requiring surgery from 67 to 43 per cent and increased the proportion of surgically proven cancers from 14 to 29 per cent[15]. In the past decade, several reports have debated the routine use of FS[7,10,12,16–21]. Some authors point out that FNAB is complementary to FS in planning the extent of surgery[20]. Others[6,21] suggest that FS can be restricted to cases with an FNAB diagnosis of 'follicular nodule' or 'indeterminate'.

In general, FNAB is considered to be more sensitive and FS more specific for the diagnosis of malignant neoplasm. FNAB is used primarily to select patients for surgery, where a high sensitivity is desirable. FS is employed to plan the extent of surgery, a role requiring a high specificity. In the present study, FS had a good sensitivity (80 per cent) and a high specificity (99 per cent), in agreement with other reports[5,10,16,20,21]. In only eight patients (4 per cent) was the intraoperative diagnosis postponed pending final histological evaluation.

The sensitivity and specificity evaluation of FNAB and FS strictly related to the handling of the respective diagnoses. Because all patients in this study had been selected for surgery, follicular lesions could be false positive or true positive. Furthermore, when FS was inconclusive and led to a conservative operation, these samples could be true negatives or false negatives. These data suggest that FNAB is good for selecting patients who need surgery, but the low specificity and accuracy do not permit adequate planning of the extent of surgery. The low specificity of FNAB could be explained by the large number of MNGs in an area of moderate iodine deficiency; the presence of multiple nodules and a higher percentage of follicular neoplasms may diminish the accuracy of FNAB. On the other hand, FS has a high specificity and led to a reduction in the number of late reoperations from 26 (13 per cent) to eight (4 per cent).

Had the surgical decision been based on FNAB only, 26 of 40 patients with malignancy would have needed a second operation. One Hürthle cell adenoma, diagnosed as a follicular carcinoma on FS, was the only false positive.

The specificity of FS was high (99 per cent) if only the follicular lesions found by FNAB were considered; accordingly, there were few inappropriate operations (seven (6 per cent) of 113). Similarly there was no difference in the accuracy of FS for patients with either solitary nodules or MNG. None of this supports the hypothesis that FS could be used selectively in specific subgroups of patients.

Total or near-total thyroidectomy is the usual surgical treatment for a well differentiated thyroid cancer[22,23]. Routine FS in patients with cancer reduces the discomfort and avoids the costs of reoperation.

In the present series, decreasing the number of reoperations as a result of routine FS led to an estimated saving of about 40 per cent. FS is probably unnecessary when FNAB is diagnostic of malignancy. In this study, the estimated cost saving of avoiding FS in 14 patients with a cytological diagnosis of papillary carcinoma was €1134.

In conclusion, FS evaluation remains a useful and cost-effective tool, complementary to FNAB. FS can be avoided when the FNAB result is consistent with malignancy, but could be of value when the FNAB result is reported as suspicious, inadequate or even benign. The results of both thyroid FNAB and FS are dependent on the pathologist. Each institution should evaluate its own ability to use these modalities in the preoperative and intraoperative assessment of thyroid nodules.

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