Post-Operative Radiation Therapy: Helpful or Harmful?

I’ve discussed the trials that have led to a general recommendation in favor of chemotherapy after surgery for patients who have stage II and IIIA NSCLC, with some ongoing questions about the value in stage IB NSCLC. I haven’t touched the issue of post-operative radiation therapy, but the question comes up from members who ask about the evidence for or against radiation, and how it might be given.

Adjuvant, or post-operative radiation therapy (PORT), has been a reasonable option for lung cancer patients for decades, but the concept took a big hit from the “PORT meta-analysis” published in the British Medical Journal in 1998 (abstract here). This meta-analysis aggregated the results from 9 different studies of surgery alone or surgery followed by radiation, for a total of over 2100 patients. Overall, the results demonstrated a significant detriment in survival from PORT, primarily from more cardiac and lung problems (2-year survival 55% vs. 48%) — the curve on the bottom is radiation, with a worse survival:

(Click to enlarge)

Now, when the results were broken down further, the patients with no lymph node involvement (N0 <–zero) or N1 (hilar nodes, inside the lung) had the worsening of survival, and patients with N2 lymph nodes (mediastinal, or mid-chest nodes on the same side as the primary tumor) involved had no significant change in survival either way, and better local control (less likely to have tumor return in the area). Because of the results of this trial, the general practice since 1998 in the US has been to not pursue post-operative radiation for stage I or II disease and to consider it for patients with stage IIIA NSCLC with N2 node involvement who did not already receive it pre-operatively.

Radiation oncologists hate this trial, and their criticisms are pretty valid. First, many of these trials were very old, going all the way back to the 1970s, and it’s fair to say that their techniques and equipment have improved greatly since then. Also, the majority of the patients on several trials were early stage, including stage I with no lymph nodes, who would be exactly the patients least likely to benefit and most likely to be harmed.

For years, this was all of the information we had. However, some recent studies have shed additional light on the situation. Lally and colleagues (abstract here) reviewed nearly 14,000 patients who had undergone either surgery alone or surgery and post-operative radiation for stage II or IIIA NSCLC after 1988 that were included in the SEER (Surveillance, Epidemiology, and End Results) database, a collection of 13 US regional registries of cancer patients that comprises 26% of the US population. As in the preceding PORT meta-analysis, the overall
survival was worse in patients who received adjuvant radiation:

And also as in the meta-analysis, the patients with N0 (with T3 disease) or N1 disease had a worse survival than patients with surgery alone:

However, patients with N2 disease actually had a better survival when they received adjuvant radiation therapy:

These results, suggesting a benefit from PORT in patients with N2 nodal involvement but a detriment for patients with earlier stage disease is an interesting extension of the results from the older meta-analysis, but they are also only a broad look at the trends from 20,000 feet in this retrospective review.

But we gained further valuable insight from a recent adjuvant chemo trial, known as ANITA-1, which was a European trial of surgery with or without post-operative chemo with cisplatin and navelbine for four cycles (abstract here) (ANITA-2 is navelbine alone vs. no chemo for marginal performance status patients after surgery, and we haven’t seen any results on that yet). The ANITA-1 trial schema is shown here:
Yes, this was a trial about the value of chemo, and the trial did confirm the survival benefit of cisplatin-based chemo, with an 8.6% improvement in 5-year survival with the addition of chemo. But the trial also included optional radiation, which was not randomized and was at the discretion of the treating center but was recommended for node-positive patients (there are geographic differences in practice patterns, and in Europe they are much more likely to recommend PORT for early stage, resected NSCLC than in North America). Of the 840 patients enrolled on ANITA-1, 232 (27%) received PORT; these were more likely to have N2 disease (52%) than N1 (35%) or N0 nodal status (only 8.4%, considered too small a group to be included in the analysis) (data were missing for 6 patients), and patients on the no chemo arm were more likely to receive RT (33%) than those on the chemo arm (22%). Radiation was 5 days per week and was between 45 and 60 Gray.

The results were interesting and complex. For patients who did not receive chemo, radiation actually improved survival for both N1 patients (5-year survival 31.4% vs. 42.6%) and N2 patients (5-year survival 16.6% vs. 21.3%). But for patients who received chemo, radiation reduced survival for patients with N1 nodal involvement (5 year survival 53% vs. 40%), while it improved it further, beyond chemo alone, for patients with N2 lymph node involvement (5-year survival 34% vs. 47%). The tabulated results are shown here in terms of median survival:

So, let’s put all of the data together. While all of these results are from trials in which patients were assigned treatment rather than randomized, which would give a more definitive answer, I think it’s possible to develop meaningful conclusions. My conclusions are these:

1) For patients with N1 involvement, while the ANITA trial suggested a survival benefit from PORT compared with no treatment at all, the survival benefit with platinum-based chemo has been seen in multiple trials over the past several years and seems more compelling, especially with all of the other data that show a worse survival with adjuvant radiation for patients with N1 disease.

2) For patients with N2 disease, the evidence supports PORT as well as chemotherapy, and the best information we have is that both may be better than one or the other.
How to administer chemo and radiation after surgery remains unclear. I'll cover the issues related to that next.