

Transthoracic Needle Aspiration Biopsy: Accuracy of Cytologic Typing of Malignant Neoplasms

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A correlation was made between the cytologic and the histologic diagnoses in 162 patients who underwent transthoracic fine-needle aspiration biopsy in whom histologic proof of the nature of the aspirated lesion was available. Compared to the histologic diagnosis, the specific cell-type cytologic diagnosis was usually in agreement when reported as squamous cell carcinoma (86%), adenocarcinoma (86%), or small cell anaplastic carcinoma (86%). In patients with a known extrapulmonary primary malignant neoplasm, the cytologic specimen was extremely helpful in identifying a new pulmonary lesion as metastatic rather than as a primary lesion in the lung. These results warrant the more extensive use of fine-needle aspiration biopsy in patients with pulmonary neoplasms in whom the specific cell type of the malignant neoplasm has important implications in therapy.

Since the pioneering work of Dahlgren and Nordenstrom [1] in the early 1960s, transthoracic fine-needle aspiration biopsy has become established, particularly at large centers, as a useful diagnostic technique with little risk to the patient and high yield of diagnostic results. Recently reported large series [2-5] indicate that malignant neoplasms can be readily distinguished from benign diseases by cytologic examination of the aspirate. However, the ability to make definite diagnoses of the specific neoplastic cell type has not been emphasized. Most North American authors report results only as positive or negative for malignant neoplasm [2, 3, 5] without further elaboration.

At our institution, in cytologic reports the cell type of neoplasm has usually been specified in addition to stating that the specimen was positive for malignancy. Since this cell type information can have a significant impact on decisions about the subsequent management of the patient, it is important to know how accurate it is. This paper analyzes the accuracy of such cytologic typing in cases where histologic typing was also available from surgical or necropsy specimens.

Materials and Methods

From 1966 through 1976, 628 transthoracic fine-needle aspiration biopsies were performed on 559 patients. Many types of lesions were aspirated including mediastinal, hilar, and pleural lesions as well as solitary and multiple pulmonary nodules. All aspirations were performed using the fluoroscopically guided approach described by Lalli et al. [6] in a 1967 report of the first 50 aspiration biopsy cases at the University of Michigan. A 20-gauge, 203 mm thin-walled needle was used. For most patients, a single procedure consisted of two or three needle placements into the target lesion. The aspirate was blown onto glass slides and spray fixed before the slightest trace of drying occurred. The fixed smears were stained by the Papanicolaou method. Several different radiologists performed these aspirations during the 11 year period, but one of us (J. R. T.) performed over 85% of these.

The charts and radiographs of all patients who underwent fine-needle aspiration were reviewed at least 3 years after the biopsy had been performed. On the basis of the available data, the cases were divided into three categories. Cases considered *Histologically Proven*

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had, at some time subsequent to the aspiration, histologic examination of the aspirated lesion either by surgery or by necropsy. Cases were considered *Clinically Correlatable* when the subsequent clinical course of the patient, including radiographic changes or histologic examination of extrapulmonary lesions, or both, indicated with reasonable certainty whether the aspirated lesions were malignant or benign. Cases were considered to have *Insufficient Follow-up* when the available data were not sufficient to determine with reasonable certainty whether or not the cytologic diagnosis had been correct. Those cases in the *Histologically Proven* category were then analyzed in detail.

Several members of the Department of Pathology made the original cytologic diagnoses, although most were made by one of us (B. N.). In each case, the accuracy of the cytologic diagnosis was judged by comparing it with the final histologic diagnosis, on the basis of the original reports in the medical record. When the cytologic and histologic diagnoses were the same, both were accepted as being correct without further review. When a discrepancy was found, the original histologic specimen slides were reviewed by one of us (B. N.) without knowledge of the initial histologic diagnosis. No change in histologic diagnosis resulted from this review.

After this histologic diagnosis review in these mismatch cases, the original cytologic specimen slides were reviewed by one of us (B. N.) to determine the reasons for the disagreements between the cytologic and histologic diagnoses. These speculations are included in the Discussion section under each cell type category. No change in cytologic diagnosis resulted from this review.

The patients tended to fall into two categories. The first consisted of those with no previously known neoplasm in whom a new pulmonary lesion had been found. Before the aspiration, most of these patients had been investigated by sputum cytology, bronchoscopy with biopsy and washings, and, where appropriate, sputum cultures and skin testing, without a diagnosis being established. However, patients with solitary pulmonary nodules without any history of malignant neoplasm usually underwent thoracotomy without fine-needle aspiration, unless there was some contraindication to operation. The second category consisted of those patients with a previously diagnosed malignant neoplasm who presented with one or more pulmonary or pleural lesions. Many of these patients underwent little or no other investigation before the aspiration biopsy.

Many of the cytologic diagnoses described the neoplasms as undifferentiated or poorly differentiated, frequently with further categorization of the lesion by use of such terms as probably or possibly as in "poorly differentiated carcinoma, probably squamous cell carcinoma" or "undifferentiated carcinoma, possibly adenocarcinoma." In such cases, when the cytologic typing of neoplasm was preceded by "probably" the cytologic diagnosis was tabulated as if this had been expressed with definiteness. When "possibly" was used, the diagnosis was treated as if it had been reported as only poorly differentiated or undifferentiated, and was tabulated in the category of anaplastic carcinoma.

Results

Of 559 patients aspirated, 185 fell into the *Insufficient Follow-up* category (101 reported as positive for malignant neoplasm, 84 negative). The diagnosis was *Clinically Correlatable* in 212 (180 positive, 32 negative). The remaining 162 were *Histologically Proven*. In the last group there were 103 male and 59 female patients aged 4-78 years (mean, 53.2).

TABLE 1: Complications of Transthoracic Fine-Needle Aspiration

Complication	No. (%)
Pneumothorax:	
No treatment	123 (19.6)
Chest tube	61 (9.7)
Aspiration	12 (1.9)
Total	196 (31.2)
Mild, transient hemoptysis	47 (7.5)
Local bleeding around lesion	59 (9.4)
Small pleural effusion	6
Transient pleuritic chest pain	6
Minimal pneumomediastinum, minimal subcutaneous emphysema, delayed hydropneumothorax, transient hypotension, subcutaneous bleeding at entry site, fever postponing operation by 1 day	1*

Note.—Data on 559 patients, 628 procedures.

* One each.

TABLE 2: Cytologic Diagnoses in 162 Histologically Proven Cases

Diagnosis	No.
Specific cell type diagnosed:	
Squamous cell carcinoma	22
Adenocarcinoma	21
Small cell anaplastic carcinoma	7
Large cell anaplastic carcinoma	3
Anaplastic carcinoma	10
Miscellaneous specific diagnoses	6
Thymoma-lymphoma group	8
Subtotal	77
Positive, no specific cell type:	
Nonspecific cytology	8
Nonspecific histology	3
Subtotal	11
False positive	1
False negative	34
True negative	39
Total	162

Complications for the entire series are listed in table 1 and are comparable to those of other series [1-3]. No deaths occurred.

Table 2 lists the cytologic diagnoses made in the *Histologically Proven* cases. There was one false-positive diagnosis and 39 cases were correctly diagnosed cytologically as being negative for malignant neoplasm, giving 40 (25%) out of 162 of *Histologically Proven* cases in which the lesion was not malignant. False-negative diagnoses (cytology read as "negative for malignant neoplasm" with the histologic specimen showing malignant neoplasm) totalled 34 cases (28%) of the malignant lesions in the *Histologically Proven* category. In 11 cases, the cytology was reported as positive for malignant neoplasm, but either no cell type was specified (eight cases) or the histologic diagnosis was not specific with regard to cell type (three cases). In 77 (88%) of 88 cases in which a correct cytologic diagnosis of positive for malignant neoplasm was made, an attempt was also made to type the neoplasm.

Table 3 compares the cytologic with the histologic typing. Of the 122 malignant *Histologically Proven* lesions, 78 were

TABLE 3: Comparison of Cytologic and Histologic Diagnoses

Cytologic Diagnoses	Squamous Cell	Adenocarcinoma	Small Cell	Large Cell	Anaplastic	Lymphoma-Thymoma	Miscellaneous	Not Specific	Total
Squamous cell carcinoma	19	2	0	0	1	0	0	0	22
Adenocarcinoma	1	18	0	1	0	0	1	0	21
Small cell anaplastic carcinoma	0	0	6	0	1	0	0	0	7
Large cell anaplastic carcinoma	0	1	0	2	0	0	0	0	3
Anaplastic carcinoma	3	3	0	1	3	0	0	0	10
Positive, not specific for cell type	2	3	0	0	2	1	0	3†	11
Lymphoma or thymoma*	0	0	0	0	0	8	0	0	8
Miscellaneous specific diagnosis	0	0	0	0	0	0	6	0	6
False negative	5	8	3	2	2	5	9	0	34
Total	30	35	9	6	9	14	16	3	122

Note.—Surgery: 77 cases; necropsy: 45 cases.

* See discussion.

† Cases where necropsy reports were nonspecific.

TABLE 4: Cytology of Metastatic Pulmonary Lesions

Cytology	No.
Total histologically proven metastatic lesions:	
False-negative cytology	12
Positive cytology	18
Cell type correctly identified, not recognized as metastatic	4
Reported as metastatic:	
Based on aspirate alone	1
Directly compared to primary neoplasm	7
Same cell type as reported for primary neoplasms	4
Positive cytology, two primary neoplasms (see discussion)	2
Lesion correctly identified as not metastatic	1

primary pulmonary neoplasms, 30 were metastatic lesions, and 14 were lymphoma or thymoma. Among the 30 metastatic lesions aspirated there were 12 false-negative reports. The remaining 18 metastatic lesions were analyzed with regard to the ability of the cytopathologist to determine whether the lesion was a metastasis or a primary pulmonary lesion (table 4).

In the 122 Histologically Proven cases, the type of lesion biopsied was categorized on the basis of its appearance on the chest radiograph done on the day of the aspiration procedure. Types of lesions and numbers of cases included: solitary pulmonary nodule (77), multiple pulmonary nodules (13), mediastinal (11), hilar (13), and chest wall including pleura (eight).

Discussion

In primary carcinoma of the lung, typing of the neoplasm is important in determining prognosis and, in conjunction with the radiographic and clinical manifestations of the neoplasm, may influence the decision to operate [7, 8]. When a pulmonary lesion develops in a patient known to have an extrapulmonary primary neoplasm, it is necessary to determine whether the pulmonary lesion is a metastasis, a second primary neoplasm, or a benign lesion. Our data

suggest that the cellular sample obtained by fine-needle aspiration can often be helpful in this situation by indicating the histologic type of the lesion.

Several reports have included some comparison of cytologic with histological diagnoses, but only that of Dahlgren [9] is comparable to ours in respect to the number of patients and types of lesions aspirated. He reviewed aspirates of many types of radiologically detectable thoracic lesions from 667 patients who were followed for at least 1 year after aspiration. Positive or suspicious cytologic reports were made in 333 cases (46%), 209 of which had surgical or necropsy specimens available for comparing the cytologic and histologic diagnoses. Among the 184 cases where further cytologic categorization of the neoplasm was made, there was agreement with the histologic diagnosis in 141 (77%).

Sinner [10] reported a comparison of cytologic and histologic typing in 40 primary carcinomas of lung, all of which were peripheral and less than 2 cm in diameter, with agreement in all of the 26 cases with a diagnosis of squamous cell carcinoma, and in 13 (93%) of 14 cases with a cytologic diagnosis of adenocarcinoma. Sinner and Sandstedt [11] found agreement in 28 (90%) of 31 cases with a cytologic diagnosis of small cell anaplastic carcinoma where histologic material was available for comparison. Pavy et al. [12] reported a series of 17 cases with various cytologic diagnoses where histologic material was available, with agreement between cytology and histology in 15 (88%). In our series of 77 histologically proven cases where a specific cytologic diagnosis had been made, overall agreement between the histologic and the cytologic typing of the neoplasms was achieved in 62 (81%).

Squamous Cell Carcinoma

In our series, when a cytologic diagnosis of squamous cell carcinoma was made, it agreed with histologic diagnosis in 19 (86%) of 22 cases. This compares favorably with 76 (81%) of 94 in Dahlgren's series [9], but does not achieve the accuracy of Sinner, 26 (100%) of 26, whose cases were

more selected [10]. In our three cases where there was disagreement with the cytologic diagnosis, the histologic specimens were reviewed. One neoplasm was a moderate to poorly differentiated adenocarcinoma, which also contained areas that might be regarded as squamous cell carcinoma. Another was an unusually poorly differentiated large cell pleomorphic carcinoma whose cells had eosinophilic cytoplasm, which may have been the reason for the cytologic diagnosis of squamous cell carcinoma. The third was a poorly differentiated adenocarcinoma.

Adenocarcinoma

When this cytologic diagnosis was made, it agreed with the histologic diagnosis in 18 (86%) of 21 cases. This again compares favorably with 24 (71%) of 34 in Dahlgren's series [9], but again does not achieve the accuracy of Sinner, 13 (93%) of 14 [10]. The lesions misinterpreted cytologically as adenocarcinoma included one poorly differentiated large cell anaplastic carcinoma, one well differentiated squamous cell carcinoma which contained some vacuolated cells simulating adenocarcinoma cells in the histologic specimen, and one fibrous histiocytoma.

Although in our series a cytologic diagnosis of adenocarcinoma was highly accurate, of 35 total cases in which a histologic diagnosis of adenocarcinoma was made, only 18 (51%) were correctly identified by cytology. There were eight false-negative aspirations in this group, and nine other cases where cytologic typing did not agree with the histologic diagnosis of adenocarcinoma. This parallels Dahlgren's experience [9] where only 24 (60%) of 40 of histologically diagnosed adenocarcinomas with positive cytology were correctly identified as adenocarcinoma.

Small Cell Anaplastic Carcinoma

This diagnosis includes the subgroup of oat cell carcinomas. Only seven of our cases had this diagnosis made on the cytologic specimen, with the histologic diagnosis agreeing in six. Disagreement occurred in a case that was originally interpreted at necropsy as a large cell undifferentiated carcinoma, but which on review was considered to be poorly differentiated, possibly squamous cell carcinoma, but quite variable in its morphologic appearance. While the number of cases in our series is small, these results approximate those of Sinner and Sandstedt [11] in which 28 (90%) of 31 cases showed agreement. Those authors emphasized the importance of establishing a diagnosis of small cell anaplastic carcinoma without operation, since many surgeons believe that operation should not be undertaken in patients with this neoplasm.

Large Cell Anaplastic Carcinoma

This diagnosis is made infrequently in our institution since our pathologists believe that in most instances they are able to make a diagnosis of squamous cell carcinoma or adenocarcinoma rather than large cell carcinoma. In three cases

where the cytologic specimen was interpreted as large cell anaplastic carcinoma, the histologic diagnosis was the same in two, and adenocarcinoma in one.

Anaplastic Carcinoma and Nonspecific Positive Cytologic Diagnosis

There were eight positive aspirates for which no cytologic typing of the neoplasm was given. The reports either had comments such as "difficult to type" or listed several possible specific diagnoses. The final histologic diagnoses in these cases included two squamous cell carcinomas, three adenocarcinomas, two anaplastic carcinomas, and one histiocytic lymphoma. Also included in this category were two additional cases where typing of the neoplasm was attempted, but the only histologic correlation in each case was a necropsy report of bronchogenic carcinoma. In one other case included in this group, the histologic diagnosis was indefinite, being reported as metastatic adenocarcinoma vs. pleomorphic Hodgkin disease.

Ten cases were assigned to the anaplastic carcinoma cytologic diagnosis category as defined in Materials and Methods. The distribution of histologic diagnoses among these cases was similar to that among the cases read simply as positive for malignant neoplasm, with three squamous cell carcinomas, three adenocarcinomas, three anaplastic carcinomas, and one large cell anaplastic carcinoma.

If the 10 cytologic diagnoses of anaplastic carcinoma and the eight diagnoses of merely positive for malignant neoplasm are grouped together, there were 18 (20%) of 88 cases with a positive cytologic diagnosis for which a more specific diagnosis could not be made.

Miscellaneous Specific Diagnoses

In six cases various miscellaneous positive cytologic diagnoses were made including the type of the neoplasm. In four of these (one adenoid cystic carcinoma, one fibrosarcoma, and two leiomyosarcomas) tissue from a previously diagnosed primary neoplasm was available for comparison. In another (malignant melanoma) the type of the primary neoplasm was known and the cytologic appearance of the aspirate was interpreted as being consistent with that of the primary neoplasm. In one other case with numerous pulmonary nodules without a known primary neoplasm, the aspirate was interpreted as a germ cell neoplasm and the subsequent histologic diagnosis was choriocarcinoma.

Lymphoma and Thymoma

These lesions were handled differently from the others in the tabulation of results. Even in histologic specimens, it is often difficult to distinguish lymphoma from thymoma. Similar difficulty was encountered with the cytologic specimens. There were only three cases in which the cytologic diagnosis of lymphoma (two patients) or thymoma (one patient) was made unequivocally. Aspirates in three other cases were read as positive for malignant neoplasm with the question of

lymphoma being raised. Two of these were diagnosed histologically as lymphocytic lymphoma and one as thymoma. In two cases where the cytologic diagnosis was "lymphoma or thymoma," one was thymoma on histology and the other was poorly differentiated lymphocytic lymphoma. In all cases in which the possibility of lymphoma or thymoma was mentioned, one of these two diagnoses was subsequently established by histology. It seems that even if it may not be possible to discriminate with certainty between thymoma and lymphoma, the cytologic identification of a lesion as belonging to the lymphoma-thymoma category is reliable, and it will usually be possible to distinguish between these two neoplasms on clinical grounds.

It is noteworthy that of the five Histologically Proven cases of Hodgkin disease, all had false-negative cytology, indicating the difficulty of making this diagnosis by fine-needle aspiration biopsy. However, there were four Clinically Correlatable cases of Hodgkin disease, where that diagnosis had been established by previous lymph node biopsy, in which transthoracic fine-needle aspiration biopsy was positive. One of these was diagnosed by cytology only as lymphoma, whereas the other three were reported as consistent with Hodgkin disease.

False-Negative Diagnoses

In 34 of the 122 Histologically Proven cases of malignancy, the cytology was reported negative for malignant neoplasm but the histologic specimen revealed the presence of malignant neoplasm. This is a false-negative diagnosis rate of 28%. In Dahlgren's series only 15 (7%) of 216 Histologically Proven cases of malignancy were cytologic false negatives. The reason for the false-negative rate difference between these two series is not certain, but the selection of the patients may have played an important part.

Most of our patients with no known extrapulmonary primary neoplasm were referred for aspiration only after bronchoscopy and sputum cytology failed to provide a diagnosis, and then often only if there was some contraindication to thoracotomy. Also, in our overall series of 559 patients, only 35% of the aspirates were reported as negative, again probably indicating a difference in the selection of patients. When Clinically Correlatable and Histologically Proven cases from our series are averaged together, there were 46 (15%) of 302 false-negative cytologic diagnoses, which is within the range of 2%–15% reported in three recent large series [2–4] in which data were compiled for both clinically correlatable and histologically proven cases.

Evaluation of Metastatic Neoplasm

Among the Histologically Proven lesions, 30 were eventually shown to be neoplasm metastatic to the lung. In 12 of these cytology was falsely negative. Table 4 assesses the usefulness of fine-needle aspiration of the lung in the remaining 18 cases where the cytology was positive. In four instances, the cell type of the lesion was correctly identified, but no extrapulmonary primary neoplasm was known at the

time of the aspiration, and it was not determined by cytology that the lesion was metastatic. In 12 cases the lesion was correctly identified as metastatic, in one of these on the basis of the aspiration alone (the germ cell neoplasm), in seven on the basis of comparison with available histologic specimens of an extrapulmonary primary neoplasm, and in four on the basis of the neoplasm being of the same cell type as a previously known primary neoplasm (even though no histologic specimen from the primary neoplasm was available for comparison).

The two remaining patients each had two separate primary extrapulmonary neoplasms. One had both endometrial adenocarcinoma and a fibrous histiocytoma, with the aspirate of the pulmonary metastatic lesion being incorrectly identified as adenocarcinoma on two occasions, whereas necropsy demonstrated this was metastatic fibrous histiocytoma. The other patient had an adenocarcinoma of the colon and a duct cell carcinoma of the breast, with the aspirate being reported as adenocarcinoma, probably metastatic, with no comment made as to the site of the primary neoplasm.

In one case aspiration correctly determined that a new pulmonary lesion was a primary anaplastic carcinoma of the lung, rather than a metastasis from a previously diagnosed squamous cell carcinoma of the larynx.

Overall Results

Many factors will affect the accuracy of the cytologic diagnoses based on transthoracic fine-needle aspiration biopsy. These include the small size of some lesions (making placement of the needle within the lesion difficult), the variability of the histologic appearance of different parts of the same lesion, problems in both histologic and cytologic diagnosis created by lack of differentiation of the neoplasm, and the small amount of the specimen obtained by aspiration biopsy. However, our data show that in a high proportion of cases cytologic diagnoses of specific neoplasms can be made with a reasonable degree of accuracy, and other reports support this contention.

A cytologic diagnosis of squamous cell carcinoma or small cell anaplastic carcinoma was particularly reliable. A cytologic diagnosis of adenocarcinoma was equally reliable in our series, but was slightly less reliable in that of Dahlgren [9]. When there was a question of metastatic or primary neoplasm of lung, cytologic typing was often very useful in establishing that a lesion was metastatic neoplasm, especially when a histologic specimen from a previously diagnosed extrapulmonary neoplasm was available.

With thymomas and lymphomas there was often difficulty in establishing a precise diagnosis, and patients with Hodgkin disease often had false-negative aspirates. However, when the cytology was positive, the lesion could usually be classified as being not only neoplasm but also as being in the lymphoma-thymoma category.

Because of the high correlation attainable between cytologic and histologic typing of neoplasms, pathologists should make every effort to type neoplasms cytologically,

thus reducing the proportion of reports that simply address the question of whether a malignant neoplasm is or is not present. In addition, our results should encourage radiologists to extend the indications for transthoracic fine-needle aspiration biopsy to patients in whom the diagnosis of a particular type of malignant neoplasm would have practical consequences in therapy.

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