Editorial

Saving time is saving lives: a delayed lobectomy predicts poorer overall survival in patients with clinical stage IA squamous cell carcinoma of the lung

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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: Yang CJ, Wang H, Kumar A, *et al.* Impact of Timing of Lobectomy on Survival for Clinical Stage IA Lung Squamous Cell Carcinoma. Chest 2017;152:1239-50.

Submitted Jul 05, 2018. Accepted for publication Jul 23, 2018.
doi: 10.21037/jtd.2018.07.115
View this article at: http://dx.doi.org/10.21037/jtd.2018.07.115

A timely treatment of patients with malignancies generally portends better clinical outcomes—a finding which has been consistently replicated for both systemic and local therapies. In this regard, studies conducted in patients with bladder and esophageal tumors have shown that a prolonged time from diagnosis to surgery can yield to pathological upstaging (1,2). Similarly, a delay in radiotherapy has been associated with an increased risk of local recurrence in head and neck malignancies (3).

However, the consequences of waiting for surgery in patients with lung tumors remain controversial. In a single-center study, Quarterman *et al.* have previously reported that time to surgery does not significantly affect survival in early-stage lung cancer (4). In an analysis of a nationwide data set, Aragoneses *et al.* examined the prognostic impact of different surgical waiting times (categorized in intervals) and—similarly—did not find any significant difference even between extreme categories (i.e., 1–20 waiting days versus >60 waiting days) (5). Contrary to these findings, Samson and coworkers have shown that longer delays for lung cancer surgery increase the risk of upstaging and adversely affect prognosis (6). Two potential explanations for these apparent discrepancies may be offered. First, an unequivocal definition of delayed surgery is still lacking, with the term "delay" indicating different time periods across studies. Second, lung cancer is a heterogeneous disease—ranging from indolent, slow-growing adenocarcinomas [presenting as ground-glass opacities (GGOs)] to highly aggressive small cell carcinomas that tend to metastasize early (7).

Using the National Cancer Data Base, the recent work by Yang *et al.* makes a remarkable attempt to shed more light on the prognostic impact of wait times for lobectomy in stage Ia squamous cell carcinoma of the lung (8). Owing to the large number of cases included in this data set, the authors were able to focus on (I) a particular patient subgroup (i.e., those with stage Ia squamous cell carcinoma of the lung); and (II) a specific surgical procedure (i.e., lobectomy). As a consequence, several potential sources of confounding (e.g., the inclusion of different histology types, disease stages, and/or surgical approaches) were ultimately removed. Another methodological strength is the exclusion of patients who underwent surgery on the same day of diagnosis (who may differ significantly in terms of general characteristics from those who had not been immediately operated).

In this well-designed retrospective study, a highly homogeneous cohort of 4,984 patients was followed-up for a median of 32 months. Using a cutoff value of 38 days to distinguish between early (<38 days from diagnosis) and late (≥38 days from diagnosis) surgical interventions, the authors found that early surgery was associated with a more favorable overall survival (OS). Notably, late

surgery was identified as an adverse independent predictor of OS in multivariable analysis (hazard ratio =1.13; 95% confidence interval, 1.02–1.25; P=0.02). Based on these results, the authors concluded that longer delays for lobectomy adversely affect prognosis in patients with stage I squamous cell carcinoma of the lung. Unfortunately, the mechanisms by which a longer time to surgery might lead to an increase in mortality were not discussed in detail. It has been previously shown that an operative delay may result in pathological upstaging (6). However, Yang *et al.* did not report significant intergroup differences in terms of pathological T and N stage in the early versus late surgery groups. These observations indicate that (I) pathological upstaging is not a critical determinant for the link between time to surgery and prognosis; and (II) the exact mechanisms underlying the observed prognostic impact of surgical wait times remain to be determined. Differently from OS (which is notoriously prone to the effect of different types of confounding), disease-free survival would have been a more suitable outcome measure in the study by Yang *et al.* However, the lack of recurrence data precluded further survival analyses. Besides patients with squamous cell carcinoma of the lung, several questions remain open with regard to cases with early-stage adenocarcinoma. Has a prolonged wait time to surgery the same adverse prognostic impact in this patient group? What is the optimal cutoff to distinguish delayed from early surgical treatment in early-stage adenocarcinoma? Do patients with adenocarcinoma presenting with GGOs require an active invasive treatment (9)? Owing to the indolent nature of pure pulmonary GGOs, some authors have advocated limited or even delayed removal (7,10,11). All of these open issues need to be specifically addressed in future studies. Notwithstanding certain methodological limitations, Yang and colleagues need to be congratulated for bringing out this significant contribution on the prognostic significance of surgical wait times. It will surely serve as a valuable reference for thoracic surgeons who care for patients with early-stage squamous cell carcinoma of the lung (8).

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Wu CF, Chao YK. Saving time is saving lives: a delayed lobectomy predicts poorer overall survival in patients with clinical stage IA squamous cell carcinoma of the lung. J Thorac Dis 2018;10(Suppl 26):S3147-S3148. doi: 10.21037/jtd.2018.07.115

