

Limited resection versus lobectomy in early-stage non-small cell lung cancer

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Submitted Oct 21, 2016. Accepted for publication Nov 01, 2016.

doi: 10.21037/jtd.2016.11.71

View this article at: <http://dx.doi.org/10.21037/jtd.2016.11.71>

The optimal surgical treatment of early stage non-small cell lung cancer (NSCLC) remains a subject of ongoing research and debate. A recent retrospective analysis of the results of limited resections compared to formal lobectomy in T1a NSCLC was performed by Dai *et al.* (1). Based on their data, the authors concluded that lobectomy was superior to more limited resection for all tumors ≤ 2 cm. For tumors >1 to 2 cm, segmentectomy appeared superior to wedge resection when a limited resection was performed.

Dai and colleagues retrospectively reviewed outcomes of over 15,000 patients who underwent resection for T1a NSCLC in the Surveillance, Epidemiology and End Results (SEER) database. They compared overall survival (OS) and lung cancer-specific survival (LCCS) amongst patients undergoing wedge resection, segmentectomy, or lobectomy. Lobectomy was associated with increased OS and LCCS both in tumors ≤ 1 cm and those >1 to 2 cm. In those patients undergoing sublobar resection, OS and LCCS was favored in the segmentectomy group for tumors >1 to 2 cm and there was no difference in tumors ≤ 1 cm. This study represents a very large review of outcomes after resection for T1a NSCLC. The survival data is strengthened by the good median follow-up interval of approximately 4 years. The study adds to the current body of evidence comparing limited resection and lobectomy and raises important questions for further studies.

While Dai *et al.* conducted a large and well-designed retrospective review, the study does have several limitations. The SEER data is limited by its composition of Medicare beneficiaries thereby neglecting many younger and non-Medicare patients. The SEER database also lacks data on recurrence (local and metastatic), a very important

consideration when comparing lobectomy to limited resection (2). As such, disease free survival cannot be assessed. Moreover, treatments and conditions that occur before Medicare eligibility cannot be determined.

This study also suffers from selection bias. As the authors state, the patients who underwent limited resection were significantly older. Data on co-morbidities are not reported in the manuscript, but it is reasonable to assume that the older sublobar resection group suffered from more medical problems than the lobectomy group. High risk and older patients may have preferentially undergone sub-lobar resections.

In addition, stage migration may be contributing to the differences in survival observed. The study includes T1aN0M0 patients. All patients with nodal disease, whether discovered pre- or intra-operatively were excluded. This would be expected to be more likely to occur in the lobectomy group, which should consistently include systematic lymphadenectomy. However, the extent of pre- and intra-operative mediastinal and hilar/intraparenchymal lymph node assessment in each group is not presented. This issue is particularly relevant when comparing segmentectomy *vs.* wedge resection patients where often lymph node staging is inadequately performed in non-anatomic sub-lobar resections resulting in a perceived difference in survival.

The imaging characteristics of the tumors are also not presented. In this group of small tumors, a significant number may have included ground-glass opacity (GGO) dominant adenocarcinomas. Quantitation and distinguishing the solid/dense component *vs.* the ground glass component in GGO lesions rather than the overall size of the lesion

may have important implications on survival. Past studies have demonstrated that the solid component size of GGO dominant adenocarcinomas is more negatively prognostic than the overall size (3). It would also be important to distinguish central from peripheral tumors given the variable metastatic potential to lymph nodes.

Additionally, no data on adjuvant therapy is presented. While routine adjuvant therapy would not be expected in these early-stage patients, those that had recurrence likely would have undergone other therapies with resultant impact on OS. Older and high risk patients in the limited resection group may have been unfit to undergo such adjuvant therapy, which may have affected OS.

In 1995, The Lung Cancer Study Group established lobectomy as the standard of care for T1N0 NSCLC with a 276 patients randomized controlled trial (4). This landmark trial demonstrated increased local recurrence and decreased survival in patients treated with a more limited resection compared to those treated with lobectomy. Since the publication of that study, the introduction of CT-based lung cancer screening in high-risk patients for lung cancer has led to increased detection of lung cancer, GGO lesions, and small solid lung nodules. As a result, there has been renewed interest in the suitability of sub-lobar (segmentectomy and wedge) pulmonary resection to treat early stage disease, particularly in high risk patients with co-morbidities or marginal lung function patients. The potential value of lung preservation is also pertinent to those patients who are at risk of developing a second primary cancer.

Several contemporary studies have supported the concept that lobectomy is the preferred operation for early-stage NSCLC. In a review of stage I or II patients in the SEER database, lobectomy was found to be associated with improved survival in patients under 71-year of age (5). Interestingly, there was no difference in survival for more limited resection in those patients 71 and older. Two other retrospective reviews comparing limited resection and lobectomy in stage I or II patients demonstrated a trend towards improved recurrence rate and OS in the lobectomy group that did not reach statistical significance (6,7). Other work has highlighted the potential importance of histology in tumors ≤ 2 cm, with lobectomy being associated with superior survival in squamous cell carcinoma compared to wedge resection or segmentectomy, and segmentectomy demonstrating equivalent survival to lobectomy in adenocarcinoma (8). Finally, a recent review of the National Cancer Database indicated that lobectomy was associated with improved OS, adequate lymphadenectomy rate, and

negative margin rate (9).

On the other hand, many recent studies have indicated positive outcomes for sublobar resection in small, node-negative cancers. Retrospective and non-randomized prospective studies from Japan comparing segmentectomy with systematic lymph node dissection to lobectomy and lymph node dissection indicate comparable outcomes for early stage disease (10-12). Similarly, single-institution, retrospective studies from the United States have demonstrated the potential for sublobar resection to preserve postoperative lung function while providing adequate oncologic outcomes in stage IA lung cancer (13,14).

As the diagnosis and treatment of lung cancer evolves, the question of the ideal operation for early-stage, node-negative disease remains in question. Lobectomy has, unquestionably, been established as an appropriate and effective treatment. However, many patients are marginal candidates for lobectomy, and could potentially benefit from more limited resection. Furthermore, with CT screening, cancers are being diagnosed at an early stage more frequently than ever before with increasing detection of non-invasive (adenocarcinoma *in situ*) and minimally invasive adenocarcinomas. If these early-stage cancers could be treated with lesser resection it could result in better recovery and long-term function for patients. The above discussed paper by Dai *et al.* bolsters this ongoing discussion and highlights the need for prospective, randomized data to truly determine the oncologic suitability of limited resection. There are currently randomized controlled trials being conducted in the United States (CALBG 140503) and Japan (JCOG0802/WJOG4607L) comparing lobectomy to limited resection in tumors ≤ 2 cm (15,16). Until these randomized data are available, the optimal treatment of early-stage NSCLC remains in question, and surgeons must consider the current evidence as well as the clinical status of each individual patient when making treatment decisions.

Acknowledgements

None.

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Chen Chen (Department of Thoracic Surgery, the Second Xiangya Hospital of Central South University, Changsha, China).

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

Comment on: Dai C, Shen J, Ren Y, *et al.* Choice of Surgical Procedure for Patients With Non-Small-Cell Lung Cancer ≤ 1 cm or > 1 to 2 cm Among Lobectomy, Segmentectomy, and Wedge Resection: A Population-Based Study. *J Clin Oncol* 2016;34:3175-82.

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Cite this article as: Toste PA, Lee JM. Limited resection versus lobectomy in early-stage non-small cell lung cancer. *J Thorac Dis* 2016;8(11):E1511-E1513. doi: 10.21037/jtd.2016.11.71