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(Accepted 13 June 1990)

Management of isolated thyroid swellings: a prospective six year study of fine needle aspiration cytology in diagnosis

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Abstract

Objective—To audit the accuracy and impact on the frequency of operation of fine needle aspiration cytology of isolated thyroid swellings.

Design—Prospective analysis over six years of cytological predictions compared with histological findings.

Setting—Thyroid clinic serving the Grampian region.

Patients—395 Consecutive patients presenting with an isolated thyroid swelling, 307 of whom underwent surgical excision. Analysis was confined to a subgroup of 283 patients with satisfactory aspirates who were operated on.

Results—The positive predictive value of aspiration cytology for detecting malignant disease was 100% and the sensitivity 83%. The sensitivity for the detection of neoplasia (frank malignancy together with follicular adenomas) was 76%. The specificity was 58% and the overall accuracy 69%. Recalculation of data in previous papers with strict criteria showed the accuracy of aspiration cytology to be variable and lower than is widely accepted. Since the introduction of aspiration cytology 21% fewer operations for isolated thyroid swellings have been performed.

Conclusions—As a basis of selection for surgical excision of isolated thyroid swellings according to prediction of neoplasia fine needle aspiration cytology is less reliable than is widely accepted. It is an adjunct to management rather than a definitive test, and negative cytological results do not exclude neoplastic disease. Further study should take

account of the implications of repeated clinic attendances for review and aspiration as these may culminate in delayed surgical treatment.

Introduction

Most isolated thyroid swellings are benign, but it is difficult to exclude malignancy without excision and histological examination. A selective surgical policy is clearly desirable, and fine needle aspiration cytology is being increasingly used as its basis. Extensive experience in Sweden,¹⁻³ together with work from other centres,^{1,4-10} suggests an accuracy of over 90%, although some authors have been less confident.^{11,12}

We previously reported the results of a two year prospective study of aspiration cytology in isolated thyroid swellings.¹⁰ During the first year cytological findings were concealed, and they were compared retrospectively with the histological diagnosis, which was available in 96% of cases. Sensitivity for detection of neoplasia was 86% and overall accuracy 92%. During the second year cytological findings were disclosed and used to influence management. The frequency of operation decreased by 25% and the proportion of operations performed for neoplasia increased from 31% to 50%. We continued this prospective evaluation to audit the accuracy and utility of aspiration cytology in our hands.

Patients and methods

In north east Scotland patients with thyroid swellings are with few exceptions referred to one

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Br Med J 1990;301:318-21

surgical team at a joint medical-surgical thyroid clinic. During the six years September 1981 to August 1987 all patients referred with a thyroid swelling were entered in a prospective study. The swelling was classified as isolated, dominant, or generalised on clinical examination. A discrete swelling was termed isolated if the thyroid was otherwise impalpable, and the present study is confined to 395 consecutive patients with such swellings.

FINE NEEDLE ASPIRATION CYTOLOGY

Fine needle aspiration cytology was performed in the outpatient clinic without local anaesthetic using a 21 gauge needle on a 10 ml disposable syringe mounted in a syringe holder. At least two smears were made and stained using the Papanicolaou and May-Grünwald-Giemsa techniques. If the aspirate was fluid smears were made before and after centrifugation. All cytological preparations were examined by one cytologist (VMMW), who also performed all aspirations after the first two years (during the first two years aspirations were performed by one surgeon).

The aspirates were classified into four categories. "Non-neoplastic" aspirates were specimens of low or moderate cellularity in a follicular pattern of whole follicles or monolayered sheets, with follicles of varying size, uniform cell nuclei, and a large amount of colloid and with or without features of degeneration or inflammation. "Possibly neoplastic" aspirates were specimens with increased cellularity in a predominantly microfollicular or trabecular pattern with some loss of cell cohesion and variation in nuclear size, accompanied by little or no colloid. "Malignant" aspirates were specimens containing either differentiated cells with features characteristic of specific malignant tumours or undifferentiated cells with unequivocally malignant nuclei. "Unsatisfactory" aspirates were specimens that yielded insufficient material for diagnosis. Cyst fluid with macrophages and scanty normal epithelial cells was classified as non-neoplastic rather than unsatisfactory.

HISTOLOGICAL EXAMINATION

The results of all histological examinations were reviewed by a pathologist with an interest in thyroid pathology (SWBE). During the course of this study it became routine to examine 10 blocks, if available, from all follicular lesions.

INDICATIONS FOR OPERATION

After the first year, during which the policy was to remove all swellings not permanently abolished by aspiration, a decision to operate was based on clinical criteria (age, sex, texture of swelling, lymphadenopathy, recurrent cysts, and the patient's wishes) together with the result of cytology.

Data were collected prospectively and stored

TABLE II—Diagnoses of 283 isolated thyroid swellings with satisfactory aspirates

Histological diagnosis	"Worst" diagnosis on fine needle aspiration cytology		
	Malignant	Possibly neoplastic	Non-neoplastic
<i>Non-neoplastic (n=118)</i>			
Cystic (n=54)		10 (19)	44 (81)
Solid (n=64)		39 (61)	25 (39)
Total		49 (42)	69 (58)
<i>Neoplastic (n=165)</i>			
Follicular adenoma (n=101)		73 (72)	28 (28)
Cystic (n=32)		14 (44)	18 (56)
Solid (n=69)		59 (86)	10 (14)
Malignant (n=64)	21 (33)	32 (50)	11 (17)
Cystic (n=15)	4 (27)	6 (40)	5 (33)
Solid (n=49)	17 (35)	26 (53)	6 (12)
Total	21 (13)	105 (64)	39 (24)

and analysed using a Honeywell 66/80 mainframe computer and the scientific information retrieval database management system package.

Results

During the six years 395 patients presented with a clinically isolated thyroid swelling (60 men (15%) and 335 women (85%)). Of the swellings, 247 (63%) were solid on aspiration and 148 (37%) yielded fluid and were termed cystic. In all, 307 (78%) patients underwent surgical excision: 106 cystic swellings (72%) and 201 solid swellings (81%) were removed. The 307 isolated swellings removed (table I) comprised 66 carcinomas (51 solid and 15 cystic), 115 follicular adenomas (80 solid and 35 cystic), and 126 non-neoplastic lesions (70 solid and 56 cystic).

In the first year of the study 96% of patients were operated on. In subsequent years a mean of 75% of isolated thyroid swellings were removed (range 66-79%), a reduction of 21%.

The cytological and histological findings in 283 patients with satisfactory aspirates who were operated on are compared in table II. In 24 (8%) patients (eight with non-neoplastic swellings, 14 with follicular adenomas, and two with malignant swellings) aspiration cytology was unsatisfactory. Where more than one satisfactory aspirate was obtained the report most suggestive of neoplasia was used in the analysis.

The accuracy of fine needle aspiration cytology was analysed, firstly for the detection of malignancy and, secondly, for the detection of neoplasia (that is, malignant swellings together with benign neoplasms in the form of follicular adenoma). In 21 patients a cytological diagnosis of malignancy had been made and was confirmed histologically in all (10 papillary, seven follicular, two medullary, one lymphoma, and one anaplastic). The positive predictive value for cytological results classified as malignant was 100%, but the sensitivity was low: 53 (83%) of the 64 malignant swellings with satisfactory aspirates were classified cytologically as malignant (33%) or possibly neoplastic (50%), and 11 (17%) were diagnosed incorrectly as non-neoplastic.

Of the 165 removed neoplastic lesions (frank malignancy or follicular adenomas) with satisfactory aspirates, 126 (76%) were correctly predicted as either possibly neoplastic or malignant. Of 101 follicular adenomas, 73 (72%) were correctly classified cytologically as possibly neoplastic and 28 (28%) were erroneously classified cytologically as non-neoplastic. Of 118 non-neoplastic lesions with satisfactory aspirates, 69 (58%) were correctly identified. The positive predictive value was 72%, and when the cytological results were reported as non-neoplastic they were accurate in 64% of swellings subsequently removed.

TABLE I—Histological and physical characteristics of isolated thyroid swellings removed from 307 patients. Values are numbers (percentages)

Diagnosis	Solid (n=201)	Cystic (n=105)	Total (n=307)
Non-neoplastic	70 (35)	56 (53)	126 (41)
Colloid degeneration	41 (20)	18 (17)	59 (19)
Chronic lymphocytic thyroiditis	2 (1)	1 (1)	3 (1)
Colloid adenoma	27 (13)	19 (18)	46 (15)
Simple cyst		18 (17)	18 (6)
Neoplastic	131 (65)	50 (47)	181 (59)
Benign:			
Follicular adenoma	80 (40)	35 (33)	115 (37)
Malignant:			
Follicular carcinoma	26 (13)	5 (5)	31 (10)
Papillary carcinoma	16 (8)	6 (6)	22 (7)
Medullary carcinoma	4 (2)	1 (1)	5 (2)
Anaplastic carcinoma		1 (1)	1 (<1)
Lymphoma	2 (1)		2 (<1)
Hürthle cell carcinoma	1 (<1)	2 (2)	3 (1)
Metastatic carcinoma	2 (1)		2 (<1)

Excluding unsatisfactory aspirates, the overall accuracy for removed swellings was 69% (sensitivity 76%, specificity 58%).

We emphasise that this analysis was based on incomplete information as 28% of cases were not included (those with no histological results or with unsatisfactory results on fine needle aspiration cytology) and the quoted accuracy may be regarded as only approximate. The positive predictive value is a true value, but the other values may be overestimates of accuracy for the whole group of 395 patients. Data were analysed in this way to allow comparison with other studies.

When data were analysed separately for removed solid and cystic swellings sensitivity was higher in solid swellings (86% v 51%) but the specificity lower (39% v 81%).

Of the cytological features that were regarded as suspicious of neoplasia, increased cellularity alone was found to be the least reliable (57%). Nuclear pleomorphism when present either alone (76%) or together with increased cellularity (83%) was more reliable in predicting neoplasia.

Discussion

The reported accuracy of fine needle aspiration cytology in thyroid swellings varies, but there seems to be a consensus that it is a reliable technique with low false positive and false negative fractions.¹⁻⁷ The results of the present analysis were therefore disappointing, particularly in view of our previous more favourable report,¹⁰ and prompted a critical evaluation of other papers. There is great disparity between studies in the clinical nature of the swellings included (that is, multinodular, isolated, or dominant) and the frequency of operation. The percentage of aspirated swellings that were ultimately excised ranged from 20% to 100%, the incidence of malignancy in excised swellings from 4% to 38%, and the incidence of neoplasia from 25% to 80%. In only one paper were isolated swellings identified separately,⁴ and few authors differentiated between cystic and solid swellings.

The methods used to calculate accuracy also varied. In several papers the calculation of false negative and positive rates was based on the whole series as the denominator⁴⁻⁶ whereas in others the total number of patients operated on was used.^{1,7,13} Few authors used, as we did on this occasion, the number of patients with histologically diagnosed non-neoplastic or neoplastic lesions as the respective denominators of specificity and sensitivity. As Frable and Frable pointed out, the use of a whole series of heterogeneous swellings as the denominator has a profound effect on the false positive and negative fractions and particularly so if only a small percentage of swellings has been removed.⁵ In calculating the false negative rate several authors included

only "malignant" cytological results in determining the numerator, excluding the "possibly neoplastic" group,^{7,14} whereas others included both groups.⁶ Depending on the definitions used the apparent accuracy may be spuriously high. In addition, follicular adenomas are variably included in analyses together with non-neoplastic lesions as benign^{12,14} or together with malignant lesions as neoplastic,^{4,6} and accuracy varies accordingly.

The inability to distinguish cytologically between follicular adenoma and follicular carcinoma is widely accepted.^{2,5,15,16} Meticulous histological examination of multiple blocks for evidence of invasion of the capsule or blood vessels is the only basis on which a confident diagnosis of follicular carcinoma rather than follicular adenoma may be made. The recent finding that DNA aneuploidy—widely held to be a feature of malignancy—often occurs in follicular adenomas as well as carcinomas^{17,18} is additional support for the view that follicular neoplasia should be regarded and treated as a single entity. The aim of preoperative investigation should therefore be to distinguish neoplastic from non-neoplastic lesions, and cytology should be assessed accordingly. We have recalculated the accuracy of cytology using this convention in a series of papers that gave sufficiently detailed data (table III). Sensitivity ranged from 46% to 94% and specificity from 44% to 94%. On this basis fine needle aspiration cytology is not the definitive diagnostic technique that has been claimed.

Cytological accuracy in our hands seems to have decreased between the first two years of the study reported earlier¹⁰ and our current analysis. This is accounted for almost entirely by retrospective histological review of all removed swellings. In the earlier study routine histological reports were accepted and consistent histological criteria were not applied. When the accuracy of fine needle aspiration cytology during 1981-2 was recalculated on the basis of revised histological results and exclusion of swellings in which these results were not available it fell from 92% to 85% and in 1982-3 from 84% to 65%.

We have not been able to match the experience of Hamberger *et al*, who found that with the use of aspiration cytology operations for isolated thyroid swellings declined from 67% to 43%.¹⁹ Although we performed 21% fewer operations during the course of this study, we still operate on 75% of patients with isolated swellings, and 59% of these are neoplastic.

Of 109 patients whose first satisfactory aspirate was classified as non-neoplastic and who underwent repeat aspiration, 68 ultimately came to operation. In 36 of these the histological diagnosis was one of neoplasia (28 follicular adenomas and eight carcinomas). The median delay from first non-neoplastic aspirate to operation in this group of patients with neoplastic lesions was three months (range 1-28 months).

In all 11 cases in which a malignant swelling had

TABLE III—Reanalysis of accuracy of fine needle aspiration cytology in patients with satisfactory cytological preparation and histological examination

Study	Date	No of patients operated on	% Of patients in series operated on	% Neoplastic	% Malignant	Sensitivity*	Specificity†	Accuracy‡	Negative predictive value§	Positive predictive value¶
Walfish <i>et al</i> ¹¹	1977	83	62	65	18	93	72	86	84	86
Gershengorn <i>et al</i> ¹²	1977	32	64	66	38	62	91	72	56	93
Schnurer and Widstrom*	1978	284	?	31	10	91	94	93	96	87
Lowhagen <i>et al</i> ¹	1979	412	100	63	23	66	90	75	61	91
Chu <i>et al</i> ⁶	1979	109	33	51	26	46	96	71	63	93
Frable and Frable ⁵	1980	132	?	26	15	91	98	96	97	94
Rosen <i>et al</i> ⁷	1981	144	40	80	27	89	62	83	58	90
Silverman <i>et al</i> ⁸	1986	57	19	72	4	83	44	72	50	79
Franklyn <i>et al</i> ⁴	1987	17	20	47	12	88	78	82	88	78
Current series	1990	283	72	58	23	76	58	69	64	72

*Sensitivity= ratio of true positive results to all patients with disease: if there is a cancer (or neoplasm) what is the probability that the test will detect it?

†Specificity= ratio of true negative results to all patients without disease: if there is not a cancer (or neoplasm) what is the probability that the test will confirm it?

‡Accuracy= ratio of true positive and true negative results to the total number of patients; fraction of test results that are correct.

§Negative predictive value= ratio of true negative results to predicted negative results.

¶Positive predictive value= ratio of true positive results to predicted positive results.

been reported cytologically as non-neoplastic the cytological specimens were reviewed. In one case from the first year of the study a retrospective cytological diagnosis of papillary carcinoma was made, but in all other cases there were no cytological features suggesting neoplasia, although in two cases the specimens would now be classed as unsatisfactory.

Aspiration cytology is an adjunct to the management of thyroid swellings but is not a definitive diagnostic test and, in particular, negative results do not exclude neoplastic disease. Definition of an optimum management policy depends on further study, which should include the financial and psychological implications of repeated clinic attendances and of repeated aspiration, which may culminate in delayed surgical treatment.

We gratefully acknowledge financial support from the Scottish Hospitals Endowment Research Trust and the assistance of the Aberdeen University Computing Centre.

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(Accepted 15 June 1990)

Activities of aminotransferases after treatment with streptokinase for acute myocardial infarction

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Br Med J 1990;301:321-2

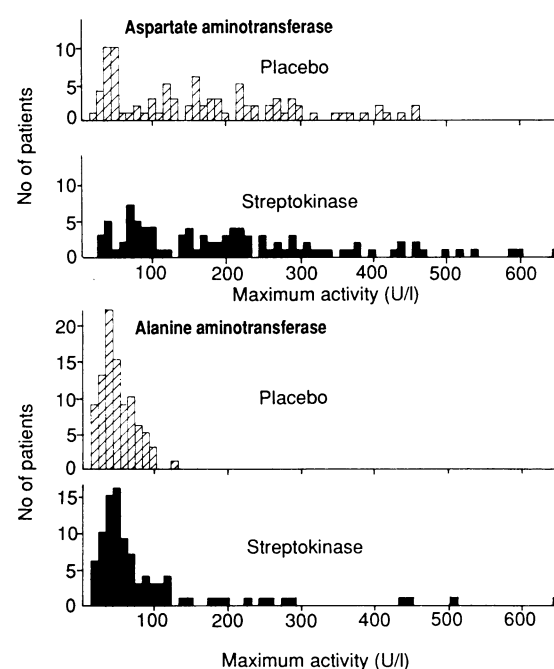
Treatment with streptokinase can increase the serum activities of aspartate aminotransferase and alanine aminotransferase.^{1,2} We examined the activities of aminotransferases in patients who had been treated with streptokinase for acute myocardial infarction to determine the incidence and clinical relevance of this drug reaction.

Subjects, methods, and results

We examined the case records of 189 patients from Dumfries and Galloway Royal Infirmary who had been entered into the second international study of infarction (ISIS 2)—a placebo controlled trial of streptokinase and aspirin in patients who had had a suspected acute myocardial infarction.³ Of our patients, 95 (64 men, 31 women; mean age 58.9 (SD 8.38) years) had received streptokinase and 94 (71 men, 23 women; mean age 56.8 (8.52) years) had received placebo. Venous blood had been taken for assay of enzyme activity on admission to hospital and then once daily for 72 hours.

The figure shows the distribution of the peak activities of aminotransferases as determined from the case records (normal range: aspartate aminotransferase 13-42 U/l, alanine aminotransferase 11-50 U/l). The geometric mean of the peak activity of aspartate aminotransferase was 157 U/l for patients who received streptokinase and 120 U/l for those who received placebo ($p < 0.05$; ratio 1.31, 95% confidence interval 1.02 to 1.66). The corresponding values for alanine

aminotransferase were 60 U/l and 43 U/l ($p < 0.05$; 1.40, 1.15 to 1.76). There was no significant difference in enzyme activity between men and women given streptokinase or between patients given aspirin and those given placebo for aspirin. (Patients in the streptokinase and placebo groups had also been randomised to receive aspirin or a placebo for aspirin.) Of the patients who received streptokinase, 79 had had myocardial infarctions, with 66 showing typical changes on electrocardiography and 71 having increased activity of β -hydroxybutyrate dehydrogenase. Of the patients who received the placebo for streptokinase, 73 had had infarcts, with 61 showing changes on electrocardiography and 64



Distribution of maximum enzyme activities after treatment with streptokinase or placebo