Editorial

Neither the maximum tumor size nor solid component size is prognostic in part-solid lung cancer: to be ground-glass opacity or not to be, is that really the question?

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Hattori *et al.* (1) retrospectively analyzed the oncologic outcomes of 1,181 patients with surgically resected clinical N0 M0 non-small cell lung carcinoma (NSCLC). They reported that maximum tumor size was a significant prognostic factor in patients with all T stages of solid tumors without a ground-glass opacity (GGO) component. Moreover, there were significant differences in 5-year overall survival (OS) among each tumor size group. In contrast, patients with pure GGO tumors had a 5-year OS rate of 100%. Patients with part-solid lung cancers had a 5-year OS of more than 90%, and additionally, maximum tumor size, solid component size, and consolidation tumor ratio (CTR) were not prognostic factors. Based on these results, the authors concluded that neither the maximum tumor size nor solid component size has any prognostic value in patients with radiologically nonsolid or part-solid lung cancer. Therefore, they recommend classifying pure GGO and part-solid lung cancers independently of the maximum tumor and solid component sizes, and describing them as clinical-Tis and clinical-T1a, respectively.

Based on the pathoradiological correlation results in the Japan Clinical Oncology Group (JCOG) 0201 study (2,3), the radiological criterion to distinguish noninvasive from invasive lung adenocarcinoma is defined as a CTR ≤0.50 in c-T1a and c-T1b tumors (<3 cm), and an excellent prognosis is predicted for such radiologically defined noninvasive adenocarcinomas (2,3). However, in their study, Hattori *et al.* evaluated and compared OS between patients with GGO-dominant (0< CTR ≤0.50) and solid-dominant tumors (0.5< CTR <1.0) in patients with radiologically part-solid lung cancer (these cases were all adenocarcinomas). The oncologic outcomes did not differ between these two groups if solid lung cancer cases were excluded from the cohort.

We were interested in the differences between the results of these two studies, both of which analyzed a patient cohort with adenocarcinoma. We have three comments for the study by Hattori *et al.* concerning this point.

- We have concerns related to their radiological evaluations on thin-section CT. They defined a pure GGO tumor as a lung tumor without a solid component (i.e., CTR =0), a part-solid tumor as a lung tumor with both GGO and a solid component (i.e., 0< CTR <1.0), and a solid tumor as a tumor showing only consolidation without GGO (i.e., CTR =1.0). We occasionally encounter tumors with a GGO component that is difficult to judge, even if the tumor histology indicates non-adenocarcinoma (4). How did the authors distinguish between tumors with slight GGO component (e.g., 0.95< CTR <1.0) and those without a GGO component (e.g., CTR =1.0)? We believe that these radiological evaluations can be subjective and can affect the outcomes of such studies directly. Our main concern is that radiological evaluations may result in discrepancies in outcomes among studies, including those of this study (1-3,5). Therefore, we support the classical radiological definition used in JCOG 0201, which does not distinguish tumors only by the presence or not of a GGO component;
- In this study, the median follow-up period was too short (median: 43 months) to determine the actual

Table 1 Survival and recurrence of postoperative patients according to *EGFR* mutation status

No. of patients (WT/mutant)	EGFR-WT	*EGFR*-mutant	Refs.
307 non-Sq (245/62)	Recurrence rate 21.6%; median DFS 7.0 yr; 5 yr OS 73%	Recurrence rate 9.7%; median DFS 8.8 yr; 5 yr OS 98%	(10)
58 adenocarcinoma (32/26)	2 yr PRS 47%	2 yr PRS 81%	(11)
172 adenocarcinoma (86/86); matched pair analysis	3/5 yr RFS 74/60%; 3/5 yr OS 80/72%	3/5 yr RFS 85/78%; 3/5 yr OS 92/87%	(12)

EGFR, epidermal growth factor receptor; Sq, squamous cell carcinoma; OS, overall survival; PRS, post-recurrence survival; RFS, recurrence-free survival; DFS, disease free survival.

oncologic outcomes for stage I or GGO tumors due to their indolent nature. Maeda *et al.* (6) reported that 21 of 519 patients with stage IA NSCLC who underwent complete resection developed a late recurrence >5 years after resection (recurrence was locoregional in 9 patients and distant in 12). Furthermore, Yoshida *et al.* (7) reported three cases of delayed cut-end recurrence after limited resection of GGO adenocarcinomas that had been intraoperatively diagnosed as Noguchi Type B. All three cases developed a cut-end recurrence >5 years after resection. Noguchi Type B is equivalent to adenocarcinoma in situ (AIS) according to the new classification for adenocarcinoma (IASLC/ATS/ERS 2011) (8). Therefore, the median follow-up time used by Hattori *et al.* was too short to confirm their conclusion regarding the importance of the GGO component as a significant clinical T descriptor. Moreover, the patient sample size was too small to conclude an outcome. The authors concluded that neither the maximum tumor size nor CTR was prognostic in 448 patients with part-solid lung cancer. Although the differences reported were not significant, a larger tumor size and higher CTR were related to a poorer outcome. The limited tumor sample size and retrospective nature of their study should be taken into consideration;

- The prognosis of patients with adenocarcinoma largely depends on the presence of driver gene mutations, including mutations in the epidermal growth factor receptor (*EGFR*) gene (9) (*Table 1*). This is because tyrosine kinase inhibitors (TKIs) markedly prolong the OS of patients with *EGFR*-mutant tumors (13,14). We must consider driver gene mutations in the assessment of OS as an oncologic outcome. Besides, the subgroups with radiologically nonsolid or part-solid lung cancers in this study included high proportions of AIS, minimally invasive adenocarcinoma, and lepidic predominant adenocarcinoma. Therefore, the *EGFR* mutation rate is also significantly higher in these subgroups than in the other subgroups, such as those with solid or other histological types (15). Therefore, *EGFR* mutation must be considered a significantly favorable prognostic factor before and after recurrence. Thus, this study's outcome may be related more to the *EGFR* mutation status than the clinical T factor.

Lung cancer staging classification has a strong effect on the management and treatment strategies for NSCLC. However, the recent development and validation of a new generation of EGFR-TKIs and immune checkpoint inhibitors have greatly prolonged the survival of patients with advanced lung cancer, even after recurrence (9,13,14,16,17). Because such new treatments affect both OS and progression-free survival (PFS), they will influence forthcoming TNM classifications. We should reconsider whether OS or PFS is more adequate to evaluate the outcome of a new treatment. Furthermore, the *EGFR* mutation status should be considered in TNM classification in this molecular-based therapeutic era.

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Footnote

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