

Fine Needle Biopsy and Scintigram in the Preoperative Diagnosis of Thyroid Lesions

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ABSTRACT

Fine needle biopsies (FNB) of the thyroid were examined from 860 patients. In 703 cases follicular cells without atypia were found and in this group of patients the clinical diagnosis was nodular goitre. Operations were performed in 138 patients and in 97 cases the cytological finding could be correlated to the histopathological diagnosis. In 33 of these patients thyroid carcinoma was histologically verified. In 26 of the carcinoma cases cytologic examination showed grave atypia or changes indicating carcinoma. The cases in which the cytological diagnoses were falsely negative are discussed. Moderate cellular atypia occurred in one case with papillary carcinoma. In two cases the cytological examination gave a false positive diagnosis of cancer, both representing thyroiditis of the lymphoid type.

The scintigrams in patients with thyroid carcinoma are also presented. Cold nodules were found in 10/19 patients and a hot nodule in 1 patient. In 3 patients the scintigrams were normal and in another 5 inconclusive. The results indicate that thyroid scintigrams can only be used as a supplement to the physical examination and a guidance for FNB. The contribution of FNB in the decision to operate is discussed and it is concluded that FNB is a valuable adjunct in preoperative diagnosis of thyroid lesions. The best diagnostic results are obtained when there is a close cooperation between clinician, radiologist, cytologist and pathologist.

INTRODUCTION

Palpable thyroid nodules may present difficulties in the differential diagnosis between a malignant tumour and a benign thyroid lesion. The thyroid gland is readily accessible for fine needle aspiration biopsy and thus a possibility is offered to distinguish morphologically between non-malignant and malignant lesions as well as between various types of malignant neoplasms (10,2,6). Scintigraphy is often used to localize areas suspected of malignancy, i.e. cold nodules. It is a valuable aid in the guidance of the fine needle

biopsy. The frequency of malignancy on scintigraphically localized cold nodules has been reported to vary between 3 and 30 %, and it increases with age (8,4,).

The present study was undertaken to analyze to what extent these two methods have proven useful to guide the clinician in the treatment of patients with thyroid lesions. To estimate the accuracy of the cytological diagnosis, the results obtained after fine needle aspiration biopsy were compared with the histopathological findings in those cases that were operated on. The presenting signs and symptoms in patients with a final diagnosis of thyroid malignancy were also investigated.

MATERIAL AND METHODS

The present study includes 896 patients with suspected or apparent thyroid disease referred to the Department of Clinical Cytology for fine needle biopsy or to the Department of Surgery for operation during the years 1979-80. Altogether 910 fine needle biopsies (FNB) of the thyroid glands were performed on 860 of these patients at the Laboratory of Clinical Cytology, University Hospital, Uppsala. In 36 patients the need for operation was clinically so obvious that neither FNB nor scintigram were regarded necessary.

Thyroid scintigrams - performed with ^{99m}Tc - were used in more than half of the patients included in this material. In this study, however, only the scintigraphic findings in the patients, who finally got a diagnosis of thyroid carcinoma, will be reported.

The FNB and the cytological examinations were performed by the same doctor. The smears were air-dried and stained according to May Grünwald-Giemsa. Cyst contents were centrifuged and two smears were prepared, one stained as above, the other ethanol-fixed and stained according to Papanicolaou.

For histological examination the surgically removed thyroid specimens (fixed or unfixed) were carefully sectioned into thin slices of $\frac{1}{2}$ -1 cm. Ten % neutral formalin was used as fixative. Five μm deparaffined sections were stained with haematoxylin eosin or according to van Gieson. All histopathological examinations were performed by the same pathologist. The histological classification according to the WHO was used.

Clinical information relevant to the present study was obtained from the medical records of the patients.

RESULTS

The hospitals and different clinics from where the patients were referred for FNB are listed in Table 1.

Table 1. The hospitals and clinics referring the patients (860) for fine needle biopsy

Hospital (H)	Clinic	Nos. of biopsies
University H. Uppsala	Medicine	257
	Oncology	201
	Surgery	116
	Otolaryngology	36
	Others	61
Regional community H*	Medicine and Surgery	159
General practitioners*		80
Total number of biopsies		910

In some patients the biopsy was repeated 1-3 times as the material was presumed not to be representative for the lesion or too scarce to permit a reliable diagnosis

* In the county of Uppsala

Table 2. Cytological findings in 910 fine needle biopsies from 860 patients

Cytological findings and diagnosis	Nos. of biopsies
Follicular cells without atypia	703
Follicular cells with atypia	
slight to moderate	46
grave or cancer	28
grave in association with thyroiditis	18
Thyroiditis	91
lymphoid type	79
granulomatous type	12
Non-thyroid lesions	6
Insufficient material	18
Total	910

* Lymphomas, metastases of renal or salivary gland carcinoma

In the majority of the FNB follicular cells without atypia were observed (Table 2). In this patient group a clinical or histopathological diagnosis of nodular goitre was usually made. Biopsies from 46 lesions showed cells with slight to moderate atypia. In another 46 cases corresponding to 5 % of the material the cellular atypia was found to be grave or suggesting malignancy. This figure includes 18 cases of lymphoid thyroiditis with grave cellular atypias. In all these 18 cases the clinical diagnosis of thyroiditis was clinically and immunologically well established. These patients were followed clinically and have hitherto not been operated on. Thyreoiditis of the lymphoid or granulomatous type was diagnosed in 91 of the biopsies (10 %). In 18 patients the material obtained at the biopsy did not permit a diagnosis and it was not possible to perform another FNB.

During the investigation period 138 patients underwent surgery of the thyroid gland, 102 of which had been examined with FNB. Most of the patients in whom the cytological smears had shown atypia, usually of a slight degree were not operated on. These patients were usually elderly with a long history of multinodular goitre. Those where the atypia was suspicious for malignancy and not associated with lymphoid thyroiditis were all operated. The main indications for surgery are given in Table 3.

Table 3. Indications for operation

Indications	Nos. of patients
Toxic (hot) nodule(s)	6
Toxic goitre	32
Cold nodule(s)	11
Nodule(s) without cellular atypia*	13
Nodule(s) with cellular atypia or cancer	25
Clinically strongly suspected malignancy**	3
Recurrence of cancer or regional metastases	18
Tracheal compression***	30
Total	138

* Based on fine needle biopsy (FNB)

** No FNB performed

*** Due to atoxic goitre

Table 4. Correlation between cytological and histopathological diagnosis in 97 patients with diseased thyroid gland

Cytological diagnosis or findings	Histopathological diagnosis							
	Goitre without cellular atypia	cellular atypia	Adenoma follicular	Adenoma type -Hürthle -cell	Follicular	Papillary	Carcinoma type Medullary Anaplastic (lymphocytic type)	Thyroiditis
Follicular cells with no atypia	48	1	2	1	2*	3	1	1
slight atypia	2		2					
moderate atypia	1				2	1		2
grave atypia		1	1			3		
NOS								
Carcinoma NOS					1	2		
Follicular					2			
Papillary						10		1
Medullary								
Anaplastic								5
Thyroiditis								2
Total	51	2	5	1	7	19	1	6

* Microinvasive type

The correlation between the cytological findings and histopathological diagnosis could be given for 97 patients (Table 4). In 33 of these patients thyroid carcinoma was histopathologically verified. In 26 of the carcinoma cases the cytological diagnoses were grave atypia or carcinoma. Moderate cellular atypia occurred in one case which turned out to be a papillary carcinoma. No cellular atypia was noted in two cases with follicular carcinoma, in 3 cases with papillary and in one case with medullary carcinoma. The 6 cases with false-negative findings at FNB will be described more extensively below.

In 2 cases there was a false-positive cancer diagnosis, made on the cytological smears, both representing cases with thyroiditis of the lymphoid type.

The histopathological examination revealed that a multifocal growth pattern of the different types of carcinomas was frequent. Of the 7 cases with follicular carcinoma 5 showed a multifocal growth pattern and in 2 the cancer had an aggressive growth extending into the adjacent cervical tissue. Eight of the 19 cases with papillary carcinoma appeared unilaterally with more or less solitary lesions.

In 11 cases the papillary cancer was growing bilaterally, 3 % of them had an infiltrative growth. Six patients with papillary cancer had regional lymph node metastases at the time of operation. The case with medullary cancer showed a multifocal growth. All anaplastic cancers exhibited an extensive growth pattern.

The main symptoms presented are briefly summerized in Table 5.

Table 5. Clinical symptoms presented in cases of thyroid malignancy

<u>Symptoms</u>	
Diffuse growth of the thyroid gland	15
Nodular growth of the thyroid gland	8
Goitre with symptoms (compression, stridor)	10
Cervical nodules	5
Local recurrence after previous surgery for thyroid carcinoma	3
Total no.	41

Nineteen of the cancer patients in this study underwent preoperative scintigrams with the following results: in one case the examination showed a toxic (hot) nodule, in 10 cases cold nodules were found, and 3 cases were normal. In the remaining 5 cases the results were inconclusive.

Carcinoma cases with a false negative cytologic diagnosis:

Case 1. A 41-year-old woman with a slowly (since 10 years) growing enlargement (partly nodular) of both thyroid lobes with slight toxic symptoms (medically treated). A scintiscan showed uptake of Tm^{99} only in one palpable nodule of the right lobe. FNB showed follicular cells without atypia. The right lobe was removed and histopathological examination showed nodular goitre in addition to a small focus of papillary carcinoma. At reoperation the left thyroid-lobe was removed and found to contain small foci of carcinoma of the same type.

Case 2. A 52-year-old woman with a bilaterally enlarged nodular thyroid gland located partly intrathoracically. No toxic symptoms. Scintigram showed lowered uptake in the right lobe. At FNB no cellular atypia was found. Subtotal bilateral thyroidectomy was performed. The histopathological diagnosis was nodular goitre with an encapsulated highly differentiated follicular carcinoma of microinvasive type in the right lobe.

Case 3. A 36-year-old woman with an enlargement of the thyroid gland during the last 3 years. No toxic symptoms but compression of the trachea. A scintigram indicated nodular colloid goitre. FNB showed follicular cells without atypia. Bilateral subtotal thyroidectomy was undertaken. The histopathological examination showed nodular goitre with multiple foci of papillary carcinoma in both lobes.

Case 4. A 48-year-old woman with a slowly (since 2 years) growing nodule in the left thyroid lobe. No toxic symptoms. Scintigram showed no uptake in the left and a normal right lobe. FNB indicated normal follicular cells. Left-sided lobectomy was performed. The histopathology showed a highly differentiated papillary carcinoma. The right lobe was removed later and also contained small foci of papillary carcinoma. A renewed examination of the cytological smears revealed a few clusters of thyroid cells with atypia and cytoplasmic nuclear inclusions indicating papillary carcinoma were found.

Case 5. A 63-year-old man with a mobile tumour above sternum since several years. The tumour and the left thyroid lobe were removed at a regional community hospital. The histopathological examination revealed a medullary carcinoma. The patient was transferred to Uppsala University Hospital for further examination. A scintigram showed focally decreased uptake of Tm^{99} in the right lobe. FNB did not reveal any cellular atypia. Bilateral thyroidectomy was performed. The following histopathological examination showed multiple foci of cell nests strongly suspected of representing medullary carcinoma in the right lobe. The diagnosis of medullary cancer was verified by elevated levels of calcitonin.

Case 6. A 52-year-old woman with a rapidly growing (since 2 months) nodule

in the right thyroid lobe. A scintigram showed uptake in this lobe. FNB indicated follicular cells without atypia. After 3 months of medical treatment with thyroid hormone the right lobe was resected. The histopathological examination demonstrated a follicular adenoma. However, behind this adenoma a small follicular carcinoma was located. Later on a left-sided lobectomy was performed. Histopathological examination did not show any signs of malignancy.

DISCUSSION

In this study 102 of 810 patients who underwent FNB were later operated and in 97 a correlation between cytological and histopathological findings was possible. Of the 33 cases with histopathologically diagnosed cancer, 5 were not diagnosed by FNB and in one the malignant cells were not observed until the smears were reexamined. Thus, false-negative diagnoses were noted in 6 (18 %) of the cancer cases. The corresponding figures for false-negative diagnoses presented by other groups varies between 7.7 and 27.5 % (see Löwhagen et al., 1981).

The difficulty to distinguish a follicular adenoma from a highly differentiated follicular carcinoma is well-known (6). According to this research group it is not feasible to make this distinction with FNB. They suggest that FNB should only aim at recognizing a follicular neoplasm leaving the definite diagnosis to the histopathological examination. This strategy seems rational as the diagnosis of a follicular neoplasm always warrants a surgical exploration. By such management it is also possible to minimize the risk of a false-negative or false-positive diagnosis. The problems in sampling the relevant i.e. malignant cells in small cancers are well illustrated by cases 2 and 6. In case 2 a small microinvasive follicular cancer was present in a nodular goitre and in case 6 a small follicular cancer was found behind a "hot" follicular adenoma. Thus, FNB is not a tool to detect occult cancers which has been pointed out also by Granberg et al. (3).

As in all diagnostic procedures false positive findings should ideally not occur in FNB. It seems difficult to avoid a low level of false positive findings if one wishes to avoid missing the diagnosis of cancer (7). The rates of false positive diagnoses presented in the literature amounts to 0-2 % (1,5). In our material there were 2 cytological biopsies falsely interpreted to show cancer cells. Both cases occurred in patients with lymphoid thyroiditis, where a grave atypia of the follicular cells is common as is a lymphocytic infiltration in the periphery of a cancer. The difficulty in making a correct diagnosis of lymphoid thyroiditis, especially in a solitary nodule has been pointed out also by Löwhagen et al (6). Even histopathology may sometimes fail to resolve differential diagnostic problems in the thyroid (9).

Only half of the cases with a histologically verified cancer had a radio-nuclide scanning (^{99}Tc) indicating cold nodule(s). In about 15 % the scintiscans were "normal" and in another 25 % inconclusive. One patient had a papillary cancer although a "hot" nodule was seen, indicating that malignancy cannot be excluded when technetium is used as radioactive compound (11). Our findings therefore point to the limitation of thyroid scintiscans and underline that scintigraphy alone cannot classify a nodule as malignant or benign. It can only be considered an adjunct of physical examination and a guidance for FNB and cytological evaluation of a thyroid lesion.

Knowledge about the growth pattern of the cancers is also valuable when analyzing the results. This is true both for the cytologist where the need for multiple biopsies is evident and for the surgeon when deciding how radical the operation has to be. In approximately half of the cases there were more than one area of cancer growth in the thyroid gland. Metastases at the time of the primary operation was also a relatively common finding. It is difficult to evaluate to what extent the results of the FNB contributed to the actual decision of surgical intervention or whether its main benefit was to help the surgeon to plan the operation. Most of the patients already had clinical symptoms suggesting malignancy. However, in two groups of patients the cytological diagnoses probably made a significant contribution to the decision to operate. These were the patients with goitre and/or adenomas and those with enlarged cervical glands.

The findings of the present study strongly indicate that FNB is a valuable adjunct in thyroid diagnosis. It is also obvious that FNB should be considered complementary and optimal results can only be obtained when there is a diagnostic cooperation among the clinician, radiologist, cytologist and pathologist.

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