European Journal of Therapeutics DOI: 10.5152/EurJTher.2018.1007

The Role of Sublobar Resections in the Treatment of Small Cell Lung Cancer

Cemal Özçelik, Alper Avcı
Department of Thoracic Surgery, Çukurova University School of Medicine, Adana, Turkey

ABSTRACT
Lobectomy is the standard treatment in the early stages of non-small cell lung cancer. Today, however, it is questioned whether lobectomy should be performed in all early diagnosed patients. Sublobar resection remains a treatment option in elderly patients with low cardiopulmonary reserve who cannot tolerate sublobar resection lobectomy. In small tumors measuring 2 cm in diameter, sublobar resections can provide local recurrence rates and long survival rates equivalent to lobectomy when performed with the appropriate techniques in eligible patients. The addition of brachytherapy can further improve the results.
Keywords: Sublobar resection, segmentectomy, wedge resection, brachytherapy

INTRODUCTION

In a randomized study in 1995, a lung cancer study group showed that local recurrence rate was higher in sublobar resection surgery than in lobectomy in patients with stage-I non-small cell lung cancer (NSCLC) (1). Lobectomy is the preferred surgical treatment for stage I NSCLC patients, whereas sublobar resections are only performed in high-risk patients who cannot tolerate lobectomy. Today, some factors make sublobar resections an acceptable technique, especially in the surgical treatment of peripherally located early stage NSCLC. These factors include the recognition of very small-sized NSCLC in high-risk patients with evolving tomography techniques and devices, increase in the literature showing the success of segmentectomy, especially in small peripheral NSCLC cases who cannot tolerate lobectomy, low perioperative morbidity and mortality rates in sublobar resections compared to lobectomy, and superiority in preserving pulmonary functions (2, 3).

Sublobar Resections in High Risk Patients

Several studies have shown that sublobar resections can be performed for lobectomy with moderate morbidity and mortality, recurrence, and survival rates in high-risk patients (4, 5). In a meta-analysis by Hou et al. (6), they reported that segmentectomy reduced mortality in patients with stage IA NSCLC compared to larger resections and provided better survival rates compared to wedge resection, but that wedge resection and segmentectomy provided equal survival rates in sub-group analyzes of T1a cases.

The Effect of Age

The incidence of lung cancer increases with age. There is an increase in the number of elderly patients with diagnosed lung cancer in direct proportion to the aging of society. Database surveys indicate that 70% of newly diagnosed lung cancer cases are over 70 years old (7).

Although age is not a contraindication alone, there is a reduction in the number of patients who can tolerate standard lobectomy in the elderly population compared to the younger population. With increasing age, operative mortality and complication rates increase in lobectomy. In the data reported by Mayo Clinic, these rates are 6.3% and 48%, respectively. In addition, co-morbidity-related mortality rates in elderly patients with early-stage NSCLC were found to be higher than cancer-related mortality rates. The literature review showed that cardiovascular disease-related mortality was higher than cancer-related mortality rates in cancer patients aged 70-79 years over the five-year period (8). Furthermore, SEER (Surveillance, Epidemiology and End Results) data indicates that 31% of these patients have not undergone lobectomy (9). Studies have shown that sublobar resections are effective and beneficial in patients over 75 years old with stage I NSCLC. In a study by Kilic et al. (10), lobectomy was compared to anatomic segmentectomy in patients older than 75 years with stage 1 NSCLC, and it was shown that segmentectomy had lower morbidity and mortality rates, whereas there was no significant difference in local recurrence and long-term survival rates.

Tumor Size, Histology and Location

Tumor size is a prognostic factor in NSCLC cases. Sublobar resections have similar oncologic outcomes as lobectomy in small-sized tumors. There was no difference in the survival rate between sublobar resection (anatomic segmentectomy) and lobectomy for peripheral tumors smaller than 2 cm (11). However, lobectomy provides superior results when the size exceeds 2 cm (12).

Corresponding Author: Cemal Özçelik **E-mail:** cozcelik61@gmail.com
Received: 01.03.2018 • **Accepted:** 17.04.2018
©Copyright by 2018 Gaziantep University School of Medicine – Available online at www.eurjther.com

Tumor histology also leads to the decision to perform sublobar resection. The prognosis after sublobar resection is associated with the histological type. Patients with adenocarcinoma in situ (AIS), minimal invasive adenocarcinoma (MIA), and adenocarcinoma with lepidic growth pattern have a good prognosis after sublobar resection. Tumors exhibiting ground-glass opacification are often considered as AIS, MIA or lepidic adenocarcinomas (13).

Tumor localization is also important in the decision to perform sublobar resection in small-sized NSCLC cases. Peripheral tumors constitute the majority of tumors undergoing sublobar resection.

Surgical Approach and Technical Features

The decision to administer a sublobar resection (wedge resection or anatomic segmentectomy) is usually made by evaluating the patient's performance, the tumor's character, and the surgeon's preference. For example, wedge resection is preferred for peripheral small tumors in patients with poor performance and poor self-care, whereas anatomic segmentectomy is preferred for larger tumors confined within the segment. For intersegmental tumors, extended segmentectomy or wedge resection with a surgical margin of at least 1 cm is performed as a sublobar resection (14). Many factors can influence the decision regarding which surgical technique to use. For example, lobectomy will be preferred to segmentectomy in lesions that have exceeded the limits of the segment, the majority of which form deep lesions. This is most frequently encountered in the lower lobe superior segment and basilar segments. The most common localization in the upper lobes is the boundary between the upper division and the lingular segment in the upper left lobe.

Mediastinal systematic lymph node sampling should be performed with all sublobar resections. For right-sided lesions, stations 4R-7 and 9 should be sampled, and for left-sided lesions, stations 5-6-7 and 9 should be sampled. In wedge resections, only station 10 is sampled as the N1 lymph node.

If wedge resection is to be performed as a sublobar resection, the surgical margins should be intraoperatively checked by frozen section or margin cytology examination.

Width of the Resection

For a sublobar resection, the analysis of the near parenchymal area is more important than the analysis of the bronchial surgical margin. This is due to the fact that the local recurrence rate is found to be increased for resections with a clear margin below 1.5 cm (15, 16). While the extent of the resection is a controversial issue, there is a consensus that a wider resection is better. There are reports recommending the intra-operative cytologic study of negative margins (17). Lobectomy should be considered if segment margins are exceeded or positive margins exist.

The local recurrence rate is the lowest with a tumor size below 3 cm, consolidation/tumor ratio below 0.5, solid tumor size of 1.2cm or below, carcinoembryogenic antigen level of 5.0ng/mL and the presence of a histological type of adenocarcinoma (18).

In wedge resections, a clear surgical margin of less than 1.5 cm in tumors smaller than 2 cm obviously reduces the local recurrence rate, whereas segmentectomy should be preferred for lower recurrence rates in tumors larger than 2 cm (16, 19). If sublobar resection is planned in stage I patients diagnosed with squamous cell NSCLC, wedge resection is not recommended, but segmentectomy should be preferred. Local recurrence and lymph node positivity rates in squamous cell carcinomas are higher than in adenocarcinomas (20).

According to the recommendations of the National Comprehensive Cancer Network (NCCN, Version 1.2016) guidelines, the distance between the tumor and the surgical margin at sublobar resections should be greater than 2 cm or at least the size of the tumor.

The rate of local recurrence is lower because the malignancy rate is lower compared to solid tumors in NSCLC cases with ground-glass opacification. It has been reported that the length of the clean surgical margin may be lower in these tumors (21).

Pulmonary Functions after Sublobar Resections

The reports of the lung cancer study group in 1995 showed that limited resection has an advantage in terms of loss of pulmonary function in the early postoperative period, but this advantage disappeared after 12 months or longer (1). However, it should not be forgotten that the patient follow-up period was indicated as a limiting factor. Takizawa et al. (22) showed that postoperative FEV_1 values were higher in patients undergoing segmentectomy compared with lobectomy, but proposed segmentectomy only for patients with limited pulmonary reserve.

Survival Rate after Sublobar Resection

In a study by Khullar et al. (23) featuring 13,606 patients, it was reported that lobectomy was still the gold standard treatment in T1A-N0 NSCLC cases, but sublobar resections may be an alternative to lobectomy in patients with limited pulmonary reserves only if surgical margin and lymph node negativity are present. Another report evaluated 2,090 patients with a tumor size of less than 1cm, and showed that sublobar resections were more commonly performed in elderly patients, female patients, and patients with adenocarcinoma and lower lobe tumors and that disease-free survival and overall survival rates were equal to that of lobectomy (24).

Sublobar Resection and Brachytherapy

As local recurrence rates are higher, sublobar resections are usually performed alternatively to lobectomy in patients with limited pulmonary function. Adjuvant RT reduces local recurrence rates, but respiratory movements and the difficulties of determining the stapler line can limit and complicate RT to be applied from outside the body. Adjuvant intraoperative RT has been successfully used in many centers through the application of iodine-125 on the stapler line (25). The direct application of radiation emitting systems on the surgical field has many advantages; it provides more specific targeting, minimizes the effect of RT on normal lung tissue, reduces the time and dose of treatment, patient tolerance is excellent, and treatment

begins immediately during surgery. In 1998, D'Amato et al. (26) covered stapler lines with I-121 Vicryl meshes during VATS sublobar resections performed in stage I tumors and demonstrated success in terms of the control of local recurrence in the postoperative period. No implant displacement, radiation pneumonia or loss of pulmonary function were observed in these studies. Although its effect on the current long-term survival rate is not entirely clear, intraoperative brachytherapy seems promising for the future. Studies have shown that local recurrence rates in sublobar stage-I NSCLC cases corroborated by intraoperative brachytherapy are reduced, even at lobectomy levels (27).

As a general safety guideline, it is recommended that children under 18 years of age and pregnant women should not get closer than 1m away from patients who have received intraoperative brachytherapy treatment for a period of three months.

CONCLUSION

Sublobar resections are considered superior to RT in terms of the application of lymph node dissection and the absence of damage to residual lung tissue after treatment. Intraoperative microscopic border analyzes are performed to reduce recurrences, which are the most important local failure of sublobar resection therapy. Intraoperative brachytherapy removes the difficulties and limitations of RT applied from outside the body. The data of patients with sublobar resection corroborated by intraoperative brachytherapy is promising in terms of presenting an alternative to lobectomy.

RECOMMENDATIONS

1. In stage-I NSCLC patients who are medically eligible, if the tumor is confined within a segment, extended segmentectomy or the addition of lymph node dissection in lobectomy is recommended, and these techniques have similar five-year survival rates.
2. In the high-risk stage I NSCLC patient group, sublobar resections in which a clear surgical margin is achieved and hilar/mediastinal lymph node sampling is added is an alternative surgical procedure to lobectomy.
3. Sublobar resection is an effective and potentially useful treatment, especially in patients over 75 years of age with NSCLC.
4. A clean surgical margin of more than 1cm is recommended for sublobar resections in stage I NSCLC cases.
5. Patients undergoing sublobar resection should be closely monitored due to high local recurrence rates, which includes follow-ups every three months for the first year, followed by follow-up every six months.
6. If sublobar resection is performed, anatomic segmentectomy should be preferred to wedge resection.
7. The distance between the tumor and the surgical margin appears to be an ineffective factor for local recurrence rates in patients undergoing R0 sublobar resection and with N0 ground-glass opacities and tumors smaller than 3 cm.

Peer-review: Internally reviewed.

Author contributions: Concept - C.Ö.; Design - C.Ö., A.A..; Supervision - C.Ö.; Resource - C.Ö., A.A.; Materials - C.Ö., A.A.; Data Collection and/or Processing - C.Ö., A.A.; Analysis and/or Interpretation - C.Ö.; Literature Search - C.Ö., A.A.; Writing - C.Ö., A.A.; Critical Reviews - C.Ö.

Acknowledgements: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Ginsberg RJ, Rubinstein LV. Randomized Trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Ann Thorac Surg 1995; 60: 615-23. [CrossRef]
2. Wada H, Nakamura T, Nakamoto K, Maeda M, Watanabe Y. Thirty day operative mortality for thoracotomy in lung cancer. J Thorac Cardiovasc Surg 1998; 115: 70-3. [CrossRef]
3. Keenan RJ, Landreneau RJ, Maley RH, Singh D, Macherey R, Bartley S, et al. Segmental resection spares pulmonary function in patients with stage I lung cancer. Ann Thorac Surg 2004; 78: 228-33. [CrossRef]
4. Martin-Ucar AE, Nakas A, Pilling JE, West KJ, Waller DA. A case-matched study of anatomical segmentectomy versus lobectomy for stage I lung cancer in high-risk patients. Eur J Cardiothorac Surg 2005; 27: 675-9. [CrossRef]
5. El-Sherif A, Gooding WE, Santos R, Pettiford B, Ferson PF, Fernando HC, 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: 408-16. [CrossRef]
6. Hou B, Deng XF, Zhou D, Liu QX, Dai JG. Segmentectomy versus wedge resection for the treatment of high-risk operable patients with stage I non-small cell lung cancer: a meta-analysis. Ther Adv Respir Dis 2016; 10: 435-43. [CrossRef]
7. Cerfolio RJ, Bryant AS. Survival and outcomes of pulmonary resection for non-small cell lung cancer in the elderly: a nested case-control study. Ann Thorac Surg 2006; 82: 424-9. [CrossRef]
8. Groth SS, Rueth NM, Hodges JS, Habermann EB, Andrade RS, D'Cunha J, et al. Conditional cancer-specific versus cardiovascular-specific survival after lobectomy for stage I non-small cell lung cancer. Ann Thorac Surg 2010; 90: 375-82. [CrossRef]
9. Dell'Amore A, Monteverde M, Martucci N, Sanna S, Caroli G, Dolci G, et al. Lobar and sub-lobar lung resection in octogenarians with early stage non-small cell lung cancer: factors affecting surgical outcomes and long-term results. Gen Thorac Cardiovasc Surg 2015; 63: 222-30. [CrossRef]
10. Kilic A, Schuchert MJ, Pettiford BL, Pennathur A, Landreneau JR, Landreneau JP, et al.Anatomic segmentectomy for stage I non-small cell lung cancer (NSCLC) in the elderly Ann Thorac Surg, 2009; 87(6):1662-1666 [CrossRef]
11. Okada M, Nishio W, Sakamoto T, Uchino K, Yuki T, Nakagawa A, et al. Effect of tumor size on prognosis in patients with non-small cell lung cancer: The role of segmentectomy as a type of lesser resection J Thorac Cardiovasc Surg 2005; 129: 87-93. [CrossRef]
12. Okada M, Koike T, Higashiyama M, Yamato Y, Kodama K, Tsubota N. Radical sublobar resection for small-sized non-small cell lung cancer: A multicenter study. J Thorac Cardiovasc Surg 2006; 132: 769-75. [CrossRef]
13. Eguchi T, Kadota K, Park BJ, Travis WD, Jones DR, Adusumilli PS. The new IASLC-ATS-ERS lung adenocarcinoma classification: what the surgeon should know. Semin Thorac Cardiovasc Surg 2014; 26: 210-22. [CrossRef]
14. Altorki NK, Kamel MK, Narula N, Ghaly G, Nasar A, Rahouma M, 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 [CrossRef]
15. Owen RM, Force SD, Gal AA, Feingold PL, Pickens A, Miller DL, et al. Routine intraoperative frozen section analysis of bronchial margins is of limited utility in lung cancer resection. Ann Thorac Surg 2013; 95: 1859-65; discussion 1865-6.
16. Mohiuddin K, Haneuse S, Sofer T, Gill R, Jaklitsch MT, Colson YL, et al. Relationship between margin distance and local recurrence among patients undergoing wedge resection for small (≤2 cm) non-small cell lung cancer. J Thorac Cardiovasc Surg 2014; 147: 1169-75. [CrossRef]
17. Higashiyama M, Kodama K, Takami K, Higaki N, Nakayama T, Yokouchi H. Intraoperative lavage cytologic analysis of surgical margins in patients undergoing limited surgery for lung cancer. J Thorac Cardiovasc Surg 2003; 125: 101-7. [CrossRef]
18. Tsunezuka H, Kato D, Okada S, Furuya T, Shimada J, Inoue M. Surgical outcome of wide wedge resection in poor-risk patients with clinical-N0 non-small cell lung cancer. Gen Thorac Cardiovasc Surg 2017; 65: 581-6. [CrossRef]
19. Sienel W, Dango S, Kirschbaum A, Cucuruz B, Hörth W, Stremmel C, et al. Sublobar resections in stage IA non-small cell lung cancer: segmentectomies result in significantly better cancer-related survival than wedge resections. Eur J Cardiothorac Surg 2008; 33: 728-34. [CrossRef]
20. Yano M, Yoshida J, Koike T, Kameyama K, Shimamoto A, Nishio W, et al. The outcomes of a limited resection for non-small cell lung cancer based on differences in pathology. World J Surg 2016; 40: 2688-97. [CrossRef]
21. Moon Y, Lee KY, Moon SW, Park JK. Sublobar Resection Margin Width Does Not Affect Recurrence of Clinical N0 Non-small Cell Lung Cancer Presenting as GGO-Predominant Nodule of 3 cm or Less. World J Surg 2017; 41: 472-9. [CrossRef]
22. Takizawa T, Haga M, Yagi N, Terashima M, Uehara H, Yokoyama A, et al. Pulmonary function after segmentectomy for small peripheral carcinoma of the lung J Thorac Cardiovasc Surg 1999; 118: 536-41. [CrossRef]
23. Khullar OV, Liu Y, Gillespie T, Higgins KA, Ramalingam S, Lipscomb J, 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. [CrossRef]
24. Kates M, Swanson S, Wisnivesky JP. Survival following lobectomy and limited resection for the treatment of stage I non-small cell lung cancer<=1 cm in size: a review of SEER data. Chest 2011; 139: 491-6. [CrossRef]
25. Odell DD, Kent MS, Fernando HC. Sublobar Resection with Brachytherapy Mesh for Stage I Non-Small Cell Lung Cancer. Semin Thorac Cardiovasc Surg 2010; 22: 32-7. [CrossRef]
26. d'Amato TA, Galloway M, Szydlowski G, Chen A, Landreneau RJ. Intraoperative brachytherapy following thoracoscopic wedge resection of stage I lung cancer Chest. 1998; 114: 1112-5. [CrossRef]
27. Birdas TJ, Koehler RP, Colonias A, Trombetta M, Maley RH, Landreneau RJ, et al. Sublobar resection with brachytherapy versus lobectomy for stage Ib nonsmall cell lung cancer. Ann Thorac Surg 2006; 81: 434-8; discussion 438-9. [CrossRef]

How to cite:

Yeşil Çınkır H. Point Reached in Targeted Therapy; Where are we? Eur J Ther 2018; 24(Suppl 1); S29–S32.