

Lobar or sublobar resection for stage I lung cancer: that is (still) the question!

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Lung cancer causes more than 1.4 million deaths annually (1). Surgery is the main treatment given with curative intent and lobectomy with lymph node resection is the standard procedure for early Stage of non-small-cell lung cancer (NSCLC), having a 5-year survival rates of up to 70% (2). This assumption is based on the results of the randomized controlled trial (RCT) reported by the Lung Cancer Study Group (LCSG) in 1995 (3). The authors compared overall survival of lobectomy versus limited resection (wedge resection and segmentectomy) for the management of Stage I NSCLC. They evaluated 495 patients with clinical stage IA NSCLC, of these 247 resulted to have a pathologic stage pIA. Limited resection compared to lobectomy presented a poorer 5-year survival rate (56% *vs.* 73%; $P=0.06$), a lower freedom from recurrence rate (62% *vs.* 78%, $P=0.04$), and three-fold increase in local recurrence rates (5.4% *vs.* 1.9%, $P=0.009$).

In the two decades since this trial, the increased screening programs using low-dose computed tomography (CT) scan, the advances in minimally invasive surgical techniques, and the significant progress in comprehending the biology of NSCLC have fueled a renewed interest in sublobar resection, especially segmentectomy, for management of early lung cancer in medically fit patients who can tolerate lobectomy. Multiple retrospective studies published in the last 20 years have contradicted the results from the LCSG, showing that intentional anatomic

sublobar resection may be similar in survival to lobectomy for the management of stage I tumors ≤ 2 cm (4-8). These results were also supported by several meta-analyses. In 2005, Nakamura *et al.* (9) analyzed all studies published between 1970 and 2004 showing that sublobar resection had similar survival to lobectomy. In 2012, Fan *et al.* (10) conducted a meta-analysis including published studies between 1990 and 2010 and found that the outcome of sublobar resection was similar to that of lobectomy only for Stage IA patients. Similarly, Bao *et al.* (11) stratified the outcome of segmentectomy and lobectomy according to the size of the tumor. They found a similar survival for ≤ 2 cm Stage I NSCLC while segmentectomy had a worse survival than lobectomy for >2 cm Stage I NSCLC. In line with Bao's study (11), Kates *et al.* (12) found similar survival rates among patients undergoing sublobar resection *vs.* lobectomy for ≤ 1 cm Stage I tumors. Additionally, other two recent meta-analyses published in 2015 (13) and in 2017 (14) showed that intentional segmentectomy for early-stage NSCLC had overall disease-free survival similar to lobectomy. Based on these evidences and on the insights of breast surgical oncologists considering lesser resection for small breast cancer, there is the growing perception that smaller lung cancer might be successfully managed with less radical resection being oncological equivalent to lobectomy but having the advantages of lung function preservation and less perioperative complications.

However, the clinical dilemma on the best treatment for these tumors (sublobar or lobar resection) is far from being solved. In fact, several studies using Surveillance, Epidemiology, and End Results (SEER) database found the superior of lobectomy over segmentectomy and these results are extended also to ≤ 1 cm Stage I NSCLC (15,16). The same results were also confirmed by two meta-analyses. Zhang *et al.* (17) evaluated 19 relevant studies published in the last decade, of which four studies privileged lobectomy, and the others 15 studies found no difference in survival. However, after pooling these studies together, sublobar resection presented a poorer overall survival or cancer-specific survival than lobectomy. Similarly, Liu *et al.* (18) found that in Stage IA patients sublobar resection causes a lower survival rate than lobectomy.

To try to answer the question whether a sublobar resection is as good as a lobectomy for patient with Stage I NSCLC, Dziedzic *et al.* (19) conducted a retrospective study using the data from the Polish National Lung Cancer Registry. They included 6,905 patients with pathological Stage I NSCLC in their analysis and used propensity score match analysis to correct the bias of patient selection and create comparable samples of patients who underwent lobectomy, segmentectomy, and wedge resection on the basis of several covariates. The end-point was the overall survival. Lobectomy and segmentectomy presented no significant difference in 5 years survival rate while wedge resection had a lower 5-year survival rate than lobectomy and segmentectomy. These results confirmed that segmentectomy must be clearly divided from wedge resection as curative treatment of NSCLC since it is more likely to provide sufficient margins and allows access to subsegmental and hilar lymph nodes. Despite all, the results of Dziedzic's study should be considered with caution before drawing definitive conclusions on the oncologically validity of segmentectomy. The authors (19) evaluated in their analysis only the overall survival but no data on the cancer specific survival, recurrence rates, and adjuvant treatment after surgery were reported. Differences in overall survival may be misleading compared with cancer specific survival, as patients died due to causes unrelated to NSCLC and the oncological efficacy of the different surgical procedures. Conversely, recurrence rates are not strongly affected by the medical comorbidities and are, therefore, an easier point for comparison the oncological outcome between sublobar and lobar resection. In addition, the administration of adjuvant therapies after surgery as radiotherapy,

chemotherapy or biological therapy in presence of recurrences could affect the overall survival independently from the type of resections. Despite adenocarcinoma was the main histological type, the different histological subtypes of adenocarcinoma as well as the radiological characteristics of the tumor, the Standard Uptake Value on PET scan, and the indications for segmentectomy were not evaluated and not used as covariates in the propensity score matching analysis. In theory, patients undergoing segmentectomy could have a pure Ground-glass Opacity (GGO) or a tumor with a low standardized uptake value (SUV) value or an indolent tumor; thus, their good survival could be due to the favorable biology of the tumor rather than oncological validity of the resection. SUV value is a predictive factor of the aggressiveness of the tumor (20) and the new classification system proposed by International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) reported that papillary, micropapillary, or solid adenocarcinoma may have significantly worse prognosis than lepidic predominant adenocarcinoma (21).

In conclusion, sublobar resection for intentionally treating patients with sub-centimeters NSCLC who are able to tolerate lobectomy remains highly controversial. Currently, two prospective, randomized, multi-institutional phase III trials are being conducted by the Cancer and Leukemia Group B (CALGB 140503) and the Japan Clinical Oncology Group (JCOG 0802) (22) to evaluate the efficacy of intentional sublobar resections for ≤ 2 cm Stage I tumors and their conclusions, when available, will help to clarify this issue. Until these trials are complete, the LCSG study (3) is the only randomized trial showing the superiority of lobectomy over sublobar resections for early stage lung cancer and this conclusion cannot be strongly questioned by the current studies (23,24). Conversely, as recommended by the NCCN, the British Thoracic Society (BTS), ERS/European Society of Thoracic Surgeons (ESTS), and the American College of Chest Physicians (ACCP) sublobar resection is an alternative to lobectomy (I) for patients with resectable lung cancer but impaired lung function or comorbidities or (II) for patients with pure GGO lesser than 2 cm in size, or having a slow, indolent growth observed during CT scan surveillance (25).

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Footnote

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

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