

# How to manage patients with subcentimeter non-small cell lung cancer?

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*Comment on:* Hattori A, Matsunaga T, Hayashi T, *et al.* Prognostic Impact of the Findings on Thin-Section Computed Tomography in Patients with Subcentimeter Non-Small Cell Lung Cancer. *J Thorac Oncol* 2017;12:954-62.

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Since the 1970s, tumor size has been a primary descriptor and significant prognostic factor for lung cancer in the tumor, node, metastasis (TNM) staging system of the Union for International Cancer Control (1). As tumor size reflects cancer progression, is strongly correlated with prognosis and is easy to measure, it has held a prominent position as a tumor descriptor. Meanwhile, advances in radiological modalities including thin-section computed tomography (CT), have allowed detection of small-sized lung cancers, and these radiological findings have enabled prognostic stratification in lung cancer. The results of several studies that evaluated correlations between radiological and pathological findings of lung cancer with regard to malignant behavior showed that radiologic non-solid or part-solid lung cancer with ground-glass opacity (GGO) components had a good prognosis (2-5).

In the current issue of *Journal of Thoracic Oncology*, Hattori and colleagues reported the prognostic impact of thin-section CT results of patients with non-small cell lung cancer (NSCLC) 1.0 cm or less in size (2). They evaluated 328 patients who received surgical resection for clinical N0 M0 NSCLC 1.0 cm or less in size. Patients were divided into three groups according to the ration of maximum diameter of consolidation to the maximum tumor diameter (CTR). The non-solid tumor was defined as a tumor of CTR =0 (n=139), part-solid tumor was defined as a tumor of 0< CTR <1 (n=123) and solid tumor was defined as a tumor of CTR =1 (n=66). They reported that 5-year overall

survival (OS) and recurrence-free survival (RFS) rates were significantly better in patients with non-solid tumors (OS and RFS =100%) or part-solid tumors (OS =97.5%, RFS =94.9%) than patients with pure-solid tumors (OS =87.6%, RFS =79.3%). They therefore concluded that radiological solid subcentimeter NSCLC should be treated as invasive cancer regardless of their small size (2). They evaluated a relatively large number of subcentimeter cases, which are a rare entity among surgically resected NSCLC, and they emphasized a malignant behavior of pure-solid tumors. In particular, 53% of pure-solid tumors were invasive adenocarcinomas, and 10.6% of those had nodal involvement. Additionally, recurrence occurred in 15.1% of the subcentimeter pure-solid tumor cases (2). The results of this study suggested that the presence of GGO was a favorable prognostic factor, and the conclusion that pure-solid subcentimeter lung cancer should be treated as invasive cancer regardless of their small tumor size may be acceptable. However, there have been several concerns regarding surgery for such small cancers.

First, how many cases of subcentimeter NSCLC have been considered for surgery with confidence that there are such subcentimeter nodules? The diagnostic and treatment strategy for small pulmonary nodules should be considered taking into account the probability of malignancy, difficulty of diagnostic study, risk of surgery, and the individual patient preference. Although the author did not mention surgical cases of non-cancerous nodules, the probability

of malignancy is 0–1% among pulmonary solid nodules smaller than 5 mm in diameter, and only 6–18% for those 5 to 10 mm in diameter according to the previous lung cancer screening trials (6). Surgically resected non-cancerous nodules may increase with the presence of surgically resected subcentimeter NSCLC without any hint of findings suggestive of cancer. Hattori *et al.* separately reported the relationship between fluorodeoxyglucose-positron emission tomography (FDG-PET) findings and subcentimeter lung cancer (7). They reported that the SUV<sub>max</sub> on FDG-PET reflected tumor invasiveness and had a great impact on the prognosis of subcentimeter NSCLC, especially in pure-solid tumors. Although PET is not indicated for small pulmonary nodules of less than 8 mm in diameter in the ACCP guidelines due to the significant risk of false-negative findings for small lesions (8), FDG-PET may facilitate accurately diagnosing subcentimeter nodules in some cases.

Second, what type of surgery is the optimal method for subcentimeter nodules? The authors recommended anatomical resection with intraoperative lymph node dissection for pure-solid tumors to prevent locoregional recurrence. Unfortunately, due to its retrospective design, surgical procedures were not uniform in their study. Lobectomy was performed in 17% of pure-GGO cases, 39% of part-solid tumors and 64% of pure-solid tumors. Wedge resection was performed on 19% of pure-solid tumors (2). In fact, there have been no lymph node metastases in pure-GGO or part-solid nodules; therefore, hilar and mediastinal lymph node dissection may be unnecessary in such cases. Thus, the appropriate surgical procedure for pure-solid tumors cannot be concluded according to the results of their study. Although wedge resection may be insufficient for pure-solid tumors in light of the possibility of lymph node metastases, it is not known whether lobectomy is needed for such cases. To address this question, randomized controlled trials with peripherally located NSCLC of 2 cm or less diameter were started by the Japan Clinical Oncology Group (JCOG 0802) in Japan (9) and by the Cancer and Leukemia Group B (CALGB 14053) in the United States. The results of those phase-III studies, which were conducted to evaluate the non-inferiority of segmentectomy compared with lobectomy in patients with small-sized peripheral NSCLC, segmentectomy may become a standard therapy for low-grade lung cancer in the future.

Third, in the 8th edition of the TNM classification for NSCLC, T classifications from T1 to part of T4 are classified by tumor size, with only the size of the solid

area on CT or the size of the invasive area at pathological examination being considered, as the size of the solid/invasive component determines prognosis (10). In the new TNM classification, subcentimeter nodules are classified into Tis, Tmi and T1a according to the size of the solid component.

Although the authors described the presence of GGO as a favorable clinical factor for survival, whether patients with solid tumors should be treated similarly to patients with part-solid tumors with equal-sized solid components is controversial. In light of the authors' recommendation, in some situations a paradoxical situation arises where anatomical resection is needed for low-grade T descriptor pure-solid cancer but wedge resection is enough for high-grade T descriptor part-solid GGO tumors. A validation large cohort study corresponding to the new TNM classification is expected to clarify treatment strategies for subcentimeter NSCLC.

In conclusion, Hattori *et al.* reported the surgical outcomes of patients with subcentimeter NSCLC. Given the progress of imaging diagnostics and the widespread use of chest CT screening, an increase in the early detection rate for small-size lung cancer is anticipated in the future. Studies that evaluate the rare entity of surgically resected NSCLC will help operative decision-making for patients with subcentimeter NSCLC in the future.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

### References

1. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997;111:1710-7.
2. Hattori A, Matsunaga T, Hayashi T, *et al.* Prognostic Impact of the Findings on Thin-Section Computed Tomography in Patients with Subcentimeter Non-Small Cell Lung Cancer. *J Thorac Oncol* 2017;12:954-62.
3. 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.
4. Matsuguma H, Oki I, Nakahara R, et al. Comparison of three measurements on computed tomography for the prediction of less invasiveness in patients with clinical stage I non-small cell lung cancer. *Ann Thorac Surg* 2013;95:1878-84.
  5. Tsutani Y, Miyata Y, Yamanaka T, et al. Solid tumors versus mixed tumors with a ground-glass opacity component in patients with clinical stage IA lung adenocarcinoma: prognostic comparison using high-resolution computed tomography findings. *J Thorac Cardiovasc Surg* 2013;146:17-23.
  6. Wahidi MM, Govert JA, Goudar RK, et al. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:94S-107S.
  7. Hattori A, Matsunaga T, Takamochi K, et al. Clinical Significance of Positron Emission Tomography in Subcentimeter Non-Small Cell Lung Cancer. *Ann Thorac Surg* 2017;103:1614-20.
  8. Patel VK, Naik SK, Naidich DP, et al. A practical algorithmic approach to the diagnosis and management of solitary pulmonary nodules: part 1: radiologic characteristics and imaging modalities. *Chest* 2013;143:825-39.
  9. Nakamura K, Saji H, Nakajima R, et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). *Jpn J Clin Oncol* 2010;40:271-4.
  10. Rami-Porta R, Asamura H, Travis WD, et al. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017;67:138-55.

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