



N1 small-cell lung cancer: where should thoracic surgeons dare?

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Small cell lung cancer (SCLC) has always been an insidious field for thoracic surgeons, due to unclear possible indications and deceiving results. The majority of studies regarding surgery for SCLC are dated and the poor outcomes obtained have discouraged their continuation. Nevertheless, since platinum-based chemotherapy protocols have been introduced and the use of new technologies, such as PET scan, allowed a more careful and precise staging, new possible indications raised. To date, surgery plays a very marginal role in the treatment of SCLC and major oncological guidelines indicate a resection only in case of a very limited disease (T1–2N0M0), which account for less than 5% of all diagnosed SCLC (1); in this highly selected group of patients, surgery associated with adjuvant therapies bring to an impressive 65% 5-year survival.

Yang and his colleagues (2) focused on clinical N1 patients, a group of localized disease which is usually not indicated for surgery. They should be congratulated.

Based on the National Cancer Data Base, they selected 1,041 patients with a clinical T1–3N1 histologically confirmed small-cell lung cancer and they compared outcomes of those who received definitive concurrent chemo-radiation [945] versus those who were operated on followed by adjuvant chemotherapy with or without radiation [96]. The authors found a significantly better survival for patients treated with surgical resection and adjuvant chemotherapy with or without radiation (5-year survival 31.6% *vs.* 27.9%; $P=0.03$), that was confirmed also in multivariate setting (HR, 0.74; 95% CI: 0.56–0.98; $P=0.04$). These interesting results were tested also in a propensity match analysis, that compared 87 patients of

each group with similar preoperative and demographic characteristics; this analysis showed a 33.3 months median overall survival for patients in the surgery arm, significantly higher than survival of patients in the chemo-radiation arm (21.1 months, $P=0.03$). Interestingly patients who had an adjuvant chemo-radiation treatment after surgery had a better survival than those who received only a chemo adjuvant therapy (HR, 0.44; 95% CI: 0.23–0.85; $P=0.01$). Concurrently, authors analysed outcomes of T1 and T2 subgroups using a propensity matched analysis between surgical and non-surgical groups. In T1 group surgery with consequent adjuvant therapies had a significant advantage in term of OS, and showed a clear trend, despite no significant differences, in T2 group. Authors correctly declared the main limitations of their study, which are the retrospective nature and the lack of some important data which might have helped to clear the real impact of surgery on outcomes; in particular only “curative” resections were taken into account, but both lobectomies and wedge resection were performed.

Only two prospective trials analysing the role of surgery are available (3,4), but their results are not favourable to surgery (5); nevertheless, both of them are more than 20-year-old and they are biased by old staging technology, PET and EBUS/EUS procedures were not available and patients selection was not accurate as it might be nowadays.

Conversely, current available guidelines (6,7) suggest the use of surgery for localized disease, in particular in case of clinical N0 patients. Clinical N-positive patients are still mainly not referred to thoracic surgeon; although previous experiences showed low survival, a careful selection of N1

patients may lead to satisfactory results as showed in the study of Yang, or potentially reach even better outcomes. In this study, none of the patients in the surgery group received a pneumonectomy which is related to higher postoperative morbidity and mortality (8) and might significantly impair patients' performance status and their possibilities to undergo further adjuvant or recurrence therapy; conversely, many of the older paper report a significant pneumonectomy rate. Consequently, a pre-operative indication for a pneumonectomy may be a contra-indication for SCLC surgery and particularly in case of N1 disease.

Interestingly, Yang did not find any statistical significant difference between patients who underwent anatomical and non-anatomical resections in terms of survival; although the real meaning of this results is not completely clear, the role of anatomical resection, which is stressed by NCCN guidelines, may not be so determinant in SCLC surgery, when surgery is always part of a multimodality treatment.

Adjuvant chemotherapy is mandatory after surgery, while additional radiation is usually reserved to patients that have a pathological nodal involvement (6). The role of neoadjuvant is still unclear and results are inconsistent (9-11).

In their paper, Yang and his colleagues reported 11 cases of upstaging and 10 patients with downstaging, but comparison of outcomes of these subgroups has not been reported. Interestingly, despite histological confirmation of nodal involvement was not performed in all patients, clinical stage was confirmed in the majority of cases; nevertheless, as N status is definitely a key factor influencing outcomes, a careful histological or cytological investigation of nodal involvement should be always carried out to better stratify patients excluding N2 involvement and to correctly assign all of patients to the best treatment.

Recently, the International Association for the Study on Lung Cancer (IASLC) introduced a new proposal for N staging in non-SCLC (12) which suggests the use of not only of an anatomical criterion for the definition of N1 and N2, but also a quantitative criteria consisting in the number of lymph-node stations involved; the use of this new proposal in the staging of SCLC might not only add prognostic information, but it might be also useful in patients' stratification and selection for surgery.

Small numbers, retrospective setting of the series, heterogeneous indications are the main limitation to understand the real role of surgery for this subgroup of patients with clinical positive N1; however, this paper points a new ray of light on a dark territory where thoracic

surgeons should dare to explore, but stronger prospective evidences are mandatory to correctly understand the potential benefit of surgery for these patients and to safely direct our clinical practise.

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References

1. Kreisman H, Wolkove N, Quoix E. Small cell lung cancer presenting as a solitary pulmonary nodule. *Chest* 1992;101:225-31.
2. Yang CJ, Chan DY, Speicher PJ, et al. Surgery Versus Optimal Medical Management for N1 Small Cell Lung Cancer. *Ann Thorac Surg* 2017;103:1767-72.
3. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary

- treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. *Lancet* 1973;2:63-5.
4. Lad T, Piantadosi S, Thomas P, et al. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. *Chest* 1994;106:320S-3S.
 5. Barnes H, See K, Barnett S, et al. Surgery for limited-stage small-cell lung cancer. *Cochrane Database Syst Rev* 2017;4:CD011917.
 6. Früh M, De Ruyscher D, Popat S, et al. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi99-105.
 7. NCCN. NCCN Clinical Practice Guidelines in Oncology. Small Cell Lung Cancer. Version 3. 2017. Available online: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site
 8. Powell ES, Pearce AC, Cook D, et al. UK pneumonectomy outcome study (UKPOS): a prospective observational study of pneumonectomy outcome. *J Cardiothorac Surg* 2009;4:41.
 9. Lucchi M, Mussi A, Chella A, et al. Surgery in the management of small cell lung cancer. *Eur J Cardiothorac Surg* 1997;12:689-93.
 10. Veronesi G, Scanagatta P, Leo F, et al. Adjuvant surgery after carboplatin and VP16 in resectable small cell lung cancer. *J Thorac Oncol* 2007;2:131-4.
 11. Eberhardt W, Stamatis G, Stuschke M, et al. Prognostically orientated multimodality treatment including surgery for selected patients of small-cell lung cancer patients stages IB to IIIB: long-term results of a phase II trial. *Br J Cancer* 1999;81:1206-12.
 12. Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2015;10:1675-84.

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