Research Article

Prediction of Histological Subtypes of Invasive Lung Adenocarcinoma Using Preoperative Transbronchoscopic Cytology

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Abstract

Objectives: To clarify the usefullnes of cytology in histological subtyping of invasive lung adenocarcinoma.

Materials and methods: Thirty-one specimens of resected invasive lung adenocarcinoma, diagnosed using transbronchoscopic cytology, were studied. Specimens were histologically classified into the primary and secondary histological subtypes according to the adenocarcinoma classification system proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society. Additionally, we prospectively classified cytological appearance of specimens into Grades 1-3, using both cell atypia and structual atypia. Grades corresponded to the following histological subtypes: Grade 1, lepidic histological subtype; Grade 2, acinar or papillary histological subtype; and Grade 3, solid histological subtype. The concordance between the assigned cytological grade and the histological subtype was analyzed.

Results: The concordances (number and rate) between the assigned cytological grade and the primary histological subtype were: Grade 1; 9 [77.8%], Grade 2; 13/20 [65.0%], and Grade 3; 2/2 [100%]. The concordances between the assigned cytological grade and the combination of both the primary and the secondary histological subtypes were: Grade 1; 8/9 [88.9%], Grade 2; 19/20 [95.0%].

Conclusions: Preoperative cytological analysis was a useful method for predicting the primary histological subtype for invasive lung adenocarcinomas.

ABBREVIATIONS

CLA: Cytology of Lung Adenocarcinoma

INTRODUCTION

Recently, a new classification system for invasive lung adenocarcinoma, proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European respiratory society [IASLC/ATS/ERS] [1], has been adopted for use by the world health organization [WHO] [2]. The primary histological subtypes in invasive adenocarcinoma are classified as follows: lepidic, formerly known as bronchiolo-

alveolar growth [3], acinar, papillary, micropapillary, solid with mucin production, and other variants. These primary histological subtypes indicate tumor aggressiveness and prognosis [4-6].

Preoperative transbronchoscopic cytology for lung adenocarcinoma is considered to be a useful diagnostic procedure. Indeed, it may be possible to predict the primary histological subtype of cytology specimens using analysis of cell atypia and structural variations.

In this study, we investigated the usefulness of preoperative cytology in predicting primary histological subtypes of invasive lung adenocarcinomas.

MATERIALS AND METHODS

Specimens from 31 invasive lung adenocarcinoma patients that underwent transbronchoscopic cytology for the past five years in our institute were studied. Comprehensive internal review board approval was obtained for this study. Resected specimens were histologically classified by a pathologist (co-author) into primary and secondary histological subtypes, according to the new IASLC/ATS/ERS and WHO lung adenocarcinoma classification system. Most cases were classified into four histological subtypes; lepidic, acinar, papillary, and solid growth appearance (Figure 1: A-D).

Additionally, we prospectively classified cytological appearance individually into Grades 1-3 before tumor resection. Cytological evaluation was performed by a clinical laboratory cytologist [co-author] and a doctor with expertise in cytology [author], who discussed each case before reaching a final diagnosis. Grades were assigned based upon the cell atypia and structural appearance, as follows: Grade 1, cytological appearance of two-dimensional and flat cell crowds, lighting cell atypia with multinuclear, ground glass nuclei, grooved nuclei, and intranuclear vacuoles, defined as the lepidic histological subtype; Grade 2, glandular or papillary structure, hobnail growth, more severe cell atypia than Grade 1, for example uneven sized cells, increased chromatin, and large nucleoli, defined as the acinar or papillary histological subtype; Grade 3, 3-dimensional clusters, severe architectural disorganization, for example extremely irregular piling, necrotic background, and more severe cell atypia displaying nuclear pleomorphism than Grade 2, defined as the solid histological subtype (Figure 2: A-D). First, the concordance between the cytological grade and the primary histological subtype was assessed. Next, the concordance between the cytological grade and the secondary histological subtype in residual unmatched cases with the primary histological subtype was assessed. Finally, concordance analysis was performed between the cytological grade and the histological subtype created by combining both the primary and the secondary subtypes.

RESULTS

Thirty-one resected lung Adenocarcinoma specimens were classified into primary histological subtypes, according to the new IASLC/ATS/ERS and WHO lung adenocarcinoma classifications, resulting in:14 lepidic, 15 acinar/papillary, and two solid subtypes. Classification of secondary subtypes resulted in;six lepidic, 17 acinar/papillary, two solid, and six of no subtype.

Additionally, preoperative transbronchoscopic cytology specimens were prospectively classified into Grades 1-3, resulting in: nine Grade 1, 20 Grade 2, and two Grade 3 classifications.

The concordances (number and rate) between the assigned cytological grade and the primary histological subtype were: Grade 1; 7/9 [77.8%], Grade 2; 13/20 [65.0%], and Grade 3; 2/2 [100%] (Table 1). The concordances between assigned cytological grade and the second primary histological subtype in residual unmatched cases with primary subtype were Grade 1;1/2 [50.0%] and Grade 2; 6/7 [85.7%] (Table 2).The concordance between the assigned cytological grade and histological subtype combining both the primary and secondary subtypes were Grade 1; 8/9 [88.9%], Grade 2; 19/20 [95.0%],and Grade 3; 2/2 [100%] (Table 3).
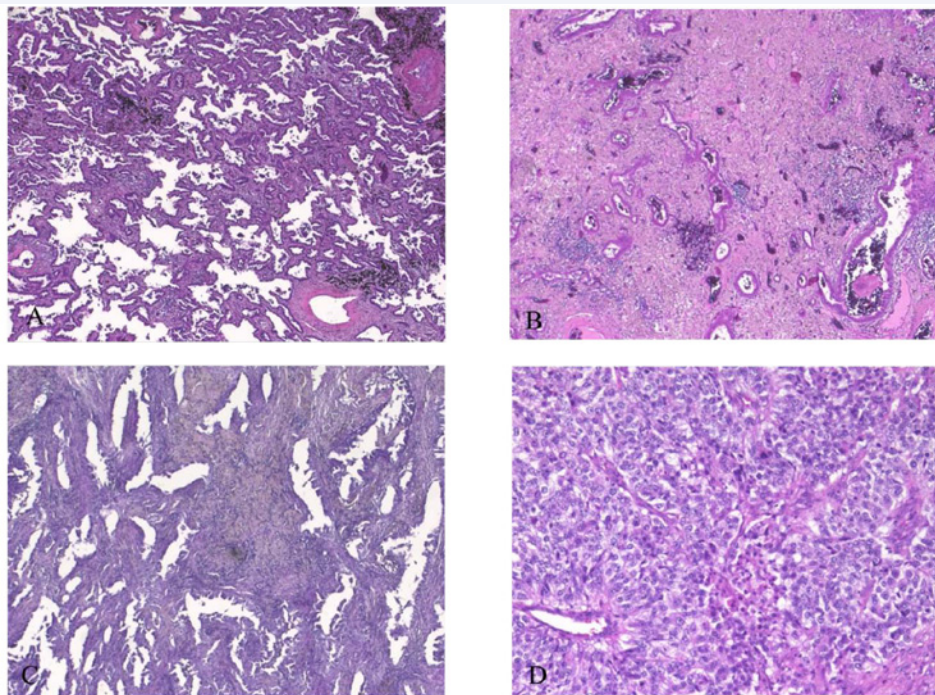
Figure 1 Resected specimens of lung adenocarcinoma were classified to 4 histological subtypes (A-D: H.E. stain. original magnification, x10) determined using the new lung adenocarcinoma histological classifications proposed by IASLC/ATS/ERS.

A: lepidic subtype. B: acinar subtype. C: papillary subtype. D: solid subtype
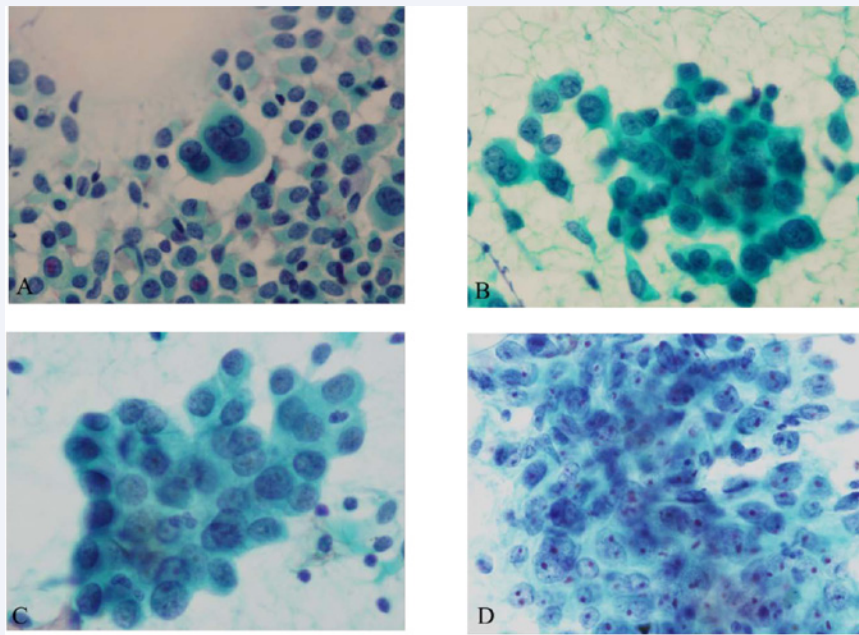
Figure 2 Using transbronchoscopic cytology specimens, we classified cytological appearance individually into Grades 1-3. Each grade was defined by both cell atypia and structural variation, as follows:

Grade 1 (A); cytological appearance of 2-dimensional and flat cell crowds, lighting cell atypia with multinuclear, ground glass nuclei, and grooved nuclei, Grade 2 (B and C); glandular (B) or papillary (C) structure, more severe cell atypia than Grade 1.Grade 3 (D); 3-dimensional clusters, severe architectural disorganization, more severe cell atypia, including nuclear pleomorphism than Grade 2.(A-D: Papanicolaou stain. original magnification,x40).

Table 1: The concordance (number and rate) between the cytological grade and the primary histological subtype.

Primary Grade by cytology	Lepidic	Acinar/Papillary	Solid	Concordance Rate
Grade 1=9	7	2	0	77.8%
Grade 2=20	7	13	0	65.0%
Grade 3=2	0	0	2	100%

Table 2: The concordance (number and rate) between the cytological grade and the secondary histological subtype in residual unmatched cases with the predominant histological subtype.

Secondary Grade by cytology	Lepidic	Acinar/Papillary	Solid	None	Concordance Rate
Grade 1=2	1	1	0	0	50.0%
Grade 2=7	0	6	0	1	85.7%

Table 3: The concordance (number and rate) between the cytological grade and the histological subtype when the primary and second subtypes were combined.

Primary and Secondary Grade by cytology	Lepidic	Acinar/Papillary	Solid	Concordance Rate
Grade 1=9	8	1	0	88.9%
Grade 2=20	1	19	0	95.0%
Grade 3=2	0	0	2	100%

DISCUSSION

A new histological classification of lung adenocarcinoma, proposed by IASLC/ATS/ERS [1], has recently been adopted for use by the WHO [2]. Invasive adenocarcinoma is classified into the following primary histological subtypes: lepidic, acinar, papillary, micropapillary, solid with mucin production, and other variants. The lepidic primary histological subtype is likely to be identical to type C adenocarcinoma, according to the classification of small-sized lung adenocarcinoma by Noguchi *et al.* [3], or bronchiolo-alveolar carcinoma containing invasive components. Invasive adenocarcinomas of the lepidic primary histological subtype are

considered to have mild tumor aggressiveness and an excellent prognosis. Conversely, the acinar/papillary primary histological subtype is considered to have a poorer prognosis than the lepidic primary histological subtype, while the solid subtype has the worst prognosis of all of the primary histological subtypes [4-6]. Papillary and acinar primary histological subtypes are thought to have similar prognoses. Thus, Kadota *et al.* [7] proposed that invasive Adenocarcinoma can be divided into 3 prognostic groups: lepidic, acinar or papillary, and solid.

Our study aim to verify whether preoperative transbronchoscopic cytology can be used to predict the histological subtypes of invasive lung adenocarcinoma. We classified cytological appearances of individual specimens into Grades 1-3using distinctive cell atypia andcell structure variations, corresponding to 3 histological prognostic groups defined by Kadota *et al.* [7]. Typical appearances of each grade were established from examples provided in Rodriguez *et al.* [8,9].

The increase in the concordance rate when the primary and secondary histological subtypes were combined can be explained by tumor heterogeneity. Bronchoscopy with exfoliative cytology indicated Grades 1 and 2 for the peripheral (histological subtype: [lepidic] and central (histological subtype: acinar) regions of the tumor, respectively according to the classification of small-sized lung adenocarcinoma by Noguchi *et al.* [7] .Curettage lesions of tumors are often used to estimate histological subtypes in bronchoscopy. Thus, cytological findings by transbronchoscopic cytology reveal not only the primary histological subtype but also the secondary or third histological subtypes [8,9].

Interestingly, Grade 3 was concordant with the solid primary histological subtype, despite there being just 2 cases. Solid histological subtype was generally minor group than the other 3 group as well as our previous study for invasive lung adenocarcinoma [6]. Nevertheless, this solid histological subtype was considered to be relatively easy to classify, given the severe cell atypia and architectural disorganization.

Our study reveals that preoperative cytological grading provides accurate information regarding either the primary or the secondary histological subtype. This method may be applicable to distinguish histological subtypes of invasive lung adenocarcinoma not only in preoperative states but also inoperable states, which demand selective systemic chemotherapy according to its prognostic grade.

There are several limitations of this study, including the small number of specimens examined, and the possibility of bias in the cytologist's diagnosis due to prior access to patient's clinical information, including that of diagnostic imaging and serum tumor markers related to lung carcinoma. However, biases were likely to be small, as the final diagnosis of each case required a discussion between 2 cytologists; a clinical laboratory expert and a medical doctor (author).

Finally, we gave the impression that preoperative cytological grading is a feasible method of predicting the primary and secondary histological subtypes of invasive lung adenocarcinomas.

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