Commentary

Adenocarcinoma containing lepidic growth

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Lepidic growth adenocarcinoma

Lepidic growth adenocarcinoma is defined as tumor cells proliferating along the surface of intact alveolar walls without stromal or vascular invasion pathologically (1). The traditional viewpoint has been that of Noguchi *et al*. (2) who demonstrated that localized bronchioloalveolar carcinoma (LBAC) showed replacement growth of alveolar-lining epithelial cells with a relatively thin stroma, that LBAC with foci of structural collapse of alveoli were in situ peripheral adenocarcinoma, and that lung cancer patients with these LABCs achieved 100% survival after lobectomy. Recently, Travis *et al*. (3) proposed a classification of lung adenocarcinoma based on the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) recommendations. They did not use the terms bronchioloalveolar carcinoma or mixed subtype, and they classified adenocarcinoma in situ (AIS) as pure lepidic growth, and minimally invasive adenocarcinoma (MIA) as predominant lepidic growth containing invasion foci of less than 5 mm for small (less than 3 cm) solitary adenocarcinomas. In addition, invasive lepidic predominant adenocarcinoma (LPA) was defined as a lepidic growth containing invasion foci of more than 5 mm. They described that solitary adenocarcinomas with pure lepidic growth, termed "AIS", defineed patients who should have 100% disease-specific survival, if the lesion was completely resected. They also described that invasive adenocarcinomas with predominant lepidic growth and small foci of invasion measuring less than 0.5 cm, termed "MIA", defined patients who have near 100%, disease-specific survival, if completely resected.

Adenocarcinoma with radiological ground glass opacity (GGO)

The previously described IASLC/ATS/ERS classification is a pathological one. It is therefore an important issue to predict pathological features clinically. A tumor with lepidic growth is classified into pure GGO or part-solid nodule based on computed tomography (CT). A pure GGO tumor almost corresponds to AIS or atypical adenomatous hyperplasia (AAH). AAH is defined as a localized tumor, ≤0.5 cm in tumor size, with proliferation of atypical type II pneumocytes and/or Clara cells lining alveolar walls (3). Conversely, a part-solid nodule almost corresponds to MIA or invasive adenocarcinomas with predominant lepidic growth.

Hattori *et al*. (4) newly reported the prognostic impact of tumor size based on the consolidation status by thin-section CT. They investigated 1,181 resected patients with clinical N0 M0 non-small cell lung carcinomas. They classified the tumor into three groups, pure GGO, part-solid, and solid nodules based on radiological features. Their pure GGO nodules (n=168) consisted of AAH (3.0%), AIS (58.3%), MIA (14.3%), LPA (14.3%), and adenocarcinoma (16.7%) pathologically. Part-solid nodules (n=448) consisted of AAH (0.7%), AIS (8.0%), MIA (12.5%), LPA (23.2%), and adenocarcinoma (55.6%). Solid nodules (n=565) consisted of AIS (0.9%), MIA (0.4%), LPA (7.2%), adenocarcinoma (57.2%), squamous cell carcinoma (26.2%), and others (8.1%). Five-year overall survival (OS) was 100% for patients with pure GGO nodules. For patients with part-solid nodules, 5-year overall survival of patients with a tumor size of ≤20 mm (n=272) was 97.7%, of 21–30 mm (n=115) was 94.6%, and of 31–50 mm (n=61)

was 93.4% (P=0.1028). The consolidation/tumor ratio (CTR) was defined as a tumor with a maximum diameter of consolidation of the maximum tumor diameter in thin-section CT (5). They classified tumors into two groups by CTR, namely, a GGO dominant (0< CTR ≤0.5) tumor and a solid dominant (0.5< CTR <1.0) tumor in the part-solid nodule group. The 5-year overall survival of GGO dominant (n=187) was 98.5% and that of solid dominant (n=261) was 95.0% (P=0.1247). They also showed that carcinoembryonic antigen (CEA) was an independent significant clinical predictor of OS as well as of relapse free survival (RFS) in multivariate analysis. However, maximum tumor size, solid component size, and CTR were not associated with either OS or RFS in part-solid nodules. Conversely, in solid nodules, the 5-year overall survival of patients with a tumor size of ≤20 mm (n=206) was 83.0%, of 21–30 mm (n=161) was 75.4%, of 31–50 mm (n=132) was 56.2%, and of >51 mm (n=66) was 45.3% (P<0.0001). They also demonstrated that age, male, and maximum tumor size were independent significant clinical predictors of OS in part-solid nodules by multivariate analysis. In overall tumor types (pure GGO, part-solid, and solid nodules), a multivariate analysis revealed that age, sex, CEA, maximum tumor size, and the presence of a GGO component were independent significant clinical predictors of OS. Tsutani *et al.* (6) demonstrated that solid tumor size has a greater predictive value for prognosis in clinical stage IA lung adenocarcinoma than that of whole tumor size. Their study (6) analyzed whole tumor types including pure GGO, part-solid, and solid nodules. Hattori's study (4) is impressive and interesting in terms of the fact that they found that evaluation of the maximum tumor size should be applied only to a solid tumor without GGO, and not to either a pure GGO or a part-solid tumor. In their study, the adenocarcinoma population was composed of 55.6% part-solid and 57.2% solid nodules. If the adenocarcinoma of the part-solid nodules showed a different prognosis compared with that of the solid nodules, the pathological features or biological behavior of part-solid adenocarcinoma may be different from those of 'pure' solid adenocarcinoma. They did not mention histological differentiation of adenocarcinoma of either part-solid or solid nodules radiologically. However, part-solid adenocarcinoma have a well differentiated lepidic growth in the outer area of the tumor, and therefore, it may have similar pathological features in the central solid area. Okada *et al.* (7) demonstrated that maximum standardized uptake value (SUVmax) of 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) was a significant preoperative predictor for surgical outcomes. They showed an optimal SUV cut-off value of 2.5 to predict high-grade malignancy. Another report, that of Hattori *et al.* (8), which was from the same author and institution from which the main introduction paper (4) in this commentary was drawn, showed that lymph node metastasis is frequently observed for 'pure' solid tumors, especially for tumors that show a high SUVmax compared with pure GGO and part-solid nodules.

Surgical procedure for GGO dominant adenocarcinoma

Lepidic growth adenocarcinoma has a good prognosis and could be candidates for sublobar resection instead of standard lobectomy (9-11). In Hattori's study (4), surgical procedures of pure GGO were lobectomy (20.8%), segmentectomy (35.1%), and wedge resection (44.1%). In part-solid nodules, lobectomy (68.8%), segmentectomy (27.7%), and wedge resection (8.5%) were performed. In solid nodules, pneumonectomy (1.2%), lobectomy (85.5%), segmentectomy (7.5%), and wedge resection (5.8%) were performed. In addition, the surgical procedure for GGO dominant (0< CTR ≤0.5) and solid dominant (0.5< CTR <1.0) tumors in part-solid nodules were lobectomy (49.7% *vs.* 73.9%, respectively), segmentectomy (37.4% *vs.* 20.7%, respectively), and wedge resection (12.9% *vs.* 5.3%, respectively) (P<0.0001). However, it is interesting that there were no significant differences in 5-year OS between the two groups. Kodama *et al.* (12) demonstrated that the 10-year OS and RFS of lobectomy and segmentectomy were not significantly different from propensity score matching analysis. Their matched characteristics were less than 70 years old, tumor size of approximately 1.5 cm, and part-solid tumor with GGO.

Conclusions

Hattori's study (4) indicated that therapeutic management of a tumor containing GGO is clearly different from that of a 'pure' solid tumor. Radiologically, an adenocarcinoma containing GGO may be considered to classify a T stage different from that of a solid tumor.

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Footnote

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Comment on: Hattori A, Matsunaga T, Takamochi K, *et al*. Neither Maximum Tumor Size nor Solid Component Size Is Prognostic in Part-Solid Lung Cancer: Impact of Tumor Size Should Be Applied Exclusively to Solid Lung Cancer. Ann Thorac Surg 2016;102:407-15.

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