Preoperative Chemotherapy Followed by Surgery Compared With Primary Surgery in Resectable Stage I (Except T1N0), II, and IIla Non-Small-Cell Lung Cancer

Authors: A Depierre, B Millerson, D Moro-Sibilot, et al.

Background
Early stage non-small cell lung cancer (NSCLC) is usually treated with surgical resection. Although early stage (NSCLC) is obviously more curable than more advanced stages, mortality continues to be quoted as approaching 50% or greater. A substantial number of patients will fail with distant metastatic disease. For these reasons, preoperative chemotherapy is investigated in this study to determine if it has an impact on increasing survival in patients with Stage I, II, and IIla NSCLC.

Methods
- 355 patients were randomized to surgical resection alone vs. preoperative chemotherapy followed by surgery.
- Stage I (except T1N0), Stage II and Stage IIla patients were accepted onto study.
- Patients well balanced with the exception of more weight loss in the surgery alone arm (29% vs. 24%) and more N2 disease in the surgery + chemotherapy arm (40% vs. 28%).
- Chemotherapy consisted of 2 cycles of mitomycin (6 mg/m2, d1-3), ifosfamide (1.5 mg/m2,d1-3), cisplatin (30 mg/m2, d1-3) three weeks apart.
- Tumors had to be resectable prior to therapy, and planned operative procedure could not be changed.
- Staged preoperatively, with lymph nodes > 1cm considered involved with disease.
- Patients who were pT3 or pN2 received postoperative radiation therapy.

Results
- 179 patients on the chemotherapy arm and 176 patients on the surgery alone arm were available for analysis.
- Chemotherapy was well tolerated with almost all patients receiving both cycles.
- 92% had complete resections in the chemotherapy arm vs. 86% in the surgery alone arm.
- Only 56% of the patients judged to have preoperative N2 disease by CT scan actually had pN2 disease.
- Radiation was delivered in 41 pts. in the chemotherapy arm vs. 72 pts. in the surgery alone arm.
- Survival was 59% vs. 52% at 2 years, 44% vs. 35% at 4 years, with a MST of 37 mo vs. 26 mo, with the chemotherapy arm showing non-significant improvements.
- Median DFS 27 mo vs. 13 mo
- Subset analysis revealed that the benefit was limited to those patients with N0 or N1 disease (RR=.68, p=.027).

Author’s Conclusions
- Preoperative chemotherapy is well tolerated and has a positive effect on survival in Stage I and Stage II patients.
- The absolute difference of this survival benefit increased from 1 to 4 years of follow up.

Discussion
This study reports on a randomized trial investigating the use of preoperative therapy in patients with earlier stage NSCLC. Although there was no significant survival advantage seen in the entire group, on subset analysis it was shown that patients with N0 or N1 disease did benefit from preoperative chemotherapy. Patients with N2 disease had no advantage to receiving preoperative chemotherapy. This conflicts with previously published papers that demonstrate the efficacy of preoperative chemotherapy in Stage IIla (N2) patients. The reasoning given in this paper was that perhaps chemotherapy is not effective in bulkier N2 disease, though this was obviously not the case in the aforementioned papers. More likely is that this study staged
patients preoperatively, which was demonstrated to be inaccurate, as only 56% of the patients judged to have N2 disease actually had N2 disease on pathologic examination. In addition, less than half of the patients underwent a full mediastinal dissection, further clouding the accuracy of their conclusions. Also, this study was not stratified or statistically powered to evaluate subset analyses. Therefore, the conclusions regarding patients in the N2 group as well as the positive finding in the N0 and N1 group is statistically flawed.

This report speaks to the feasibility of preoperative chemotherapy in early stage NSCLC and presents the conclusion that preoperative chemotherapy may indeed be beneficial in these patients. However, because of the reasons listed above, a definitive conclusion cannot be reached from this study alone.