

## Occasional Review

### Fine needle aspiration cytology in isolated thyroid swellings: a prospective two year evaluation

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#### Abstract

During 1 September 1981 to 31 August 1982 aspiration cytology was carried out in all isolated thyroid swellings referred to the Aberdeen Thyroid Clinic: cytological findings were not disclosed, did not influence management, and were compared retrospectively with the histological diagnosis. In a total of 70 swellings sensitivity for the detection of neoplasia was 86% and overall accuracy 92%; the positive predictive value was 80% and negative predictive value 96%. During the second year (1 September 1982 to 31 August 1983), when cytological findings were used to influence management, the frequency of operation for isolated thyroid swellings decreased by 25% and the proportion of operations for neoplasia increased from 31% to 50%. In terms of bed occupancy the potentially avoidable surgical workload for benign disease was reduced by 34%.

Aspiration cytology, carried out at the first clinic attendance, makes a sound basis for selective surgery and leads to economy in the management of isolated thyroid swellings.

#### Introduction

Some 60-70% of clinically isolated thyroid swellings are localised areas of colloid degeneration, about 10% are carcinomas, and about 20-30% are follicular adenomas. Though infrequent, the possibility of carcinoma dictates management, and since clinical diagnosis is unreliable a selective surgical policy commonly depends on isotope and ultrasound scanning. Selection on the basis of isotope scanning is very imprecise, for though most (but certainly not all) carcinomas are "cold" on scintiscanning, this is also true for most benign swellings, which are far more common. In addition, the utility of ultrasound is limited to the determination of physical characteristics: there is no evidence that it will predict reliably the histological diagnosis. The ability to distinguish cystic from solid swellings should not influence management, since the incidence of malignancy in association with thyroid cysts is similar to that in solid swellings (Al-Sayer *et al*, paper submitted for publication).

Clearly, histological examination of the removed swelling is the most accurate way to determine the pathology, and therefore the most rigorous attitude to the detection of differentiated thyroid carcinoma implies removal of all or most isolated swellings: in

effect, lobectomy (or isthmusectomy in a few patients) becomes the diagnostic as well as the therapeutic method. Such a policy, however, represents overtreatment in many patients. An alternative, which has been in routine use in Sweden for over 20 years but is only now receiving attention in Britain, is fine needle aspiration cytology. The overall accuracy of fine needle aspiration cytology when related to the histological diagnosis has varied from over 80% to over 90% in several studies. The widest experience, from the Karolinska Hospital, has been extensively reported<sup>1-4</sup> and shows that a cytological diagnosis of malignancy is almost completely reliable but that there is a small incidence of false negativity. It was uncertain whether such accuracy could be matched elsewhere without similar long experience. Our traditional policy of removing almost all isolated swellings gave a good opportunity of prospective evaluation of cytological accuracy, in that with very few exceptions the histological findings were available. Once fine needle aspiration cytology had been shown to be accurate it was possible to assess objectively its effect on the frequency of operation and on surgical workload by retrospective comparison with previous experience.

#### Patients and methods

During the first year (1 September 1981 to 31 August 1982) fine needle aspiration cytology was carried out in all patients with clinically isolated thyroid swellings referred to the thyroid clinic. A total of 70 patients were studied (56 women, 14 men; female:male ratio 4:1; mean age 47 years (range 24-78)) and, with few exceptions, aspiration was performed and smears prepared by one of us (HAS). According to characteristics defined below, smears were classified as benign, suspicious, malignant, or unsatisfactory, but these results were not disclosed and did not influence management. Of the 70 patients, 67 subsequently had their swellings removed; in three patients in whom cystic swellings were abolished by aspiration and did not recur during two subsequent attendances operation was thought no longer justifiable. At the end of the year cytological predictions were compared with the final histological diagnosis.

During the second year (1 September 1982 to 31 August 1983) fine needle aspiration cytology was carried out as before in all patients presenting, but results were disclosed and used to influence management. Of the total of 62 patients (53 female, 9 male; female:male ratio 6:1; mean age 49 years (range 12-77)), 44 were operated on.

#### TECHNIQUE OF FINE NEEDLE ASPIRATION CYTOLOGY

Fine needle aspiration cytology was carried out in the outpatient clinic without local anaesthesia using a 22 gauge (0.6 mm) needle on a 10 ml disposable syringe mounted in a syringe holder. The technique of aspiration was as described by Löwhagen and coworkers.<sup>2,4</sup> At least two smears were made, one dried in air and the other fixed in absolute alcohol with 0.2% acetic acid. If the aspirate was fluid from a cyst, two smears were made; the remaining fluid was centrifuged and smears made from the sediment. Smears were stained using both Papanicolaou and May-Grünwald-Giesma stains.

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CLASSIFICATION OF CYTOLOGICAL APPEARANCES

Several smears were reported as unsatisfactory on the basis of an apparently inadequate tissue sample containing only blood and colloid with few or no follicular cells. Adequate smears were classified according to the number and arrangement of follicular cells and on nuclear characteristics. A smear was classified as benign if the aspirate contained scattered follicular cells of normal appearance occurring singly and in small groups with or without associated colloid. Cyst fluid was classified as benign if it contained macrophages with or without a few follicular cells. Smears were classified as suspicious either because of more than usual cellularity in the form of large clumps or sheets of follicular cells with regular nuclear features or because of irregularity in nuclear size or density or nuclear crowding. Smears were classified as malignant on the basis of either (a) florid variability in nuclear size and shape with prominent chromatin or large nucleoli or (b) characteristic features of specific neoplasms, such as the cytoplasmic granules and spindle shaped nuclei of medullary carcinoma or the papillary formations and nuclear inclusions of papillary carcinoma.

Results

Table I compares the cytological and histological findings during the first year (assuming that the three cysts treated by aspiration were associated with colloid degeneration). Of the 45 swellings reported as cytologically benign, 43 were areas of colloid degeneration, one was a follicular adenoma, and one a papillary carcinoma. Of the fourteen aspirates reported as suspicious, six were follicular adenomas and five were malignant (three papillary carcinomas, two follicular carcinomas). The remaining three swellings were

TABLE I—First year accuracy of fine needle aspiration cytology (FNAC) in isolated thyroid swellings

Classification	FNAC	Histological picture		
		Benign	Malignant	Follicular adenoma
Benign	45	43	1	1
Suspicious	14	3	5	6
Malignant	1	—	1	—
Unsatisfactory	10	3	—	7
Total	70	49	7	14

Decision analysis (unsatisfactory specimens excluded (see text)): sensitivity 86% (12/14); specificity 93% (43/46); accuracy 92% (55/60); false positive fraction 7% (3/46); false negative fraction 14% (2/14); positive predictive value 80% (12/15); negative predictive value 96% (43/45).

benign, showing histological features of colloid degeneration in two and chronic lymphocytic thyroiditis in one. One aspirate reported as malignant was a medullary carcinoma. Finally, 10 patients had an unsatisfactory aspirate; seven of these were follicular adenomas and three were areas of colloid degeneration.

The decision analysis shown in table I was based on exclusion of the unsatisfactory specimens. We justify the exclusion because the analysis is that of cytological accuracy in relation to histological findings rather than an assessment of the utility of fine needle aspiration cytology in management. In addition, the rather high incidence of unsatisfactory smears (14%), which we attribute to a learning phase in the technique of aspiration, reflects an unnecessarily restrictive design: had unsatisfactory smears been disclosed aspiration could have been repeated, as in the second year. When aspiration is repeated (more than once if necessary) the incidence of unsatisfactory smears is low and does not seriously detract from the usefulness of cytology.

A cytological appearance of increased follicular cellularity is common to follicular adenoma and well differentiated follicular carcinoma. Löwhagen and coworkers<sup>3,4</sup> report increased cellularity more specifically as "follicular neoplasm," whereas we have termed the appearance suspicious. Differentiation between a follicular adenoma and a well differentiated follicular carcinoma depends on scrupulous histological technique and a careful search for evidence of breach of the capsule or angioinvasion. We therefore believe that all follicular adenomas should be removed, and in analysing cytological accuracy we have classified follicular adenoma as equivalent to follicular carcinoma. In effect, cytology is being assessed in terms of the accuracy with which it can predict neoplasia, with one qualification: localised areas of apparent colloid degeneration with low cellularity are occasionally encapsulated and may therefore be termed histologically as "colloid adenoma." The presence of a capsule suggests that these are variants of neoplastic rather than degenerative change, but they are otherwise indistinguishable from colloid degeneration and are, to the best of our knowledge, never associated

with invasive features. "Colloid adenomas" were therefore classified as equivalent to colloid degeneration.

Analysis showed that the sensitivity of cytology in detecting neoplasia was 86% and the specificity for benign conditions 93%; overall accuracy was 92%. The false positive and false negative fractions were 7% and 14% and the positive predictive and negative predictive values 80% and 96% respectively. There were no complications of fine needle aspiration cytology, which was very well tolerated, and the observed accuracy justified further prospective evaluation of its usefulness in clinical decision making.

During the second year fine needle aspiration cytology was again carried out in all patients (62) referred with clinically isolated thyroid swellings. Results were disclosed and used to influence a more selective surgical policy. Aspirates resulting in unsatisfactory smears were repeated, and after repetition only one swelling with an unsatisfactory aspirate remained. A histological diagnosis was available in 44 patients and operation was avoided in 18. Table II compares the cytological findings with the final diagnosis. Of

TABLE II—Second year accuracy of fine needle aspiration cytology (FNAC) in isolated thyroid swellings

Classification	FNAC	Final diagnosis		
		Benign	Malignant	Follicular adenoma
Benign	33	32	—	1
Suspicious	25	8	2	15
Malignant	3	—	3	—
Unsatisfactory	1	—	—	1
Total	62	40	5	17

Decision analysis (unsatisfactory specimens included): sensitivity 91% (20/22); specificity 80% (32/40); accuracy 84% (52/62); false positive fraction 20% (8/40); false negative fraction 4.5% (1/22); positive predictive value 71% (20/28); negative predictive value 97% (32/33).

33 swellings reported cytologically as benign, 31 were areas of colloid degeneration (assuming that the 18 patients not operated on had colloid degeneration), one was a localised area of chronic lymphocytic thyroiditis, and one a follicular adenoma. Of 25 aspirates reported as suspicious, 15 were follicular adenomas and two were malignant (one follicular and one medullary carcinoma); the remaining eight were areas of colloid degeneration in seven and chronic lymphocytic thyroiditis in one. The three aspirates reported as malignant proved to be malignant (follicular carcinoma, papillary carcinoma, and anaplastic carcinoma), and the patient with unsatisfactory aspirates has a small follicular adenoma.

The decision analysis shown in table II (and which includes the unsatisfactory specimen) should be given less weight than in the first year because of the smaller number of patients with histological data and the unproved assumption that patients not operated on had benign disease. Compared with the first year the specificity and the positive predictive value were lower and the false positive fraction much higher. In other words, a sizable proportion of aspirates classified as suspicious were from areas of colloid degeneration.

EFFECT ON SURGICAL WORKLOAD

During the first year 67 of the 70 patients (96%) were operated on compared with 44 of the 62 (71%) during the second year, a reduction of 25%. The reduction, however, was not entirely attributable to fine needle aspiration cytology. Of the 18 patients in whom operation was avoided, advanced age and concomitant disease were important contraindications in three. In addition, four patients who had had previous lobectomies for colloid degeneration and presented with enlargement of the opposite lobe would probably have escaped operation in the absence of cytology. None the less, benign cytological appearances in these seven patients gave added reassurance in the decision not to operate. The proportion of operations necessary because of neoplasia (carcinoma and follicular adenoma) increased from 31% (21 of 67) to 50% (22 of 44).

During the first year the mean duration of postoperative stay was 2.2 (SD 0.6) days and the total number of days during which a bed was occupied by patients operated on for isolated thyroid swellings, assuming that each patient occupied a bed for one day before operation, was 284. During the second year the mean duration of postoperative stay was 2.4 (SD 0.9) days and the total bed days for isolated thyroid swellings 194. The bed requirements for malignant disease were unchanged at 33 and 29 days in each year, but requirements for benign disease were 251 compared with 165, a reduction of 34%.

## Discussion

Fine needle aspiration cytology is claimed to permit differentiation of benign from malignant thyroid swellings with much greater accuracy than has been possible hitherto.<sup>2,3,6</sup> Much published work, however, gives biased conclusions, in that the cytological diagnosis has been allowed to influence the selection of patients for operation. The predictive accuracy of cytology can be reliably established only by "blind" comparison with the histological diagnosis, and our study is one of the few which satisfy this criterion. As a result it is clear that the accuracy of fine needle aspiration cytology in isolated thyroid swellings is reproducible despite lack of experience, though lack of experience was evident during the first year in the relatively high incidence of unsatisfactory specimens. That this need not detract from cytology, however, is shown by the low incidence of sampling failure in the second year. Ideally, as has been shown in aspiration cytology of breast swellings,<sup>5</sup> experience should be concentrated in the hands of one person, preferably the cytologist, who, through routine attendance at the thyroid clinic, becomes increasingly familiar with the clinical examination of the thyroid, with location of areas of abnormality, and with the technique of aspiration and preparation of smears.

The main concern in relying on fine needle aspiration cytology to detect neoplasia is the occurrence of false negative predictions. During the first year the false negative fraction was 14% and in the second year 4.5%, on the basis (which we think appropriate) that follicular adenomas are considered equivalent to follicular carcinoma. The false negative fractions for carcinoma alone were 7% and zero. In the first year the false negative smears were from a 37 year old man with a large, firm swelling which proved to be a papillary carcinoma and from a 39 year old man with a similar firm swelling which proved to be a follicular adenoma. In the second year the false negative result was associated with a large follicular adenoma which had recently increased in size.

These observations emphasise that, despite the evident accuracy of cytological diagnosis, clinical judgment is an overriding arbiter of the indications for operation. A swelling which is clinically suspicious because of size, consistency, or other reasons but is benign cytologically should nevertheless be removed. As a result it is difficult to avoid operation in teenagers and young adults of both sexes, and especially in men over 50 because of the known risks of malignancy.<sup>2,7</sup> In addition, there are other indications for the removal of isolated thyroid swellings, including size, pressure symptoms, cosmesis, and the patient's wishes and anxieties.

During the second year 15 cytologically benign swellings were removed. Nine of these were cysts that were either not abolished by aspiration or recurred, and in the remaining six solid swellings the decision to remove them was influenced by the above factors. Conceptually, it is difficult to reverse overnight a traditional policy of removing virtually all isolated swellings, and probably in the future, with increasing confidence in cytology, a larger proportion of patients with benign aspirates will be spared operation.

The incidence of false positivity on the infrequent occasions when

a cytological diagnosis of malignancy was made was zero, but when aspirates classified as suspicious were included the false positive fraction was 20% (8 patients) during the second year. The false positive results were attributable to apparently increased cellularity rather than to nuclear variability in all eight patients. We believe that this reflects the caution of developing experience in the knowledge that predictions were a determinant of management: the subjective criteria of what represents increased cellularity are likely to become better defined in the future.

Despite these restrictions a worthwhile reduction in the frequency of operation for isolated thyroid swellings of 25% was achieved together with a 34% reduction in bed requirements for non-neoplastic swellings. At the Mayo Clinic, which used a less aggressive policy beforehand, the introduction of fine needle aspiration cytology was associated with a 25% reduction in the cost of medical care, and the proportion of patients with isolated thyroid swellings undergoing operation decreased from 67% to 42%; while the yield of carcinomas increased from 14% to 29%.<sup>8</sup> We, however, believe that follicular adenomas should be removed and that there are other indications for operation in non-neoplastic swellings, so we doubt whether the frequency of operation can be reduced to less than 50% in our centre. Additional attractions of fine needle aspiration cytology are, firstly, that a cytological diagnosis of malignancy is often type specific, which permits surgical strategy to be defined before operation; in addition, suspicious lymph nodes can be aspirated at the same time. Secondly, less specific investigations such as isotope and ultrasound scanning are largely avoided. Thirdly, generalised thyroid enlargements with dominant, suspicious areas may more confidently be managed without operation on cytological diagnosis of a non-neoplastic process. Fourthly, in anaplastic carcinoma and lymphoma open biopsy is usually avoidable before treatment with radiotherapy; and, finally, metastatic deposits in the thyroid may be diagnosed cytologically.

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**WORDS BLUE BLOOD.** The hereditary possession of blue blood is traditionally the prerogative of royalty and the higher aristocracy. As W S Gilbert has reported, when speaking (or rather singing) through the agency of Lord Tolloller (*Iolanthe*, Act I),

We boast an equal claim  
With him of humble name  
To be respected!  
Blue blood! blue blood!

Certain hereditary disorders of the blood have affected the royal families of Europe, but haemophilia does not discolour the blood, and porphyria merely discolours the urine. Although the veins depicted in anatomy textbooks are printed a bright blue, when medical students transfer to clinical studies they soon learn that an exposed vein is predominantly grey with a faint bluish tinge. Furthermore, while arterial blood is scarlet, venous blood is maroon.

The *Oxford English Dictionary* tells us that "blue blood" is a translation

from the Spanish *sangre azul*, and is "that which flows in the veins of old and aristocratic families, who claimed never to have been contaminated by Moorish, Jewish, or other foreign admixture; the expression probably originated in the blueness of the veins of people of fair complexion as compared with those of dark skin." This was eloquently evoked by Robert Browning: "Blue as a vein o'er the Madonna's breast."<sup>1</sup> Long before the blood groups and their genetics were known, blood was popularly treated as the typical component of the body which is inherited from parents and ancestors; hence blood in this sense denotes family, kindred, or race. The blueness of veins seen through translucent, lightly pigmented skin is partly due to scattering of light at the blue end of the visible spectrum when reflected against the dark veins beneath, much as the sky is blue against the blackness of outer space.—B J FREEDMAN.

1 Browning, R. The Bishop orders his tomb at St Praxed's Church. In: *Dramatic Romances and Lyrics*, 1845.