



Inaccuracy of lung adenocarcinoma subtyping using preoperative biopsy specimens

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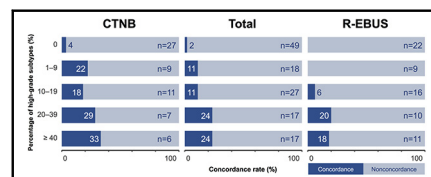
ABSTRACT

Background: The prognostic significance of the new classification of lung adenocarcinoma proposed in the 2015 World Health Organization guideline has been validated. This study aimed to compare the preoperative classification of the adenocarcinoma subtype based on computed tomography-guided 18-gauge core needle biopsy (CTNB) or radial probe endobronchial ultrasound (R-EBUS) specimens, with the postoperative classification based on the resected specimens.

Methods: We retrospectively analyzed a consecutive series of 128 patients (60 CTNB and 68 R-EBUS) who underwent surgery for preoperatively confirmed lung adenocarcinoma between 2010 and 2014. Comprehensive histological subtyping was performed according to the 2015 World Health Organization classification system. Diagnostic concordance of subtypes between small biopsy and resection specimens was assessed.

Results: Concordant subtyping of adenocarcinomas between the predominant pattern on resections and biopsy sections was observed in 58.6% of cases (75 of 128; 95% confidence interval [CI], 49.9%-66.8%). Preoperative subtyping was accurate in only 30% of samples (3 of 10) with a predominance of solid patterns. None of the 5 micropapillary predominant cases was detected by CTNB or R-EBUS. For the concordance of the presence or absence of micropapillary/solid component, the sensitivity was as low as 16.5% (95% CI, 9.1%-26.5%). The detection rate by CTNB/R-EBUS increased with the increase in the percentage of micropapillary/solid component; however, even in the $\geq 40\%$ micropapillary/solid group, only 24% of cases were detected by CTNB/R-EBUS.

Conclusions: The accuracy of the estimation of adenocarcinoma histological subtype based on preoperative biopsy sections was unsatisfactory. (*J Thorac Cardiovasc Surg* 2017;154:332-9)



Detection of high-grade adenocarcinomas by preoperative biopsy section.

Central Message

The accuracy of estimation of adenocarcinoma histological subtype based on preoperative biopsy sections was unsatisfactory.

Perspective

The identification of the presence or absence of micropapillary/solid components of an early-stage lung adenocarcinoma preoperatively is a crucial but unresolved issue. We show that the accuracy of estimation based on preoperative biopsy sections was unsatisfactory. Surgeons should not rely solely on preoperative biopsy findings when making decisions regarding the choice of limited resection or lobectomy.

See Editorial Commentary page 340.

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Adenocarcinoma is the most common subtype of lung cancer, which is the leading cause of cancer-related deaths worldwide.¹ However, adenocarcinoma is a heterogeneous disease with variant morphological features. To predict clinical prognosis, the International Association for the Study of Lung Cancer, the American Thoracic Society, the

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Abbreviations and Acronyms

CI	= confidence interval
CT	= computed tomography
CTNB	= computed tomography-guided 18-gauge core needle biopsy
DFS	= disease-free survival
GGO	= ground glass opacity
IQR	= interquartile range
PET	= positron emission tomography
R-EBUS	= radial probe endobronchial ultrasound
TDR	= tumor disappearance rate
WHO	= World Health Organization

European Respiratory Society, and the 2015 World Health Organization (WHO) guidelines classify adenocarcinomas based on the molecular characteristics and predominant architectural subtypes as lepidic, acinar, papillary, micropapillary, or solid.^{2,3} These classification systems recommend comprehensive histological subtyping based on pattern recognition and a semiquantitative assessment of each pattern in 5% increments for evaluating the single predominant pattern in invasive adenocarcinomas.^{2,3}

The predominant architectural subtype of adenocarcinomas is correlated with clinical prognosis. Nakamura et al⁴ reported that standardized fluorodeoxyglucose uptake values for positron emission tomography (PET)/computed tomography (CT) were higher in adenocarcinomas with predominant micropapillary and solid patterns. In early-stage lung adenocarcinomas, following complete resection, predominant micropapillary and solid subtypes have been associated with poorer disease-free survival (DFS), whereas a predominant lepidic subtype was associated with favorable outcomes.^{5,6}

Even a small proportion of micropapillary or solid component has a significant negative impact on prognosis.⁷⁻⁹ In clinically N2-negative lung adenocarcinoma, the presence of micropapillary or solid component was associated with pathological N2 disease.^{10,11} Furthermore, the percentage of micropapillary or solid component increased with the increasing likelihood of pathological N2 disease.¹⁰ Lymph node metastasis is one of the most important factors in determining the treatment plan for a resectable lung adenocarcinoma. Patients with pathological N2 stage IIIA lung adenocarcinoma who received neoadjuvant therapy before surgery showed better outcomes compared with those who underwent primary surgical resection followed by adjuvant therapy.¹² Therefore, precise preoperative staging integrated with PET/CT, endobronchial ultrasound-guided transbronchial needle aspiration, or endoscopic ultrasound-guided fine-needle aspiration¹³ may be performed to increase the reliability of preoperative pathological N2 detection in patients with micropapillary or solid

component lung adenocarcinoma. In contrast, predominant early-stage lepidic adenocarcinomas demonstrated better prognosis.^{5,6} Although lobectomy is a standard treatment for resectable lung adenocarcinomas, sublobar resection may be an option for elderly patients and those with a ≤ 2 -cm tumor and predominant lepidic subtype.¹⁴

Therefore, if a preoperative small biopsy specimen were capable of replacing an operative large specimen for subtyping lung adenocarcinoma, this could have a significant impact for surgeons. For example, if the preoperative small biopsy specimen by CT-guided 18-gauge core needle biopsy (CTNB) or radial probe endobronchial ultrasound (R-EBUS) could be used to accurately subtype lung adenocarcinoma, then sublobar resection might not be an option for patients with a small peripheral lung adenocarcinoma containing micropapillary/solid components. For elderly patients with lung adenocarcinoma presenting with ground-glass opacity (GGO), surgeons could change their decisions regarding lobectomy in cases where a predominantly acinar subtype was proven by perioperative CTNB. Therefore, the identification of the predominant lepidic subtype and presence or absence of micropapillary/solid component of a lung adenocarcinoma, either preoperatively or intraoperatively, is a crucial but unresolved issue for surgeons.

Bittar et al¹⁵ and Yeh et al¹⁶ have reported that it is difficult to predict a primary adenocarcinoma subtype in a frozen sample that is intraoperatively collected because of poor quality and sampling artifacts. Accurate subtyping of non-small-cell lung cancer into squamous cell lung cancer or adenocarcinoma can be achieved by CTNB or R-EBUS.^{17,18} The accuracy of small biopsy subtyping of adenocarcinoma has not yet been completely validated, however.¹⁹

Therefore, in this study, we aimed to compare the preoperative biopsy specimens by CTNB or R-EBUS with the postoperative classification of resected specimens with 3 objectives. First, we investigated the concordance of predominant subtype classification of lung adenocarcinoma. Second, we investigated the concordance of the presence or absence of micropapillary/solid component. Third, we investigated the lung cancer stage and radiologic parameters that could predict the concordance of the presence or absence of micropapillary/solid components.

MATERIALS AND METHODS**Study Participants**

The medical records of 580 patients who underwent surgery for lung cancer between January 2010 and December 2014 at the China Medical University Hospital in Taichung, Taiwan were retrieved from a prospective registry database and were reviewed retrospectively. The decision to obtain preoperative specimens was routinely made at the discretion of the individual clinician. Generally, R-EBUS was performed as a part of the diagnostic workup of near-central pulmonary nodules, whereas CTNB was performed for peripheral pulmonary nodules. Before each invasive biopsy procedure, the benefits and risks were explained and signed informed consent was obtained from each patient. The resected samples of primary lung cancer were

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