

Diagnostic accuracy of cytology and biopsy in primary bronchial carcinoma

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SUMMARY The accuracy of diagnosis in 656 patients with the four common histopathological types of primary lung cancer has been assessed by comparing the cell type diagnosis made on cytological and histological investigation with that determined by examination of the surgically resected or necropsy specimen. The accuracy of diagnosis achieved by cytological examination of sputum and bronchial aspirate, and by bronchial biopsy histology was over 85%. The least accurate diagnostic procedure was percutaneous needle biopsy (62%). Squamous and small cell tumours were accurately diagnosed by all four investigations but errors were made in the diagnosis of large cell and adenocarcinomas. Nearly half the number of patients (43%) with large cell carcinoma were later reclassified as having squamous carcinoma and of the patients with adenocarcinoma 32% had been predicted to be squamous and 18% large cell carcinoma. We consider such quality control of pretreatment diagnosis mandatory in management of individual patients and before enrolment in clinical trials.

In 1979 a study was reported from Papworth Hospital, Cambridge which examined the accuracy of diagnosis of cell type in patients with primary lung cancer.¹ The presumptive cell type as predicted by cytology and biopsy techniques was compared with the true histological cell type as determined by histological examination of tumour tissue obtained at surgical resection or necropsy. The results indicated that the true cell type was most accurately predicted by sputum cytology (88%), closely followed by bronchial aspiration (84%) and bronchial biopsy (80%). The least accurate procedure was percutaneous needle biopsy (48%). Diagnostic accuracy was highest in patients with squamous cell carcinoma while particular difficulty was experienced in diagnosis of patients with adenocarcinoma.

Inevitably, with such a study limited to a four-year period in a single hospital, the number of patients in each histological group was relatively small. We have therefore undertaken a larger study of 673 patients with confirmed lung cancer seen at two centres, Papworth Hospital, Cambridge and Brompton Hospital, London and this includes the results of the original work from Papworth.

Material and methods

We have reviewed the results of cytological and histological investigation in a series of consecutive patients with primary lung cancer seen at Papworth and Brompton Hospitals in the years 1974-1979 inclusive and who had surgical resection or necropsy examination. Tissue for final diagnosis was obtained by thoracotomy in 603 patients and at necropsy in 69 patients, the "true histological cell type" being taken to be that of the resected or necropsy specimen. The "presumptive histological cell type" was that reported in the four investigative methods studied; cytological examination of sputum and bronchial aspirate, histological examination of bronchial biopsy, and cytology of percutaneous needle aspiration biopsy. All patients had one or more of these investigations.

CYTOLOGY OF SPUTUM AND BRONCHIAL ASPIRATE

The number of sputum samples obtained from each patient ranged from one to eight and cytology results were included in the study only if the sputum specimen contained alveolar macrophages as an indication of pulmonary origin. Smears of sputum

and centrifuged deposit of bronchial aspirate were stained with Papanicolaou's stain at Papworth and with methylene blue at Brompton.

BRONCHIAL BIOPSY

Bronchoscopies were carried out with either a rigid or fiberoptic bronchoscope. Bronchial biopsy material was formalin-fixed and embedded in paraffin. Sections were routinely-stained with haematoxylin, phloxine and saffron at Papworth and with haematoxylin and eosin at Brompton. Additional stains for mucin were performed when considered necessary.

PERCUTANEOUS NEEDLE BIOPSY

Percutaneous biopsies were carried out with either a short bevelled 19 gauge aspiration needle or a Nordenstrom biopsy needle.² Smears were prepared and stained with Papanicolaou's stain and methylene blue at Papworth and Brompton respectively.

Nomenclature

The carcinomas were classified histologically into squamous, small cell, adenocarcinoma and undifferentiated large cell carcinoma. The criteria for diagnosis were similar to those of Payne *et al.*¹ and were in general agreement with those recommended for the first four common histopathological types of the World Health Organisation (WHO) classification.³ The pathologists at the two hospitals worked independently, but established subsequently that they had adopted the same criteria for cell typing. Sections and cytological smears were reported independently.

Less common tumours corresponding to Types V to XIII of the WHO classification were not included in the present study. The cytological classification was the same as the histological and was based on the diagnostic criteria employed by Koss⁴ and Naib.⁵

Results

The results of investigation of 673 patients were examined initially. The true cell type as determined by histological examination of the resected or necropsy specimen was squamous carcinoma in 415 (62%), small cell carcinoma in 49 (7%), adenocarcinoma in 145 (22%), and large cell undifferentiated in 47 (7%). In addition, seven patients (1%) had a true mixed adenosquamous carcinoma, eight (1%) had bronchioloalveolar carcinoma and two (0.3%) had alveolar cell carcinoma but these have been excluded from the study as explained above. Of 656 patients analysed, 387 (59%) had cytological examination of sputum, 342 (52%) cytological examination of bronchial aspirate, 379 (58%) histological examination of bronchial biopsy and 82 (13%) cytological examination of percutaneous needle biopsy specimens.

We examined the results from both centres separately and found them to be in general agreement and therefore we feel justified in combining the results in this study to obtain the benefit of greater numbers.

DIAGNOSTIC YIELD OF EACH METHOD OF INVESTIGATION

It was not the main purpose of this study to examine the yield from these investigations since not all patients had all four investigations. However, comparisons of different techniques must be based on both yield and accuracy and the yield of each investigation is, therefore, presented in Table 1. Percutaneous needle biopsy was the most successful method for obtaining confirmatory evidence of carcinoma, malignant cells being found in 66 (80%) of 82 patients. Malignant cells were likewise seen in 67% of 379 patients investigated by bronchial biopsy, in 42% of 387 patients investigated by sputum cytology and in 37% of 342 patients in-

Table 1 Yield obtained with each method of investigation

Investigation	True histological cell type				
	Squamous	Small cell	Adenocarcinoma	Large cell	Total
Sputum cytology					
No tested	231	31	92	33	387
No showing malignancy	116 (50)	12 (39)	25 (27)	8 (24)	161 (42)
Bronchial aspirate					
No tested	227	27	73	15	342
No showing malignancy	103 (45)	10 (37)	10 (14)	3 (20)	126 (37)
Bronchial biopsy					
No tested	280	28	50	21	379
No showing malignancy	199 (71)	22 (79)	24 (48)	9 (43)	254 (67)
Percutaneous biopsy					
No tested	40	2	32	8	82
No showing malignancy	37 (93)	2 (100)	21 (66)	6 (75)	66 (80)

Percentages in parentheses.

vestigated by cytological examination of bronchial aspirate. In a small number of patients with positive bronchial biopsies at Brompton Hospital, the bronchial aspirate was not examined cytologically and this will have resulted in a lower yield than expected from this method of investigation.

With all four investigative procedures, the yield of malignant cells was lowest in those patients with adenocarcinoma or large cell undifferentiated tumours.

DIAGNOSTIC ACCURACY OF EACH METHOD OF INVESTIGATION

Tables 2-5 present the likelihood of a positive cell type diagnosis obtained on investigation being correct when compared to the tissue cell type as determined by surgical resection or necropsy examination.

Since the presumptive histological cell type is often based on very small samples, the reports for the large cell carcinoma group, particularly at the Brompton, are often worded "carcinoma with large cells." This is to ensure that the clinician appreciates that the tumour may be reclassified when a larger surgical specimen is obtained. In this paper a presumptive diagnosis of carcinoma with large cells has been incorporated into the large cell carcinoma group.

Sputum cytology (Table 2)

Malignant cells were seen in 161 patients investigated by cytological examination of sputum. The presumptive cell type agreed with the true histological

diagnosis in 143 (89%). For a predicted diagnosis of squamous cell carcinoma, small cell or adenocarcinoma, the accuracy of diagnosis was good (91-94%), but of 12 predicted diagnoses of large cell carcinoma, only five (42%) were correct. Four of this group had squamous tumours and three had adenocarcinoma.

Bronchial aspirate (Table 3)

Carcinoma was diagnosed by cytological examination of bronchial aspirate in 126 patients and in 108 (86%) the presumptive cell type agreed with the final diagnosis. The cell type was correct in 96 (93%) of 103 patients with a predicted diagnosis of squamous carcinoma and in all of seven patients with a predicted diagnosis of small cell carcinoma. However, where the diagnosis was adenocarcinoma on investigation, only three (50%) of six were correct, two patients having small cell carcinoma and one having squamous carcinoma, and for a presumptive diagnosis of large cell carcinoma, only two (20%) agreed with the final histology, six patients having squamous tumours and two having adenocarcinoma.

Bronchial biopsy (Table 4)

In 254 patients carcinoma was diagnosed by bronchial biopsy and the cell type was correctly predicted in 233 (92%). All 21 presumptive diagnoses of small cell carcinoma were correct. Of 203 patients with a predicted cell type of squamous carcinoma, 193 (95%) agreed with the final diagnosis, seven patients having adenocarcinoma and three large cell carcinoma. Eighty-two per cent of 17 patients diagnosed

Table 2 Accuracy of sputum cytology (161 cases with a diagnosis of malignancy on cytological examination of sputum)

Presumptive cell type	No of patients	True histological cell type			
		Squamous	Small cell	Adenocarcinoma	Large cell
Squamous	120	111 (93)	1	6	2
Small cell	12	1	11 (92)	0	0
Adenocarcinoma	17	0	0	16 (94)	1
Large cell	12	4	0	3	5 (42)

Percentages in parentheses.

Table 3 Accuracy of bronchial aspirate cytology (126 cases with a diagnosis of malignancy on cytological examination of bronchial aspirate)

Presumptive cell type	No of patients	True histological cell type			
		Squamous	Small cell	Adenocarcinoma	Large cell
Squamous	103	96 (93)	1	5	1
Small cell	7	0	7 (100)	0	0
Adenocarcinoma	6	1	2	3 (50)	0
Large cell	10	6	0	2	2 (20)

Percentages in parentheses.

Table 4 Accuracy of bronchial biopsy histology (254 cases with a diagnosis of malignancy on histological examination of bronchial biopsy)

Presumptive cell type	No of patients	True histological cell type			
		Squamous	Small cell	Adenocarcinoma	Large cell
Squamous	203	193 (95)	0	7	3
Small cell	21	0	21 (100)	0	0
Adenocarcinoma	17	1	1	14 (82)	1
Large cell	13	5	0	3	5 (38)

Percentages in parentheses.

as having adenocarcinoma were correctly diagnosed but in only five (38%) of 13 patients was a presumptive diagnosis of large cell carcinoma correct. Five of this group had squamous carcinoma and three adenocarcinoma. Separate analysis of bronchial biopsy results showed no significant differences in either yield or accuracy between rigid bronchoscopy and fiberoptic bronchoscopy.

Percutaneous needle biopsy (Table 5)

Of 66 patients having percutaneous needle biopsy, the presumptive diagnosis was correct in 41 (62%). A predicted diagnosis of squamous carcinoma was correct in 29 (73%) of 40 patients, eight having adenocarcinoma and three large cell carcinoma at surgery or necropsy. All seven presumptive diagnoses of adenocarcinoma were correct but of 16 patients diagnosed as having large cell carcinoma, only three (19%) were correctly diagnosed, seven having squamous tumours and six adenocarcinoma.

ACCURACY OF DIAGNOSIS OF EACH HISTOLOGICAL TYPE (Table 6)

Patients with squamous cell carcinoma

The accuracy achieved in diagnosis of patients with squamous cell carcinoma was uniformly high. Over 90% of those patients investigated by sputum cytology, bronchial aspirate, and bronchial biopsy were correctly diagnosed, as were 81% of those investigated by percutaneous needle biopsy. Twenty-six tumours in this group were later reclassified, large cell carcinoma had been the presumptive diagnosis in 22. Two other patients were incorrectly diagnosed as having adenocarcinoma and two as having small cell carcinoma.

Patients with small cell carcinoma

Ninety-five per cent of 22 patients with small cell carcinoma investigated by bronchial biopsy and 92% of 12 patients investigated by sputum cytology

Table 5 Accuracy of percutaneous needle aspiration cytology (66 cases with a diagnosis of malignancy on cytological examination of percutaneous needle aspirate)

Presumptive cell type	No of patients	True histological cell type			
		Squamous	Small cell	Adenocarcinoma	Large cell
Squamous	40	29 (73)	0	8	3
Small cell	3	1	2 (67)	0	0
Adenocarcinoma	7	0	0	7 (100)	0
Large cell	16	7	0	6	3 (19)

Percentages in parentheses.

Table 6 Accuracy of diagnosis of each histological type

True histological cell type	Sputum cytology			Bronchial aspirate			Bronchial biopsy			Percutaneous biopsy		
	No positive	No correct	% correct	No positive	No correct	% correct	No positive	No correct	% correct	No positive	No correct	% correct
Squamous	116	111	96	103	96	93	199	193	97	37	29	78
Small cell	12	11	92	10	7	70	22	21	95	2	2	100
Adenocarcinoma	25	16	64	10	3	30	24	14	58	21	7	33
Large cell	8	5	63	3	2	67	9	5	56	6	3	50

were correctly diagnosed. Both patients who had percutaneous biopsy for peripheral small cell tumours were correctly predicted but only seven of 10 bronchial aspirate results were correct, the predicted cell type being adenocarcinoma in two and squamous carcinoma in one.

Patients with adenocarcinoma

The accuracy of diagnosis of patients with adenocarcinoma was poor. Only 64% examined by sputum cytology, 30% by bronchial aspirate, 58% by bronchial biopsy and 33% by percutaneous needle biopsy were correctly diagnosed. The incorrect presumptive diagnosis in two thirds of these patients was squamous carcinoma and in one third, large cell carcinoma.

Patients with large cell undifferentiated carcinoma

Accurate diagnosis of patients with large cell carcinoma varied from 50% to 67% but the number of positive results in this group was small. Nine out of 11 patients incorrectly diagnosed were thought to have poorly differentiated squamous cell carcinomas, the other two being thought to have adenocarcinoma.

Discussion

It is important to know accurately the true histopathological cell type in cases of primary lung cancer and to know the accuracy of diagnosis achieved by the cytological and histological procedures. In the individual patient it will influence decisions on operability,⁶ and other types of treatment⁷⁻⁹ and will allow prediction of prognosis.^{6 10-12} In addition it is a prime consideration in many therapeutic trials in lung cancer and as such will govern the entry of the individual patient into such trials.

To obtain a sufficient number of patients for analysis we have looked at the results of investigation at two different centres. However, there are inherent problems in such a study. Observer variability in the histopathological diagnosis of lung cancer is well recognised, especially in the interpretation of poorly differentiated carcinomas^{13 14} and this may assume importance with the involvement of different pathologists in two centres, although in our case we have found no major differences of terminology between Papworth and Brompton. The policy at Brompton Hospital of not examining bronchial aspirate material in some patients with a positive diagnosis of carcinoma on bronchial biopsy will have reduced the yield of malignancy by bronchial aspiration but accuracy of diagnosis of cell type should not have been affected.

The frequency of individual cell types in our patients reflects their selection on the basis of surgical resection (90%) and necropsy examination (10%). The distribution is similar to that of other reported series of surgical cases^{15 16} but is obviously unlike that of most trials of chemotherapy or radiotherapy.

Our overall success rate in accurately predicting the true histological cell type by sputum cytology (89%) was similar to that achieved by Mouriquand and Mouriquand (90%)¹⁷ and somewhat better than the results of Oswald *et al.* (82%).¹⁸ We found that the likelihood of a presumptive diagnosis of squamous, small cell, or adenocarcinoma being correct was high but a diagnosis of large cell carcinoma was correct in less than half the patients. It has been suggested that sputum specimens are more accurate than bronchoscopic material for cytological diagnosis¹⁹ but this has not been our experience.

We have examined the likelihood of predicting accurately the cell type in different types of carcinoma. The level of accuracy achieved by sputum cytology, bronchial aspiration, and bronchial biopsy in patients with squamous carcinoma was over 85%. The least accurate procedure was percutaneous aspiration biopsy, though this method was the most effective means of obtaining carcinoma cells. Tao *et al.*²⁰ have recently discussed the problems in diagnosing aspiration cytology specimens and stressed the need for critical retraining in this technique because the appearances differ from those seen in exfoliative cytological preparations. In patients with small cell cancer, accuracy of diagnosis was also high in all investigations except bronchial aspiration, an important factor relevant to non-surgical treatment trials involving patients with this type of tumour.

In contrast, the accuracy of diagnosis of large cell carcinoma and adenocarcinoma was low. Patients with true large cell tumours were frequently thought to have squamous tumours and of those patients with adenocarcinoma, the incorrect diagnosis in two thirds was squamous carcinoma and in one third, large cell carcinoma. This pattern was reflected in the results of each investigative procedure and underlines the difficulties in interpreting the results of therapeutic trials based on cytological or biopsy diagnoses of large cell carcinoma.²¹

In any classification there has to be a group in which to place cases that cannot be classified into any of the other better-defined groups. In the context of this paper the undifferentiated large cell group is this residual group. It is not surprising therefore that a higher proportion of diagnoses based on small samples are reclassified when larger amounts of tissue are available for examination and

occasional areas of squamous or adenocarcinomatous differentiation are seen.

The difficulty in accurate cell typing resulting from the small size of sample in biopsy and cytology specimens is reflected in the underdiagnosis of adenocarcinomas. The diagnostic features of tubules, mucin vacuoles, terminal plates, solid three-dimensional cell clumps, typical nuclei with prominent nucleoli, may well not be present or they may be masked by cell overlap in the limited sample available. One of the outcomes of the earlier paper¹ has been a re-examination of the criteria for diagnosing adenocarcinoma with special attention to tubule formation, terminal plates, and mucin vacuoles.

We consider it mandatory that centres involved in the diagnosis and treatment of bronchial carcinoma should undertake this type of quality control since it not only helps in the management of individual patients but also aids the interpretation of clinical trials of treatment regimens.

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