

Invited Editorial on “the timing of surgery after neoadjuvant chemoradiation in locally advanced non-small cell lung cancer”

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Comment on: Gao SJ, Corso CD, Wang EH, *et al.* Timing of Surgery after Neoadjuvant Chemoradiation in Locally Advanced Non-Small Cell Lung Cancer. *J Thorac Oncol* 2017;12:314-22.

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Although the current standard of care in patients with locally advanced non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy, neoadjuvant chemoradiotherapy (NCRT) followed by surgery is increasingly used for selected Stage IIIA patients with potentially resectable tumors and limited N2 involvement. It is well known that randomized trials have not demonstrated a significant survival advantage of trimodality treatment unless a lobectomy can be performed and when there is substantial mediastinal downstaging (1-4).

The studies on trimodality treatment mainly report the rates of pCR, R0 resection, mediastinal downstaging, local control, overall survival, treatment morbidity and mortality. There is no evidence about the ideal timing of surgery after NCRT. This interval changes between 3 to 6 weeks in randomized and retrospective studies (1-5). The article by Gao and colleagues entitled “Timing of surgery after neoadjuvant chemoradiation in locally advanced NSCLC” is an important article investigating the effect of the time interval between NCRT and surgery on overall survival in patients with potentially resectable clinical stage IIIA NSCLC (6).

The authors performed a retrospective analysis using the National Cancer Data Base (NCDB) and obtained the records for patients in whom clinical T1-3 N2 NSCLC was diagnosed between 2004 and 2012 (6). They identified 1,623 patients who underwent concurrent NCRT followed by surgery. The patients were categorized on the basis of the interval between NCRT and surgery as follows: 0 to ≤3 weeks (7.9%, n=129); >3 to ≤6 weeks

(50.5%, n=819); >6 to ≤9 weeks (31.9%, n=519), and >9 to ≤12 weeks (9.6%, n=156). The median interval to surgery was 40 days. In multivariate survival analysis no significant difference in survival was detected in patients who underwent surgery within six weeks after NCRT (P=0.107). However overall survival decreased significantly in patients who had an operation >6 to ≤9 weeks after NCRT (P=0.043), and >9 to ≤12 weeks after NCRT (P=0.030). No difference in 30-day mortality was observed between groups. Nevertheless there was a trend toward increased 90-day mortality in patients with an interval to surgery of >6 to ≤9 weeks (90-day mortality 8.7%) and >9 to ≤12 weeks (90-day mortality 9.6%) compared with patients in the 0 to 3 weeks reference group (90-day mortality 3.9%) (P=0.068 and P=0.059 respectively). The authors concluded that the overall survival may be significantly lower in patients who undergo surgery later than 6 weeks after NCRT so unnecessary delays in surgery is discouraged (6).

From the oncological point of view the risk of tumor repopulation and distant metastases increases as the interval to surgery increases, so a decrease in survival is unexceptional. From the surgical point of view the main drawbacks of NCRT are technically challenging surgery and increased rate of postoperative complications. A short interval may carry a risk of excessive bleeding and multiple organ failure due to systemic toxicity of NCRT. If the interval is too long the native anatomy of the mediastinum disappears, dissection becomes harder due to fibrosis and thickening of the tissue planes, and radiation induced

vascular change leads to diminished bronchial blood flow rendering poor wound healing (7).

In Gao *et al.*'s study, patients who had surgery within 3 weeks after NCRT had the highest median overall survival (60.7 months) compared with the other study quartiles (45.2 months for >3 to ≤6 weeks; 44.1 months for >6 to ≤9 weeks; 36.1 months for >9 to ≤12 weeks). Fewer than 5% of these patients had surgery within 1 week after NCRT, and 75% between 2 to 3 weeks (6). This is a finding supporting the idea that a lung resection after NCRT should not be done too early, a recovery period is needed. This analysis also demonstrated a trend toward increased 90-day mortality in patients with an interval to surgery of longer than 6 weeks supporting the idea that lung resection after NCRT should not be done too late.

Although there are several limitations of this study due to its retrospective nature, lack of detailed information in NCDB regarding surgery, surgical complications, tumor staging, disease recurrence and disease specific survival as stated by the authors, the most impressive aspect of this article is that it is the first in the literature evaluating the effect of interval between NCRT and surgery in NSCLC making a valuable contribution to an unanswered question. Although the results of this study are needed to be confirmed, it is unlikely to be validated in a prospective randomized trial as it is well known that even randomized studies of trimodality treatment have been challenging to conduct due to poor accrual.

In conclusion since the randomized or retrospective studies used the interval of 3 to 6 weeks, and the results of the study by Gao and associates emphasized that the overall survival is significantly higher in patients who undergo surgery within 6 weeks, it is of utmost importance not to delay surgery more than 6 weeks. In my personal opinion the optimal interval should be 3 to 4 weeks and it should be carried out in high-volume centers.

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Footnote

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