Prospective evaluation of fine needle aspiration in the diagnosis of lung cancer

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ABSTRACT The role of fine needle aspiration biopsy has been assessed prospectively in the diagnosis of discrete lung shadows. A questionnaire was completed before each of 100 biopsies (in 97 patients) to determine the clinician's pretest diagnosis and the likelihood of malignancy. The latter estimates were combined with the previously established sensitivity (71%) and specificity (100%) of the procedure for diagnosing malignancy in the unit to allow calculation in each case of the change in certainty of malignancy as a result of the investigation. Among the 100 biopsies there were 73 true positive and 13 true negative results. There were no false positive results but there were 14 false negatives (cases where malignancy was later proved but where the biopsy did not show unequivocal evidence of malignancy). Among the 27 negative biopsy results the clinician had estimated the likelihood of malignancy as 80% or more in 13 cases. In 11 of these 13 patients the eventual diagnosis proved to be a malignant tumour; on the other hand, six of the 10 patients given a less than 50% chance of malignancy had a benign outcome. A positive biopsy result was therefore quantitatively of greatest value when the prior estimate of malignancy was low. In the case of the false negative results the prior probability of malignancy was usually sufficiently high to merit further investigation. It is estimated that the procedure led to the avoidance of thoracotomy in up to 14 of 97 patients.

Introduction

Fine needle aspiration biopsy of lung lesions was first used 100 years ago,¹ but the procedure has become established only in the last 20 years. There are several reports of the application of the technique but all are retrospective.²⁻⁴

Appropriate selection and interpretation of diagnostic procedures is helped by combining the principles of diagnostic reasoning with knowledge of the characteristics (sensitivity, specificity) of the test.⁵ The intelligent use of information generated by a procedure requires the clinician to be aware of the uncertainties that exist before the procedure and how much the procedure will reduce these uncertainties. Hence the probability of a disease once the results of a

diagnostic test are known depends on the pretest probability and on the characteristics of the test in question.⁵

Theory

The sensitivity and specificity of a test for identifying a disease in a population of patients are calculated from the number of results that are true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN). Sensitivity represents the proportion of patients with the disease in whom the result of the test is positive—that is, $TP/(TP + FN)$ —and specificity the proportion of patients without the disease in whom the result is negative—that is, $TN/(TN + FP)$.⁵ The sensitivity and specificity, however, indicate only the proportions of a series of patients with the disease who will have a positive or negative result; they do not predict the value of the test in an individual. This information can be calculated by combining a knowledge of the test characteristics with

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Table 1 Application of a test for malignancy with a sensitivity of 71% and specificity of 100% to a patient with a prior probability of malignancy of 30%

	% of similar patients	
	with tumour	with no tumour
Clinician's estimate	30	70
Test result will be:		
positive	21.3 (TP)	0 (FP)
negative	8.7 (FN)	70 (TN)
Predictive value of:		
positive result	$\frac{TP}{TP + FP} = \frac{21.3}{21.3 + 0} = 100\%$	
negative result	$\frac{TN}{TN + FN} = \frac{70}{70 + 8.7} = 89\%$	

TP, true positive; FN, false negative; FP, false positive; TN, true negative.

the clinician's prior estimate of the likelihood of disease in the individual patient based on history, examination, and results of previous investigations.⁵

In the example shown in table 1 we have taken a diagnostic test with a previously established specificity for malignancy of 100% and sensitivity of 71% and have assessed the value of the test in a patient in whom the clinician estimated the chance of malignancy to be relatively low at 30%. This is taken to imply that, in the clinician's judgment, in a large "population" of such patients 30% would have a malignant tumour. As the specificity of the test is 100%, no false positive results are anticipated; so the 70% with no tumour would all have a negative result. As the sensitivity of the test is 71%, a true positive result would be expected in 71% of the 30% with a tumour (21.3%) and 8.7% would have a false negative result. In this example (table 1) the predictive value of a positive result ($TP/(TP + FP)$) is 100% and of a negative result ($TN/(TN + FN)$) 89%. If a negative result is obtained, then, as the clinician was 70% certain of the absence of malignancy before the test and 89% certain after the test, the certainty has increased by 19%; this increase is termed the "ruling out gain." On the other hand, if the result is positive, the likelihood of malignancy would be increased from 30% to 100%, a "ruling in gain" of 70%.⁵

The most important aspect of a diagnostic test is whether it leads to a change in clinical management, and this is impossible to assess from a retrospective analysis. We therefore set out to examine the use of fine needle aspiration by prospective study in an attempt to define the value of the investigation for an individual patient.

Methods

To define the sensitivity and specificity of fine needle

aspiration biopsy for malignancy in our unit we first performed a retrospective analysis of 95 consecutive biopsy procedures. The outcome in these patients was confirmed by operation, necropsy, or progress during follow up for at least one year.

We then devised a questionnaire to analyse prospectively the place of fine needle aspiration in the diagnostic work up of a further cohort of patients with peripheral radiographic lung shadows. The referring clinician was asked to indicate the diagnosis he suspected on the basis of clinical assessment and the results of tests up to that point, and to estimate (to the nearest 10%) the probability that the lesion under investigation was malignant. A further question inquired about likely operability on the evidence available so far. Each questionnaire was completed by a consultant surgeon or physician or a senior registrar in respiratory medicine responsible for the patient's management. The final outcome was confirmed either at operation (33 cases), by further investigation (16 cases), or from the patient's subsequent clinical course over at least 12 months after the biopsy (48 cases).

The needle biopsies were performed under biplanar screening with one to three passes of a 22 gauge needle into the lesion. A cytology technician was at hand to prepare slides from the specimens obtained, and he was able to inform the operator whether they were of adequate cellularity.

Results

In the retrospective series of 95 biopsies there were 52 true positive results, 22 true negative results, and 21 negative biopsies where malignancy was subsequently proved (false negative results). No results were falsely positive for malignancy. The sensitivity of the test was therefore 71% and the specificity 100% (table 1).

In the prospective study 97 patients were entered from July 1984 to January 1986. The patients were referred consecutively by physicians and surgeons at Freeman Hospital. Questionnaires were completed twice for each of three patients undergoing needle biopsy on two occasions (after an initially negative result), thus making a total of 100 questionnaires for analysis. Forty seven of the patients were under investigation by physicians and 50 patients by surgeons. There were 36 women and 61 men, with a mean age of 60.6 (range 31–78) years.

Cytological examination of 73 of the 100 specimens showed unequivocally malignant cells: each of these was a true positive result with malignancy subsequently confirmed on further investigation, treatment, or follow up. Thirteen patients had true negative results: in eight of these the biopsy gave a definitive negative result indicating a non-malignant condition; in the other five the results were inconclusive but showed no

Fig 1 Clinician's prediction of the likelihood of malignancy and subsequent result of fine needle biopsy.

evidence of malignancy. On 14 occasions a false negative result was obtained, although in three of these cases the cytological appearances were reported as "suspicious of malignancy."

COMPARISON OF DIAGNOSIS BEFORE AND AFTER BIOPSY

A single diagnosis was suspected in 86 of the 100 questionnaires and in 63 this was a primary malignant tumour. In 14 instances more than one possible diagnosis was indicated, the commonest combination being tumour and tuberculosis (table 2).

The pre-test probability of malignancy (fig 1) was estimated to be 90% or more in 51 cases. On only 20 occasions was the patient considered to have a 50% chance or less of having a malignant tumour.

The final diagnoses (fig 1) showed that in general the clinicians' estimates of the likelihood of malignancy were accurate. Of the 87 patients who eventually proved to have malignant tumours, 71 were rated before the procedure as having a 70% or greater chance of malignancy; six of 10 patients given a less than 50% chance of malignancy did indeed prove to have a benign condition.

Combining the sensitivity and specificity of the test (calculated from the retrospective series) with the clinician's estimate of malignancy in each case allowed calculation of the incremental gain for each patient deriving from the result of the test (fig 2). Because of the high pre-biopsy probability of malignancy in most of the 73 patients with true positive results, the "ruling in" gain was generally small, being 10% or less in 40 cases. In the 14 false negative cases the "gain" was negative (fig 2)—that is, the result of the test reduced the certainty of malignancy. In 11 of these 14 patients, however, the prior estimate of malignancy was 80% or

greater; so the clinician was usually still left with a fairly high probability of malignancy.

Of the 13 patients with true negative results, nine had been assessed before biopsy as having a probability of malignancy of only 50% or less (fig 1); so the ruling out gain in these cases was small (fig 2).

Combining the results of our retrospective and prospective series gave 125 true positive, 35 true negative, and 35 false negative results; so for the combined series the sensitivity was 78% and the specificity 100%. The sensitivity of the test in the prospective series was 84%, possibly owing to greater experience with the technique.

ASSESSMENT OF OPERABILITY

Sixty two patients were judged operable on clinical grounds before undergoing needle biopsy, but in only 31 was surgery subsequently performed (table 3). Of the remaining 31 patients, six had a true negative biopsy result. The other 25 had a true positive biopsy

Table 2 Pre-biopsy diagnoses

Single diagnosis suspected
Primary tumour
Secondary tumour
Benign tumour
Tuberculosis
Abscess
Total
Two or more diagnoses indicated
Primary tumour or tuberculosis
Primary or secondary tumour
Primary or benign tumour
Primary or secondary tumour or chronic inflammation
Tuberculosis or benign tumour
Tuberculosis or chronic inflammation
Abscess or benign tumour
Total

Fig 2 Positive and negative "gain" calculated from the prior probability of malignancy related to the final diagnosis.

result but surgery was considered inappropriate because of the cytological result, because further investigation showed evidence of the spread of malignancy, or because the patient was thought to be unfit for surgery.

Discussion

We have analysed the value of fine needle aspiration biopsy prospectively, using the results of a questionnaire administered before the test. One important consideration is that, for the type of patient submitted to such a biopsy in our unit, clinicians' estimates of the likelihood of malignancy have a high level of accuracy and the value of the investigation has to be interpreted against that background. Personal experience with similar patients is probably the most important influence on probability estimates. In this series only four patients who were subsequently found to have a malignancy were given a less than 50% chance of having a malignant lesion. Similarly, on only four occasions was there a benign outcome when the prior estimate of malignancy was 50% or more. No consistent differences in the accuracy of prediction were found between individual physicians and surgeons.

We took as a negative result any biopsy report where the cytologist found no specific features of

malignancy. Three of the 14 "false negative" reports indicated the presence of cells "suspicious of malignancy": in seven cases necrotic material was seen and the report indicated the possibility that the sample had come from the centre of a necrotic tumour. In keeping with the earlier studies,^{6,7} five of these seven patients were subsequently shown to have malignant tumours. The definition of a "false negative" report was therefore strict, and if suspicious features had been accepted as indicating malignancy the false negative rate would have been reduced from 14% to 4%, but at the expense of a false positive rate of 2% rather than zero.

The use of fine needle aspiration biopsy in patients with a very high likelihood of malignancy has been justified on the grounds that the diagnosis of a small cell tumour is an important distinction.⁸ Only three of our 97 patients had small cell lung cancer, however, and in one of these fine needle aspiration biopsy produced a false negative result, the tumour subsequently being diagnosed by fiberoptic bronchoscopy. Small cell lung cancers are most commonly centrally placed and, as peripheral small cell tumours do not necessarily have a bad prognosis after resection,⁹ preoperative identification of the cell type of peripheral bronchial carcinomas is probably of less importance than might appear at first sight.

The true value of an investigation depends on whether it results in a change in management of the patient.⁵ In our prospective series of 97 patients we estimate that thoracotomy may have been avoided as a result of the biopsy in as many as 12 patients (table 3); in a further two patients the finding of small cell carcinoma at biopsy was a contributory factor in deciding not to operate.

The analysis presented here represents a formal

Table 3 Reasons for not proceeding with surgery in 31 patients

Biopsy result	14
Benign condition	6
Secondary tumour	5
Hodgkin's lymphoma	1
Small cell carcinoma	2
Subsequent information	17

exposition of the diagnostic process, where the value of an investigation in certain types of patients may be intuitively obvious. We have shown how such intuitive conclusions may be quantified so that the role of fine needle aspiration biopsy can be evaluated and the indications for its use refined. The results of investigation are inevitably dependent on the population of patients studied, but as this analysis combines information about the patients with characteristics of the test it would also facilitate comparisons of the uses and yield of the investigation in different centres.

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