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Is less more for early-stage non-small-cell lung cancer? Current evidence for performing segmentectomy

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Keywords: Segmentectomy • Lobectomy • Early-stage • Non-small-cell lung cancer

Recently, Winckelmans *et al.* [1] conducted a meta-analysis comparing the effect of segmentectomy with that of lobectomy in treating patients with early-stage non-small-cell lung cancer (NSCLC). They found that segmentectomy could yield long-term outcomes comparable to that of lobectomy, only in patients with stage IA NSCLC <2 cm, suggesting that segmentectomy might be a valuable alternative to lobectomy in tumours <2 cm whereas for larger tumours, lobectomy should remain as the first option. The authors are to be complimented for performing a subgroup analysis based on tumour size and for finding a unique group of patients with early-stage NSCLC (tumours < 2 cm) who might be fit for segmentectomy. We quite agree with the authors that lobectomy should remain as the prior choice for treating NSCLC >2 cm, considering the high risk of intrapulmonary lymph node (LN) metastasis [2]. However, is less more in treating early-stage NSCLC <2 cm? As a matter of fact, previous similar meta-analyses comparing the effect of segmentectomy with lobectomy for NSCLC <2 cm yielded significantly conflicting results [1, 3]. Moreover, even by analysing the same Surveillance, Epidemiology, and End Results database, previous studies have also revealed significantly different results when comparing segmentectomy with lobectomy in the treatment of NSCLC <2 cm [1, 4]. Therefore, we believe that heterogeneity might exist even in NSCLC <2 cm. Hence, in our previous study, we analysed the pattern of intrapulmonary LN metastasis in cIA NSCLC and found that even in tumours <2 cm, significantly different patterns of intrapulmonary LN metastasis were observed: NSCLC $\leq$1.5 cm had a low rate of N1 (1.8%) and peripheral (12–14#) LN metastasis (1.8%) while NSCLC >1.5 but $\leq$2 cm had a relatively high rate of hilar (6.5%) and peripheral (12–14#) LN metastasis (18.3%) [5]. Therefore, in view of intrapulmonary LN metastasis, our study suggests that segmentectomy might be utilized for NSCLC $\leq$1.5 cm while for NSCLC >1.5 but $\leq$2 cm, lobectomy should still be preferred [5]. However, direct evidence from the Japanese trial (JCOG0802/WJOG4607L) and North American trial (CALGB140503) is still warranted [6].

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Reply to Deng and Tang

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Keywords: Non-small-cell lung cancer • Segmentectomy • Lobectomy • Limited resection

We thank Drs Deng and Tang [1] for critically reading our paper and for sharing their view on this topic. An interesting point is raised: when considering tumour size, at what point exactly should segmentectomy rather than lobectomy be recommended? While our paper suggested a role for segmentectomy in tumours <2 cm [2], others have found similar evidence for smaller or even larger tumour sizes, making this subject all the more controversial [3–4]. We believe heterogeneity plays a role in these conflicting results and, as suggested, this might still not be completely eliminated in our subgroup analysis of tumours <2 cm. Ideally, this group should be further divided into even smaller subgroups, but unfortunately evidence on these specific tumour sizes is currently limited. The view that segmentectomy might be more appropriate for tumours even smaller than suggested in our article is supported by the results of a recent evaluation of the Surveillance, Epidemiology, and End Results (SEER) database [5] where tumours <1 cm and 1–2 cm were analysed separately. We like to emphasize that besides tumour size, many other factors influence the decision to perform surgery. These include factors related to patient history, such as pulmonary function and comorbidities but also pathologic factors and radiologic features such as the location of the tumour within the segment and invasive characteristics of the lesion. We have to await the final results of the randomized trials before we can make stronger recommendations for daily practice based on a higher level of scientific evidence. Once again, many thanks for your letter and interest on this topic.

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Non-small-cell lung cancer with pathological complete response after induction therapy followed by surgical resection: which is the pattern of failure and which are the future perspectives?

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Keywords: Locally advanced non-small-cell lung cancer • Induction therapy • Pathological complete response • Immunotherapy

Melek *et al.* [1] recently reported an interesting retrospective analysis of a relatively large series of patients with non-small-cell lung cancer (NSCLC) in which they compared the long-term survival (LTS) rate of patients with early-stage NSCLC treated initially with surgery with that of patients in whom surgical resection was performed after induction chemoradiation. The authors correctly stated that ypTNM staging (restaging after induction treatment) (IT) remains the most important prognostic factor for patients who undergo surgery after IT. In this context, several authors [2-3] have suggested that the LTS rate of patients surgically treated after IT was worse in those staged after ypTNM compared to those staged after pTNM, even though the stages were substantially similar. In the subgroup of responders, those who experienced a pathological complete response (pCR) represented those with the best life expectancy. According to Melek *et al.* [1], patients who had a pCR had worse results than those who were stage 1a but had results similar to those who were stage 1b and better compared to those who were stages 2, 3 and 4, with an estimated 5-year survival rate of 72.2%. In line with these results, the authors suggested that this subgroup should be classified as stage 1b instead of stage 0, but strategy of care for and prognosis of this subpopulation are far from clear.

We wish to contribute to this debate by commenting on the paper by Melek *et al.* [1]. A few years ago, our research team reported in EJCTS a similar experience [2] on LTS in patients with NSCLC who underwent radical surgery after IT (195 locally advanced [LA] cases). Among them, pCR was achieved in a remarkable proportion of cases (37 patients, 27% of the surgical cohort); the 5-year LTS rate was 64%. Interestingly, among other prognostic factors, adjuvant therapy ($P = 0.005$) was found to be strongly prognostic for these patients (hazard ratio: 8.21, 95% confidence interval: 2.16–31.16; $P = 0.002$). Indeed, when evaluating the pattern of failure in patients who had pCR, we observed that 46% of them experienced a recurrence, more frequently at a distant site (63%) than locally. Therefore, the combined approach (IT + surgery) guaranteed satisfactory local control of disease but suboptimal control at a distance. Similarly, in Melek's analysis [1], patients who had pCR had the potential for recurrence of up to 23.6%; the majority had distant metastases (70.6%) rather than local recurrence. This observation deserves special attention from physicians who are looking for a more accurate staging system (and accordingly, treatment) in this subpopulation. Indeed, if IT seems to "fail" in controlling metastatic disease, this situation provides the opportunity to include (when feasible) an adjuvant systemic treatment (the so-called sandwich protocol).

In this framework, immunotherapy could be of great help in the future in improving distant control of disease in different oncologic scenarios (including locally advanced NSCLC). Indeed, preliminary data from *in vivo* studies [4] have suggested that platinum-based chemotherapy increases the immunogenicity of NSCLC (increase of PDL1-expression before and after chemotherapy), which provides proof of the principle of applying it in combined approaches. Therefore, we could theorize in the not-too-distant future that a multimodal approach (immunotherapy together with chemotherapy and/or radiotherapy) could be applied in patients with locally advanced NSCLC, increasing the life expectancy in this subgroup of patients. We would greatly appreciate the authors' response to the points raised.

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Reply to Lococo *et al.*

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Keywords: Pathological complete response • Induction treatment • Neoadjuvant treatment • Lung resection

Thank you for giving us an opportunity to reply to Lococo *et al.* [1]. There is still uncertainty pertaining to the indications, treatment options and