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Distinctive histopathological features of lepidic growth predominant node-negative adenocarcinomas 3–5 cm in size

Yusuke Takahashi[a,b,c], Genichiro Ishii[b,*], Keiju Aokage[a], Tomoyuki Hishida[a], Junji Yoshida[a], Kanji Nagai[a]

[a] Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan
[b] Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan
[c] Division of General Thoracic Surgery, Tokyo Metropolitan Cancer and Infectionus Disease Center, Komagome Hospital, Bunkyo-ku, Tokyo, Japan

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ABSTRACT

Introduction: Adenocarcinoma of the lung is a morphologically heterogeneous group of tumors which includes a variable portion of different histologic subtype components: lepidic growth (LG), and acinar, papillary and solid subtypes. Among these, LG is a non-invasive component which is one of the major histological subtypes in small-sized adenocarcinoma (2 cm or less). However, in large adenocarcinomas (3–5 cm in size), the clinicopathological significance of LG components remains unclear.
Methods: A series of 135 lung adenocarcinomas 3–5 cm in size, without lymph node involvement, were reviewed and classified according to their percentage of LG components. We examined the correlation between the percentage of LG components and clinicopathological factors of these tumors.
Results: There were 41 (30.4%) tumors with 50% or more LG (LG-predominant group). Female gender ($p = 0.039$), smoking history of <20 pack-years ($p = 0.039$), absence of pleural invasion ($p = 0.003$), and absence of vascular invasion ($p < 0.001$) were significantly more frequently observed in the LG-predominant group. LG-predominant tumors showed a significantly higher percentage of non-cancerous cell collapse area to tumor area compared with non-LG predominant tumors ($p < 0.001$). The outcome of the LG-predominant type patients was significantly better than that of the non-LG predominant type patients in both recurrence-free survival ($p < 0.001$) and overall survival ($p < 0.001$). Multivariate analysis showed that LG-predominant tumor to be an independent favorable prognostic factor (HR = 0.285, 95% confidence interval: 0.148–0.547, $p = 0.014$).
Conclusion: Node-negative LG-predominant adenocarcinomas of 3–5 cm in size showed less invasiveness compared to non-LG predominant tumors. And LG-predominant type patients had excellent surgical outcome.

1. Introduction

Adenocarcinoma is defined as a malignant epithelial tumor with glandular differentiation or mucin production, consisting of either bronchioloalveolar, acinar, papillary, solid with mucin growth patterns, or a mixture of these patterns. Among these, adenocarcinoma of mixed subtype is the most frequent, representing approximately 80% of surgically resected lung adenocarcinomas [1].

Bronchioloalveolar carcinoma (BAC) or a lepidic growth (LG) component, which demonstrates a replacing growth pattern within the alveolar epithelium, is generally considered to be a non-invasive component. It has been reported that LG-predominant histology is a statistically significantly favorable prognostic indicator in small adenocarcinomas 2 cm or less. In contrast, patients with more aggressive disease often have tumors with little or no LG components, exhibiting predominantly compressive or destructive extension within the alveolar structure [2–4].

The newly proposed International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system suggests that, the term BAC is no longer used and the growth pattern of BAC is referred to as LG pattern, tumors should be subclassified as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive

Abbreviations: NSCLC, non-small cell lung cancer; p-stage, pathological stage; LG, lepidic growth; BAC, bronshioloalveolar carcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; VVG, Victoria van Gieson; TNM, tumor; node, metastasis; HE, hematoxylin and eosin; OS, overall survival; RFS, recurrence-free survival; EGFR, epidermal growth factor receptor.

* Corresponding author at: Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa-City, Chiba 277-8577, Japan. Tel.: +81 0 4 7134 6855; fax: +81 0 4 7134 6865.
E-mail address: gishii@east.ncc.go.jp (G. Ishii).

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adenocarcinoma [5]. It was also suggested that invasive adenocarcinomas are classified according to predominant subtype. Of special interest is the new categories AIS and MIA that represent small (≤3 cm), solitary adenocarcinomas consisting purely of LG component lacking invasion or predominantly of LG component with ≤0.5 cm of invasion, repspectively. However, LG predominant larger adenocarcinoma (>3 cm) with minimally invasion was not defined in this classification.

Several researchers have similarly reported that a proportion of LG components was associated with tumor aggressiveness and prognosis in small adenocarcinomas 3 cm or less in size [6]. However, to our knowledge, there have been no reports which have described LG components in adenocarcinomas greater than 3 cm in size, and the clinicopathological significance of LG components of these tumors remains unclear.

With these backgrounds, we aimed to explore the clinical behavior and histopathological characteristics of LG predominant node-negative adenocarcinomas 3–5 cm in size because it will facilitate to clarify the association between tumor size and non-invasive properties. And it may provide new insight about progression pattern of adenocarcinoma additionally.

2. Patients and methods

2.1. Patients

During the period from January 2000 to December 2005, a total of 1428 patients underwent surgical resection for primary lung cancer at our institution, and there were 947 patients with pathologically diagnosed adenocarcinoma. Of these, 135 consecutive patients with adenocarcinoma of the lung who had undergone complete resection of adenocarcinoma 3–5 cm in size without pathological lymph node involvement were the subject of this study. There were 72 men (53.3%) and 63 (46.7%) women, with a median age of 68 years (range: 20–86 years).

All patients had a solitary lesion, and patients who had received chemotherapy or thoracic radiation before or after surgery, who underwent limited resection less than lobectomy, or who did not undergo systematic lymph node dissection were excluded. The preoperative evaluation included a physical examination, blood chemistry analysis, measurement of tumor markers, bronchofiberscopy, chest radiography, and computed tomography (CT) of the chest.

On the basis of our postoperative follow-up policy, we examined patients at 3-month intervals for the first 2 years and typically at 6-month intervals thereafter, on an outpatient basis, and aimed at continuing follow-up for 10 years after resection. The follow-up evaluation included physical examination, chest radiography, and blood examination, including pertinent tumor markers. Whenever any symptoms or signs of recurrence were detected, further evaluation were performed, including CT of the chest and abdomen, brain MRI, bone scintigraphy. Since 2004, integrated PET scan and CT scan has also been performed when appropriate.

Data collection and analyses were approved, and the need to obtain written informed consent from each patient was waived by the Institutional Review Board in February 2011.

2.2. Histopathologic analysis

Surgically resected specimens from every case were fixed with 10% formalin or pure methyl alcohol and embedded in paraffin. Tumors were cut into 5-mm slices, and serial 4-μm sections were stained with hematoxylin and eosin (HE), alcian blue periodic acid Schiff stain, and Victoria blue-Van Gieson (VVG). All slides containing the maximum surface area of the tumor from each case were coded and masked for identifiable information, and were reviewed by 2 pathologists (Y.T. and G.I.). The median of slides from each case we reviewed in our study was 9 (range: 5–21).

Histological type was determined according to the World Health Organization classification [1], and disease stages were based on the TNM classification of the Union for International Control of Cancer, 7th edition [7,8]. The histological patterns were divided into distinct subtypes, and we assessed the proportion of each component: BAC/LG, acinar adenocarcinoma, papillary adenocarcinoma, and solid adenocarcinoma with mucin production. The presence of each component was recorded as the percentage of the total tumor composition in 10% increments. An LG component was considered to be positive if the tumor cells showed pure lepidic growth without invasive lesions (Fig. 1A–C) [1]. We performed univariate prognostic analysis employing various percentage cut-offs of LG components in 10% increments, to obtain the cut-off percentage that yielded the most evident difference in prognosis when the groups above and below the cut-off were compared.

2.3. Variables for prognostic analysis

We reviewed the medical records of each patient for their clinical data. The following 8 clinicopathological factors were assessed in the prognostic analysis: age (<68 years vs. ≥68 years), gender, smoking history (<20 pack-years vs. ≥20 pack-years), preoperative serum carcinoembryonic antigen level (CEA, institutional normal cut-off level: 5.0 ng/mL, <5.0 ng/mL vs. ≥5.0 ng/mL), pleural invasion (absence vs. presence), vascular invasion (absence vs. presence), lymphatic permeation (absence vs. presence), and percentage of LG components.

2.4. Measurement of non-cancerous cell collapse area

Fig. 1 shows the representative histological findings of a case with predominant LG components (80%), seen mostly in the tumor periphery (Fig. 1B and C). In the center of such tumors, a relatively large collapse area with few or no cancer cells was often observed (Fig. 1D). We defined these areas without cancer cells, which areas were separated from the closest cancer cells by greater than 1 mm, as non-cancerous cell collapse areas (NCCA). We identified collapse area on VVG staining (Fig. 1F) and then marked NCCA according to the definition on each maximum tumor surface area slide under a microscope and captured digital photographic images on a 20× magnification field (Fig. 1A and E dot-line). These images were then traced and measured for their marked areas by using an image analysis software, Image J (NIH, Bethesda, MD). NCCA was represented as percentage of maximum tumor surface area.

2.5. Measurement of tumor disappearance rate on chest computed tomography

To investigate the correlation between the proportion of LG component and computed tomographic findings, we compared tumor disappearance rate (TDR) in the histologically most representative 20 cases each from the 2 groups: LG-dominant type (LG component occupying 50% or more of the entire tumor) and non-LG dominant type. We calculated TDR using the following definition of tumor dimensions on chest high-resolution CT [9]: pDmax, the maximum dimension of a tumor on pulmonary window setting images; pDperp, the largest dimension perpendicular to the maximum axis on pulmonary window setting images; mDmax, the maximum dimension of a tumor on mediastinal window setting images; mDperp, the largest dimension perpendicular to the