Editorial

Should a therapeutic strategy be based on how the disease was diagnosed?

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Provenance: This is an invited Editorial commissioned by the Section Editor Mong-Wei Lin (Division of Thoracic Surgery, Department of Surgery, National Taiwan University Hospital and Taiwan University College of Medicine, Taipei).

Comment on: Flores RM, Nicastri D, Bauer T, *et al.* Computed Tomography Screening for Lung Cancer: Mediastinal Lymph Node Resection in Stage IA Nonsmall Cell Lung Cancer Manifesting as Subsolid and Solid Nodules. Ann Surg 2017;265:1025-33.

Submitted Jan 26, 2018. Accepted for publication Feb 12, 2018.
doi: 10.21037/jtd.2018.02.92
View this article at: http://dx.doi.org/10.21037/jtd.2018.02.92

As computed tomography (CT) screening has become routine, an increasing number of early-stage lung cancers are being identified. Thus far, surgical resection is considered to provide the best opportunity to cure stage IA non-small cell lung cancer (NSCLC) and other early-stage tumors. However, the extent to which the lung and lymph nodes should be resected is unclear. The retrospective analysis by Flores *et al.*, "*Computed Tomography Screening for Lung Cancer: Mediastinal Lymph Node Resection in Stage IA Nonsmall Cell Lung Cancer Manifesting as Subsolid and Solid Nodules*" published in the *Annals of Surgery* (1) tackled this important question in a comparison of the long-term survival rates of patients with primary clinical stage IA NSCLC. These patients were part of a large cohort within the International Early Lung Cancer Action Program (I-ELCAP) study who underwent CT screening with or without mediastinal lymph node resection (MLNR) (either lymph node sampling or dissection). The authors concluded that MLNR is not mandatory when screen-diagnosed NSCLC manifests as a subsolid nodule. However, this conclusion has been questioned in several comments and editorials pointing out the multiple limitations of an ad-hoc retrospective analysis (2-4). The controversy has highlighted the importance of this topic.

Among the multiple limitations of this study, the selection bias between the MLNR and non-MLNR groups is particularly important. The MLNR group indeed comprised patients with a higher oncological risk than the non-MLNR group; their tumors were more centrally located and of larger size and the patients had a longer smoking history. Consequently, in the MLNR group lobectomy rather than limited resection was more often performed. It is plausible that surgeons assessed these patients and their disease to the best of their ability, based on their experience and knowledge, and selected what they considered to be the appropriate surgical procedure (i.e., lobectomy and complete lymph node dissection for higher-risk patients), such that the results were similar. The survival of patients who presented either with a subsolid nodule or a nodule consisting either totally or partially of ground glass opacity (GGO) was reported to be 100%. However, given the heterogeneity of the compared groups, it is rather misleading to conclude that their outcomes were not statistically different and that lymph node resection is therefore unnecessary.

Moreover, the authors' conclusion implied that MLNR in patients with subsolid stage IA NSCLC could be omitted if the tumors had been screen-diagnosed, as was the case in the study population. However, a screen-based diagnosis clearly does not provide any biological information regarding the lung cancer; rather, it enables the detection of lung cancer at an earlier, less invasive biological stage, which is indeed the purpose of cancer screening. NSCLCs manifesting as a subsolid nodule are heterogeneous and so are those detected by screening. A screen-based diagnosis is therefore unable to reveal any of the biological features of

an individual nodule, but the therapeutic strategy for lung cancer or any other form of cancer should be determined based on the biological characteristics and clinical staging of the tumor as well as the patient's condition, regardless of the method used in disease detection.

Ideally, in the era of precision medicine and increasingly personalized therapeutic strategies, decision-making by surgeons should reflect the best of our efforts and be based on accurate clinical staging and the radiological characteristics of the tumor, especially in the absence of a molecular diagnosis or genomics information. The final results of prospective randomized trials such as JCOG 0802/WJOG4607L and CALGB140503, comparing lobectomy and sublobar resection, are still awaited but the days of standard lobectomy with lymph node dissection (5) may finally be ending, at least for small tumors with a GGO component. The impact of the degree of GGO has been assessed in multiple studies. For example, Haruki *et al.* reported that among 133 patients with GGO-dominant clinical stage I lung adenocarcinoma none had pathologically positive mediastinal lymph nodes, while 10% of the patients with solid-dominant adenocarcinoma had mediastinal metastasis (6). Although it was unclear how many of the mostly solid tumors contained a GGO component or corresponded to the subsolid nodule in the study of Flores *et al.*, the study demonstrated the occurrence of mediastinal lymph node metastasis in a certain percentage of them, including the subsolid nodules. Moreover, the measurement of GGO% remains more or less subjective despite the introduction of the 8th edition of the UICC-TNM classification. In a multi-institutional confirmatory phase III trial in Japan (JCOG0804/WJOG4507L) aiming at evaluating the efficacy and safety of sublobar resection (basically, wedge resection) for peripheral GGO-dominant lung cancer, approximately one-fourth of the tumors thought to be non-invasive adenocarcinoma were pathologically diagnosed as Noguchi type C or higher (7), suggesting that radiologically benign characteristics do not guarantee less invasiveness as determined pathologically. In the prospective randomized study American College of Surgeons Oncology Group (ACOSOG) Z0030, addressing lymph node dissection, there was no difference between complete mediastinal lymph node dissection and sampling, on the strict condition that the patients were free of hilar N1 disease (8). This was not the case in the study of Flores *et al.*, in which complete lymph node dissection and sampling were grouped together and compared with no lymph node resection regardless of hilar N1 disease. Thus, before lymph node dissection or even sampling can be safely omitted, more precise strategies, such as sentinel node navigation surgery (9) or examination of the effect of lobe-specific lymph node resection, are required.

While further stratification is certainly needed for "screen-diagnosed" subsolid stage IA NSCLC, there are data that stratify patients better than simple screen-diagnosed subsolid stage IA. It is therefore premature for surgeons to abandon the special tools that enable the highly sensitive and specific diagnosis of mediastinal (and hilar) lymph nodes and thus accurate staging, as these methods increase the opportunity of achieving disease cure by appropriate and complete lung resection with or without adjuvant chemotherapy. However, pulmonary function, quality of life, and the possibility of second and third primary lung cancer in the future may also be taken into account in determining the surgical strategy. Nonetheless, the negative impact of mediastinal lymph node dissection should be much less than that of recurrent disease even in clinical stage IA lung cancer.

Acknowledgements

I thank the Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Footnote

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

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Cite this article as: Sato M. Should a therapeutic strategy be based on how the disease was diagnosed? J Thorac Dis 2018;10(3):1245-1247. doi: 10.21037/jtd.2018.02.92

