



# Should lobectomy still be considered the treatment of choice for stage IA non-small cell lung cancer?

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Lobectomy has always been considered the gold standard surgical procedure for non-small cell lung cancer (NSCLC), even for the treatment of early stage tumors, while the indication for sublobar resection has usually been limited to elderly patients or to those with impaired cardiac and respiratory function.

Though in the last few decades sublobar resection has been proposed as an alternative to lobectomy by many authors in different settings, only one randomized controlled trial compared the outcomes of lobectomy and sublobar resection in terms of overall survival (OS) for stage IA lung cancer back in 1995 (LCSG821) (1). According to the results of LCSG821, given its association with higher death rate and a three-fold risk for local relapses, sublobar resection for early-stage lung cancer has only been indicated for selected patients with poor pulmonary reserve or other major comorbidities contraindicating lobectomy, while lobectomy was established as the procedure of choice. Since then the scenario has changed rapidly, and the trial's results were challenged in the following years by the increased utilization of low-dose helical computed tomography (CT) as a screening strategy in high-risk patients, that allowed the detection of smaller and more peripheral tumors (2). In the same time, there has been a significant demographic increase in the older segment of the population, which may benefit more from sublobar resection if diagnosed with a small peripheral NSCLC. These factors contributed to a renewed interest of the surgical and oncological communities in the value of sublobar resection.

A number of retrospective studies have suggested that sublobar resection, in patients with early stage lung cancer,

provides equivalent locoregional disease control compared to lobectomy, while sparing lung parenchyma (3-5). For this reason, sublobar resection is increasingly offered in the current clinical practice to patients with poor pulmonary function or to those whose comorbidities render them to be otherwise borderline surgical candidates. Another even more conservative option the main application of which are medically non-operable patients, but which has become increasingly popular in recent years as an alternative to surgery in fitter patients with small peripheral tumors, is stereotactic body radiotherapy (SBRT). Results from a pooled analysis of two randomized trials (6) comparing survival of patients with operable early stage NSCLC undergoing either surgical resection or SBRT (both studies were stopped early due to slow recruitment) suggested that SBRT might be a valid alternative to surgery in terms of OS, with perhaps the advantage of being better tolerated (7). Several randomized controlled trials are ongoing and will provide additional information in the debate between surgery and SABR.

Of course, the non-inferiority of sublobar resection is not universally agreed. A more recent comparative study has shown an increased risk of recurrence in patients undergoing sublobar resection compared to patients who underwent lobectomy (8). An argument that has been suggested to explain this result is that the lymphadenectomy during such operations is frequently insufficient, although it is widely demonstrated that an inadequate lymphadenectomy is a major factor for recurrence (9).

Consequently to these equivocal results, an intense debate on the matter has been sparked, which culminated

in two different trials, a North American one (Alliance/CALGB 140503) (10), which has not been published yet but has been presented at the latest International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer, and a Japanese one (JCOG/WJOG 0802), the results of which have been recently published (11).

JCOG 0802 was a multi-institutional and intergroup randomised, open-label, phase 3, randomised controlled trial at 70 institutions in Japan designed to support the non-inferiority of segmentectomy for OS versus lobectomy, in patients with clinical stage IA small-sized ( $\leq 2$  cm; consolidation-to-tumour ratio  $>0.5$ ) peripheral NSCLC. Systematic or selective lymph node dissection was mandatory for all operations while lymph node sampling was not allowed. According to the results of JCOG/WJOG 0802, not only segmentectomy has been proven to be non-inferior to lobectomy in this particular subset of patients, but also it showed a better 5-year OS compared to lobectomy (94% *vs.* 91.1%). Locoregional relapse was higher in the segmentectomy group, but no significant difference was found in the 5-year relapse-free survival (88.0% and 87.9%). Death from other cancers (including second primary lung cancer), respiratory disease, and cerebro-vascular disease, occurred more frequently in the lobectomy group than in the segmentectomy group, while the incidences of second other cancers and second primary lung cancers in both groups were similar. The difference in OS between the two groups, though not entirely clear, might be explained by both the less invasiveness of the parenchymal-sparing procedure, which leads to a lower probability of death from comorbidities, and the wider post-operative functional reserve that allows more treatment possibilities (other surgery or chemo-radiation therapy) in case of a second tumor.

CALGB 140503 was multicenter international non-inferiority phase III trial in which NSCLC patients clinically staged as T1aN0  $\leq 2$  cm were randomly assigned to lobar or sub-lobar resection, once hilar and mediastinal pathological node negativity was confirmed at intraoperative frozen section. Over a median follow-up of 7 years, sub-lobar resection was non-inferior to lobar resection with regard to the primary endpoint of disease free survival (DFS). The 5-year DFS rates were a comparable 63.6% and 64.1%, respectively.

Sub-lobar resection was also non-inferior to the lobar approach for the secondary endpoint of OS, with respective 5-year rates of 80.3% and 78.9%.

The trial also evaluated the post-operative pulmonary

function, finding that the percentage of predicted forced expiratory volume in 1 second (FEV<sub>1</sub>) and forced vital capacity (FVC) worsened in both the sub-lobar and lobar resection study arms at 6 months postsurgery, but to a significantly lesser degree in the sub-lobar group.

A key difference between the two trials is that while in JCOG 0802 the sublobar resection group is strictly represented by segmentectomies, in CALGB 140503, once the randomization had assigned a patient to the sublobar group, wedge resections were also allowed and the choice of the type of resection, anatomical or not, was left at the discretion of the surgeon. This might explain why the results from JCOG 0802 show a higher percentage of both 5-year DFS and 5-year-OS than CALGB 140503, since segmentectomy is widely considered to provide a better oncological outcome than wedge resection (12).

Overall, both trials proved sublobar resection to be non-inferior compared to lobectomy in this particular subset of patients, strongly suggesting that segmentectomy should be the treatment of choice for small peripheral NSCLC, even in younger and fitter patients.

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