



Neoadjuvant versus adjuvant chemotherapy for resectable non-small cell lung cancer debate revisited

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The use of adjuvant platinum-based chemotherapy for surgically resectable non-small cell lung cancer (NSCLC) has been well established by several randomized trials and meta-analysis which demonstrated clear survival benefit over no chemotherapy (1-5). However, evidence is less robust regarding the benefit of neoadjuvant chemotherapy (NC). Goals of administering chemotherapy in the preoperative setting (neoadjuvant) include increasing operability by possibly reducing tumor size, improving the likelihood of receiving the maximal planned dose, and reducing the likelihood of micrometastasis. Potential pitfalls of NC include delaying surgery, unnecessary preoperative toxicity affecting postoperative morbidity, and rendering the tumor unresectable (6). A meta-analysis of NC plus surgery versus surgery alone showed significant benefit on survival (7). The National Comprehensive Cancer Network (NCCN) guideline recommends administration of adjuvant chemotherapy (AC) following surgery for T2-4N0-1 NSCLC but do acknowledge the use of NC instead. The study by Brandt *et al.* serves to evaluate whether administration of NC or AC is better for patients with T2-4N0-1 NSCLC undergoing surgical resection (8).

Brandt *et al.* performed a propensity score match analysis of a single institution patients with T2-4N0-1 NSCLC who underwent surgical resection and compared outcomes after NC versus AC. The NC and AC groups

were matched for age, year of surgery, gender, body mass index (BMI), Charlson comorbidity score, type of surgery (pneumonectomy, bilobectomy, lobectomy, or segmentectomy), tumor laterality, histology subtype (adenocarcinoma, squamous, large cell, mixed, other), clinical stage (IB, IIA, IIB, IIIA) and pretreatment tumor SUV_{max} which created a balanced group of 92 patients each. The 5-year overall survival (OS) was 64% (95% CI: 54–75%) for NC and 61% for AC (95% CI: 50-74) which were not significantly different on univariate and multivariate analysis HR 1.21 (95% CI: 0.63–2.30, P=0.57). Several previous investigators have tried to answer this question. For example, the three arm NATCH trial compared NC plus surgery versus AC plus surgery versus surgery alone and found no benefit of NC nor AC to surgery, the study had a number of limitations (9). The NATCH trial was criticized for being overly optimistic with a power analysis of 15% difference in disease-free survival (DFS) at 5 years and over representation by stage I disease patients (75%). Since there are limited head to head trials comparing NC to AC, the meta-analysis of NC versus AC by Lim *et al.* also did not show difference in overall and DFS between NC and AC (10).

The argument for using chemotherapy before rather than after surgery largely comes from a difference in tolerability of chemotherapy that was supported by the NATCH

phase 3 trial which showed that 90% of the preoperative cohort completed 3 cycles of chemotherapy compared to only 61% in the postoperative cohort (9). Consistent with this prior study, the NC group in Brandt *et al.* were more likely to complete chemotherapy compared to AC group (86 versus 72 patients). Nonetheless, improvement in the number of chemotherapy cycles delivered did not result in improvement in OS in other studies (9,11) and in the study by Brandt *et al.*

The concern of NC is the theoretical worsening of surgical outcome due to toxicity. In Brandt *et al.*'s study, the severe postoperative complication rate in NC was 14% compared to 7% in AC group but was not significantly different. The relatively small number of patients in each group may have limited the detection of significance. In comparison, with 624 patients, the peri-operative mortality in the NATCH trial was similar between NC plus surgery versus AC plus surgery versus surgery alone groups (9).

The use of NC has been shown to have a greater potential to eradicate micro-metastasis leading to 10% absolute benefit on distant recurrence at 5 years (7). Since NC has greater effect on preventing metastasis and AC better for local control (4), the combination of NC and AC may confer greater benefit on local and distant control leading to better survival. The open label randomized trial by Westeel *et al.* did not show survival difference in early-stage NSCLC patients receiving 4 cycles of preoperative chemotherapy compared to patients receiving 2 cycles preoperatively followed by 2 cycles postoperatively (11). Unfortunately, the inclusion of patients with stage 1A (17.4%) and 1B (47%) in which the benefit of combining chemotherapy with surgery is less clear, may have affected the study outcome.

The author showed that NC might provide additional prognostic information based on chemotherapy response of the resected tumor. Major pathologic response (MPR) is defined as 10% or less residual viable tumor after NC (12). Kaplan-Meier curves of MPR indicated better OS and DFS versus no MPR in the NC group. And the tumor Response Evaluation Criteria in Solid Tumor (RECIST) response to NC was significantly associated with improve DFS. This indicates their potential use as surrogate measurement of survival, available by the use of NC. The inclusion of stage 1B NSCLC patients in this study which comprise 10% and 12% of neoadjuvant and adjuvant groups respectively may have affected the results because the evidence for use of chemotherapy in this group is less established than in stage II and III. Although stage 1B patients was

included in the landmark AC trials (1-5), the CALGB 9633 which only studied AC in stage 1B patients did not show survival advantage (13). Nevertheless, the study maybe underpowered (14). The NCCN guidelines only recommends AC in stage 1B NSCLC with negative margin if the patient is high risk. Definition of high risk includes poor differentiated tumors, vascular invasion and visceral pleural involvement. Hence, a study comparing NC versus AC in resectable NSCLC should focus on stage II-III (N1 disease) where the indication for chemotherapy is clear but the timing is not clear, rather than on stage 1A or 1B (N0 disease).

A general limitation of all propensity score match study is that if a crucial variable is omitted, the groups will be unbalanced leading to bias. This is especially true in retrospective studies that use a preexisting database which is limited to the variables collected rather than having all the variables needed to make the groups balanced (15). In this study, although the risk from surgery was accounted for by the including the type of surgery into the propensity score, the pulmonary function tests measurements such as forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) were not included. Post pneumonectomy AC was found to improve OS in patients with preoperative FEV₁ of more than 2 L but has no effect on patients with preoperative FEV₁ of less than 2 L (16). Another important variable to consider in the propensity score matching is the surgical margin which was also not included in this study. The process of propensity score matches the patients in the middle where their score overlaps. However, these patients might not be representative of their parent groups. The patient may be the upper extreme of one group and the other patient is of the lower extreme of the other group (15). The patients in NC group were more likely to have earlier year surgery, pneumonectomy, higher clinical stage, higher pretreatment SUV_{max} and adenocarcinoma than the AC group before propensity score matching. By make the groups similar, the outcome showing no difference in OS between NC and AC might be because the two matched groups are very similar but is not representative of their actual unmatched patient cohort, which makes the findings not generalizable.

While this study tries to tackle a problem that surgeons have been wrestling with for a long time, it may soon be irrelevant. There is a distinct movement within thoracic oncologists toward NC. Neoadjuvant immunotherapy and chemoimmunotherapy is logical as it takes advantage of the presence of the tumor to generate an immune response

before its removal. If this becomes the standard of care for chemotherapy, then the current debate of timing may become irrelevant. For the present, the best timing for chemotherapy in resectable N1 NSCLC is unclear in view of the different benefits and drawbacks associated with each approach. At this point, the decision should be personalized to the treatment team and the patients while waiting for additional prospective studies to answer the optimal timing of chemotherapy in surgically resectable N1 NSCLC patients.

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Footnote

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

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