Micropapillary and solid subtypes of invasive lung adenocarcinoma: Clinical predictors of histopathology and outcome

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Objective: To evaluate the clinical effect of the presence of a micropapillary or solid subtype on the outcomes in lung adenocarcinoma and to determine the predictors of such a histopathologic diagnosis.

Methods: A total of 511 patients with lung adenocarcinoma ≤3 cm were included. According to the presence of micropapillary or solid subtypes, we classified the patients into 4 subgroups: both subtypes absent (MP−/S−, n = 87), either subtype present (MP+/S−, n = 207 and MP−/S+, n = 196), and both present (MP+/S+, n = 21) to determine the association between the micropapillary or solid subtype and survival outcome or clinical and imaging conditions. Univariate and multivariate analyses were undertaken to determine the parameters, allowing the prediction of the presence of the micropapillary or solid subtype.

Results: Overall survival (OS) and disease-free survival (DFS) differed significantly among the 4 subgroups ($P < .001$ and $P = .004$, respectively). The MP−/S− tumors showed better DFS than those containing either the micropapillary or solid subtype. Patients with the micropapillary subtype had significantly worse OS than patients without the micropapillary subtype. This difference remained significant, together with stage, after adjustment for gender, age, adjuvant therapy, tumor size, and solid subtype (DFS and OS, $P = .016$ and $P = .002$, respectively). On multivariate analysis, greater than stage I, tumor size ≥2.5 cm, solid mass, and maximal standardized uptake value of ≥7 were independent predictors of the presence of a micropapillary or solid subtype.

Conclusions: Micropapillary and solid subtypes are common in tumors greater than stage I, with size ≥2.5 cm, pure solid type, and maximal standardized uptake value of ≥7, which were predictors for poor DFS. The presence of the micropapillary subtype was a single prognostic factor for OS. (J Thorac Cardiovasc Surg 2014;147:921-8)

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With advances in the understanding of lung adenocarcinoma (ADC), a new classification was published by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) in 2011.[1] In this novel proposal, they defined 5 distinctive subtypes of invasive lung ADCs in association with the prognosis, stating lepidic as favorable, acinar and papillary as intermediate, and micropapillary and solid as poor. In particular, micropapillary, which was not included in the 2004 World Health Organization classification, was added, and the clinical effect of this new subtype is one of the academic issues.

To date, several studies have attempted to determine the prognostic value of the histologic subtypes of the new lung ADC classification.[2-5] From these previous studies, we hypothesized that additional work about the predictive value of the histologic subtypes according to the IASLC/ATS/ERS proposal,[1] especially the micropapillary and solid patterns as poor prognostic factors, would improve the clinical relevance of this novel classification. In addition, clinical and radiologic parameters that can allow one to suggest the presence of a micropapillary or solid subtype would help predict the prognosis of patients with invasive ADC preoperatively.[6] In the present study, we investigated the effect of the presence of a micropapillary or solid pattern on overall survival (OS) and disease-free survival (DFS) in patients with invasive pulmonary ADC of all tumor stages. We also performed analyses to determine the clinical and radiologic predictors that could provide suggestions regarding the presence of a histopathologically proven micropapillary or solid pattern of ADC.

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Abbreviations and Acronyms

ADC = adenocarcinoma
ATS = American Thoracic Society
CI = confidence interval
CT = computed tomography
DFS = disease-free survival
ERS = European Respiratory Society
GGO = ground glass opacity
IASLC = International Association for the Study of Lung Cancer
MP = micropapillary
OR = odds ratio
OS = overall survival
PET = positron emission tomography
ROC = receiver operating characteristic
S = solid
SUVmax = maximal standardized uptake value

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METHODS

The institutional review board approved the present study (approval no. 2008-10-057), and informed consent was waived for the use of the patients' medical data.

Patients

Using an oncology database at Samsung Medical Center from September 2003 to August 2011, we identified 621 patients with completely resected solitary invasive lung ADC that was ≤3 cm. None had a history of neoadjuvant treatment. The diagnoses were made according to the criteria of the current World Health Organization classification for lung cancer.[7] Of the 621 patients, 68 were excluded because of prognosis-related factors: the presence of micrometastasis at surgery in 25 and the concomitancy of other cancer in 43. Another 42 patients were excluded because of radiology- or pathologically related factors: (1) insufficient pathologic slides for evaluation of the whole tumor (n = 26); (2) poor computed tomography (CT) image quality (n = 10); and (3) limited tumor evaluation owing to combined extensive inflammation or infarction (n = 6).

Thus, 511 patients (279 males, 232 females; median age, 61 years) were included in the present analysis (Figure 1). The median follow-up period was 77 months (range, 10.1-255.8). First, the patients were classified by the most predominant subtypes as follows: 49 (10%) with lepidic-predominant tumors, 267 (52%) with acinar-predominant tumors, 61 (12%) with papillary-predominant tumors, 107 (21%) with solid-predominant tumors, and 27 (5%) with micropapillary-predominant tumors. Next, we classified patients into 4 subgroups according to the presence of the micropapillary and solid subtypes: both subtypes absent (MP−/S−), micropapillary subtype present and solid subtype absent (MP+/S−), micropapillary subtype absent and solid subtype present (MP−/S+), and both present (MP+/S+). Such subtyping was conducted to determine the association between the micropapillary and/or solid subtype and OS and DFS and the clinical and radiologic findings. Of the 511 ADCs, 87 were classified as MP−/S− (17.0%), 207 as MP+/S− (40.5%), 196 as MP−/S+ (38.4%), and 21 as MP+/S+ (4.1%). Finally, to investigate the clinical and radiologic parameters predicting the presence of the micropapillary or solid subtype, we divided the patients into 2 groups: those with tumors containing either the micropapillary or solid subtype (n = 424) and those without tumors containing either subtype (n = 87).

Clinical Assessment

The clinical information was available from the patient medical records. We screened the data, including gender, age, tumor stage using the TNM classification, resection type, adjuvant therapy, survival, and disease progression. OS was defined as the interval from surgery to the date of death or final follow-up visit. DFS was defined as the interval from surgery to the point of any definite clinical or pathologic evidence of local or distant disease recurrence or last evaluation.

Imaging and Interpretation

The imaging characteristics of each primary lung tumor were evaluated using chest CT and the positron emission tomography (PET) component images of PET-CT (see Appendix E1). PET-CT and chest CT were performed within the 2-week period from surgery. The imaging methods have been described in detail in previous reports.[2,8]

Two radiologists (E.J. L. and H.S.H., with 5 and 7 years of experience in chest radiology, respectively), who were unaware of the clinical information, independently evaluated the CT scans. The CT scans were retrieved using the Picture Archiving and Communications System (Centricity, GE Healthcare, General Electric, Fairfield, Conn). The radiologic parameters, including tumor size, lesion density, tumor solidity, margin status, and the presence of spiculations or lobulations were recorded. The largest diameter measurements were obtained manually using the Picture Archiving and Communications System measurement electronic tool in all cases. For measurements of lesion density, the region of interest covering each target lesion was drawn on the axial postcontrast-enhanced scan as large as possible (at least two thirds of the longest diameter). The mean CT attenuation value with standard deviation was measured in Hounsfield units. Tumor solidity was categorized as solid, partly solid, and ground glass opacity (GGO). GGO on the CT scans was defined as a hazy increase in lung density without obscuration of the pulmonary vessels. The tumor margin was classified as well-defined or ill-defined. Spiculation or lobulation was defined as a radiologic outline of the lesion showing sharp points or smooth protrusions into the surrounding tissue, respectively.

All PET images were reviewed by an experienced nuclear medicine physician (B.T.K., with 13 years of experience in PET-CT interpretation). The fluorodeoxyglucose uptake of the primary cancer was quantified by calculating the maximal standardized uptake value (SUVmax) using PET region-of-interest analysis.

Pathologic Evaluation

Whole tumor tissue sections were obtained, and each was placed on a slide. Comprehensive histologic subtyping was performed by 2 pathologists (J.H.H. and J.Y.J., with 18 and 5 years of experience in pulmonary pathology, respectively), together at a multihead microscope, and discussed until consensus was achieved. The tumors were divided into 6 distinctive subtypes according to the IASLC/ATS/ERS classification scheme as (1) lepidic, (2) acinar, (3) papillary, (4) micropapillary, (5) solid, and (6) a variant, including mucinous (Figure E1). For each case, histologic subtyping was performed for the primary tumor in a semiquantitative manner, to the nearest 5% level, summing to a total of 100% subtype components per tumor. For the micropapillary and solid subtypes, we also considered the micropapillary or solid subtype to be present when the subtype occupied ≥1% of the entire tumor.[9] Next, the most predominant pattern in a mixed-type ADC was defined as the histopathologic subtype that constituted the greatest percentage of the tumor. The lowest limit for the predominant subtype was set at 30%, as previously described.[1]

Statistical Analysis

The clinical prognostic parameters of each subgroup were compared using 1-way analysis of variance with the post hoc test of Bonferroni. The DFS and OS were estimated using the Kaplan-Meier method, and the log-rank test was used to evaluate the differences among the subgroups.