The Case Against Post-Operative Chemotherapy for Stage I NSCLC

Over the last several years, chemo for resected early stage NSCLC has become a standard of care, but while it's pretty widely accepted for stage II and IIIA patients after surgery, the role for chemo is much more debatable for stage I patients. I'll try to explain why, starting with the downside, and then turn to some of the reasons to consider it.

Several years ago, the first large randomized trial that showed a survival benefit for adjuvant (post-operative) chemo, the International Adjuvant Lung Trial (abstract here) included over 1800 patients ranging from stage I to stage III, and it showed a rather modest, 4% survival benefit at 5 years. The trial looked at different subsets, and there were no significant differences, but the benefits were greater in the patients at higher risk for recurrence, with higher stage and more extensive lymph node involvement:

(Click image to enlarge)

In the wake of this trial, many experts felt that post-operative chemo was appropriate for most patients, but we would generally be less inclined to recommend chemotherapy for a stage I NSCLC.

The year after the IALT trial was first presented, two additional trials were presented at our ASCO meeting, both including stage IB patients as the earliest stage included, since it was widely felt that stage IA patients had too favorable a prognosis to benefit from chemotherapy. The BR.10 trial, led by the NCI-Canada, included stage IB and II patients who received either cisplatin/navelbine for four cycles of chemo alone. Highly positive, it demonstrated the greatest survival benefit we've seen thus far for adjuvant chemo, with a 15% improvement in 5-year survival. The initial presentation (ASCO abstract here) didn't show a breakdown by stage.
Immediately after that presentation, Dr. Gary Strauss presented the CALGB trial 9633 ([ASCO abstract here](http://cancergrace.org/lung/2007/09/28/cons-of-adjuvant-chemo-st-ia-nsclc/)), which randomized 344 patients, all with stage IB NSCLC, to 4 cycles of post-op carbo/taxol or no further therapy. This also showed a significant survival benefit. With both of these trials adding to the rather scant evidence for stage I patients on the earlier trial, it seemed appropriate to treat the vast majority of eligible stage IB patients with chemo, with some consideration for stage IA patients. Since the distinction between IA and IB is often by the size of the tumor (3 cm cutoff), why should a 3.1 cm tumor need chemo but a 2.8 cm tumor not benefit from it?

But the value of adjuvant chemo for stage IB NSCLC came into much greater question in the following year. First, the actual publication from the BR10 trial in the New England Journal of Medicine ([abstract here](http://cancergrace.org/lung/2007/09/28/cons-of-adjuvant-chemo-st-ia-nsclc/)) actually provided survival curves broken down by stage, and this showed that the stage IB patients did not seem to benefit, with the improvement from chemo apparently derived from the stage II patients:

![BR.10 – Survival Curves by Stage](image)

Winton, NEJM 352:2882, 2005

Then Dr. Strauss presented an update of the CALGB 9633 trial with longer follow-up ([abstract here](http://cancergrace.org/lung/2007/09/28/cons-of-adjuvant-chemo-st-ia-nsclc/)), now showing that there was no longer any significant survival benefit for these stage IB patients:
Finally, one additional post-operative chemotherapy trial, called ANITA-1 (abstract here), included patients with resected stage IB to IIIA NSCLC who received cisplatin/navelbine or no chemo and reported positive results overall but no benefit for the stage IB patients who received chemotherapy:

And the results for stage III look very similar to stage II, with a clear, convincing separation of the curves, favoring chemotherapy.

Taken together, the trial dedicated to stage IB patients was no longer positive for a survival benefit, and all of our positive adjuvant chemotherapy trials that included a range of stages,
including those with stage IB NSCLC, showed that the stage IB subset of patients appeared to be receiving little or no benefit compared to the higher stage patients at higher risk for recurrence, and with more to potentially gain from adjuvant chemotherapy.

And what about the stage IA patients? They really haven’t been included in the majority of our clinical trials, but last year there was a study called the LACE Meta-Analysis (for Lung Adjuvant Cisplatin Evaluation) (abstract here) in which the results of five separate trials, including a total of more than 4500 early stage NSCLC patients that had been randomized to cisplatin-based chemo or observation, were pooled together. As with the larger trials that included many stages, the meta-analysis was positive, with an approximately 5% improvement in survival at 5 years. Similar to the appearance of the breakdown by stage in the IALT trial, the benefit was stronger in higher stage patients, and overall quite minimal for stage IB patients. But the effect of adjuvant chemotherapy was actually on the detrimental side for stage IA NSCLC patients, about a 40% difference in the wrong direction:

One key point is that the majority of the patients with stage IA disease received an older chemotherapy regimen rather than cisplatin/nervebine (which itself isn’t exactly cutting edge, but the other cisplatin combination regimens were so old they were really irrelevant to current practice). Because cisplatin/nervebine was also found to be the most effective chemo regimen, it’s always possible that the stage IA patients didn’t do as well because they most commonly got a less effective regimen. But the available evidence, weak though it is, seems to suggest that the stage IA patients may be more likely to be harmed than helped from post-operative chemotherapy.

So these are all arguments against giving chemotherapy after surgery for stage I patients. Next I’ll cover some reasons why there is still a role for individualizing treatment recommendations, specifically why it may still be appropriate to strongly consider adjuvant chemo for patients with resected stage I NSCLC tumors.