

Treatment of non-small cell lung cancer ≤ 2 cm in size: less may not be more

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As the timely detection of earlier stage non-small cell lung cancer (NSCLC) improves with the heightened adoption of lung cancer screening, it becomes imperative to establish clear surgical treatment guidelines for smaller, early stage tumors, with a goal of obtaining superior oncologic outcomes and improved patient survival. Much controversy has existed in the past regarding the optimal surgical approach to stage 1 NSCLCs (1). The Lung Cancer Study Group's prospective multi center randomized clinical trial of lobectomy versus limited resection, reported over two decades ago, led to recommendations of restricting sublobar surgical resections to higher-risk stage 1 NSCLC patients with poor pulmonary reserve. This was due to the finding of inferior outcomes with the sublobar approach (2), and was related to increased local tumor recurrence and decreased survival in these patients, when compared with lobectomy. Other studies have also shown worse long-term outcomes of patients treated with limited resections for early stage NSCLC when compared with lobectomy (3-5), while a 13-year analysis of sublobar resection versus lobectomy for stage 1 non-small cell lung cancer, published in 2006 by El-Sherif et al. found no difference in disease-free survival between these two types of resection (6). More recently, mounting evidence suggests that sublobar resection may be an acceptable surgical treatment in certain patients with smaller early stage NSCLC (7), with equivocal

survival noted with wedge resection when compared with segmentectomy (8,9).

This study, published in the *Journal of Clinical Oncology* by Dai *et al.* (10) demonstrates that lobectomy is still the surgical treatment of choice for NSCLCs ≤ 1 and > 1 to 2 cm, over sublobar resection, both in terms of overall patient survival and lung-cancer specific survival. In addition, the authors note superior outcomes in patients who underwent segmentectomy over wedge resection for tumor size greater than 1–2 cm. However, they found no survival advantage of performing a segmentectomy over wedge resection in patients with non-small cell tumor size equal to or less than 1cm. The authors utilized the Surveillance, Epidemiology, and End Results Program's database to analyze data on patients with pathologically confirmed T1aN0M0 NSCLC ≤ 2 cm in size, who had undergone surgical treatment, with either lobectomy or sub-lobectomy, with segmentectomy or wedge resection, between the years 2000 and 2012. Patients who had received radiation treatment, or those whose treatment status was unknown, were excluded from the analysis. They identified 15,760 patients of whom, 11,520 patients had undergone lobectomy, and 4,240 sub-lobectomy. Overall survival and lung cancer specific survival were compared amongst patients, who received lobectomy, segmentectomy or wedge resection. Their goal was to determine the procedure of choice for NSCLCs ≤ 1

and $>1-2$ cm. Data on age, sex, race/ethnicity, and tumor characteristics was analyzed. Patients were divided by surgical type. Median follow up of lobectomy patients was 52 and 43 months in the sublobar groups. Three thousand three hundred and sixteen patients underwent a wedge resection and 769 a segmentectomy. Sublobar resection was more commonly performed in elderly and patients with tumors less than 1 cm. Survival analysis showed lobectomy was significantly associated with better overall survival and lung cancer specific survival in patients with NSCLCs ≤ 2 cm, and superior survival was demonstrated after segmentectomy when compared with wedge resection in this size of tumors. Results of a subgroup analysis of tumors $>1-2$ cm showed a significantly decreased overall survival and lung cancer specific survival rate in patients who underwent a segmentectomy or wedge resection over lobectomy with tumor size $>1-2$ cm, and also for patients who received a wedge resection over segmentectomy in this group. In patients with tumor size ≤ 1 cm, there was a clear survival advantage demonstrated in the group of patients who underwent a lobectomy, over both segmentectomy and wedge resection. However, there was no survival advantage seen for segmentectomy over wedge resection in this group of patients. Findings highlight that patients who underwent a wedge resection when compared to patients who underwent segmentectomy, had decreased overall survival if tumor size was $>1-2$ cm, however no survival advantage was noted if tumor size was ≤ 1 cm. Additionally, results showed that patients >65 years old and male patients were independent risk factors for survival in all NSCLCs ≤ 2 cm, regardless of surgical approach.

The topic of surgical approach for small sized early stage NSCLC becomes even more important as we move toward a sub-classification of stage T1a tumors, as recently proposed by the IASLC (11). The 8th Edition of the TNM Classification for Lung Cancer is due to be published later this year, and proposed changes to T and M descriptors affecting staging, is based on analysis of over 100,000 lung cancer cases from multiple centers from more than 19 countries. Revisions will include further sub-classification of T1 tumors into T1a, T1b and T1c, (with 1 cm increment changes up to 3 cm in size), and also the upstaging of T1 tumors with N1 disease. Additionally, among other notable changes, the new classification system will include minimally invasive adenocarcinoma. These new changes do show improved 2- and 5-year overall survival in all clinical stages, and of note, the data set utilized for the new classification, has showed a significant increase in patients

who had undergone surgery as part of their treatment.

The question of whether limited lymph node sampling in the sublobar surgical resection of larger tumors contributed to the decreased survival rates in these patients remains unanswered in this study. Adequate lymph node assessment for accurate staging is important regardless of surgical approach to lung cancer and evidence has shown limited lymph node resection to have negative implications in relation to long-term lung cancer survival and recurrence (5). This will become especially important in Stage 1 disease and N1 nodes when utilizing the new 8th TNM Classification system. The difference in upstaging will obviously affect further patient treatment plans and could potentially account for recurrence and survival differences in T1 subgroups.

The authors do acknowledge the limitations of their study related to the retrospective design, and also the inability of the SEER database to provide concise data on ground-glass opacity-dominant adenocarcinoma (10). They do not, however, address the additional important limitations of the SEER database. Patients who continue to smoke after surgery may be at higher risk of dying from other smoking-related diseases. Even though the relative survival demonstrated in the SEER database does adjust for the expected mortality that the cohorts would expect from other causes of death, the differences in survival due to variations in overall health, and more importantly, other tobacco-related co-morbidities, are not considered. It is very likely in this study, that overall survival is decreased in the group of patients with larger lung nodules after sublobar resection, because of poorer pre-operative performance status related to concurrent diseases. This is a strong bias that cannot be eliminated from the authors' study.

Despite these limitations, the results of this study serve to caution treatment teams not to abandon lobectomy for small tumors, even those less than 1 cm in size. In addition, an indirect corollary is to bring into question the comparison of stereotactic body radiation therapy (SBRT) and lobectomy for patients at acceptable surgical risk. The results also provide surgeons additional impetus to participate in trials comparing sublobar resections with lobectomy, such as CALGB 140503 (12). These trials will hopefully inform us on the clinical management of this increasing subgroup of patients. Pending these results, it seems that lobectomy is the best treatment modality in patients at acceptable risk and segmentectomy is better than a wedge resection for patients at a high risk for lobectomy for NSCLC, if a surgical resection is preferred over SBRT.

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Footnote

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

References

1. Miller DL, Rowland CM, Deschamps C, et al. Surgical treatment of non-small cell lung cancer 1 cm or less in diameter. *Ann Thorac Surg* 2002;73:1545-50; discussion 1550-1.
2. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1995;60:615-22; discussion 622-3.
3. Speicher PJ, Gu L, Gulack BC, et al. Sublobar Resection for Clinical Stage IA Non-small-cell Lung Cancer in the United States. *Clin Lung Cancer* 2016;17:47-55.
4. Landreneau RJ, Sugarbaker DJ, Mack MJ, et al. Wedge resection versus lobectomy for stage I (T1 N0 M0) non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 1997;113:691-8; discussion 698-700.
5. Khullar OV, Liu Y, Gillespie T, et al. Survival After Sublobar Resection versus Lobectomy for Clinical Stage IA Lung Cancer: An Analysis from the National Cancer Data Base. *J Thorac Oncol* 2015;10:1625-33.
6. El-Sherif A, Gooding WE, Santos R, et al. Outcomes of sublobar resection versus lobectomy for stage I non-small cell lung cancer: a 13-year analysis. *Ann Thorac Surg* 2006;82:408-15; discussion 415-6.
7. Zhang L, Li M, Yin R, et al. Comparison of the oncologic outcomes of anatomic segmentectomy and lobectomy for early-stage non-small cell lung cancer. *Ann Thorac Surg* 2015;99:728-37.
8. Altorki NK, Kamel MK, Narula N, et al. Anatomical Segmentectomy and Wedge Resections Are Associated with Comparable Outcomes for Patients with Small cT1N0 Non-Small Cell Lung Cancer. *J Thorac Oncol* 2016;11:1984-92.
9. Kodama K, Higashiyama M, Okami J, et al. Oncologic Outcomes of Segmentectomy Versus Lobectomy for Clinical T1a N0 M0 Non-Small Cell Lung Cancer. *Ann Thorac Surg* 2016;101:504-11.
10. 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.
11. Eberhardt WE, Mitchell A, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revision of the M Descriptors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. *J Thorac Oncol* 2015;10:1515-22.
12. Altorki N, Kohman LJ, Veit LJ, et al. Limited resection as a cure for early lung cancer: time to challenge the gold standard? *Bull Am Coll Surg* 2015;100:57-8.

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