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Oncology Scan—Thoracic Cancers

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We have decided to focus on 1 topic for the thoracic cancers-themed "Oncology Scan," specifically the role (or lack thereof) of thoracic radiation therapy (RT) for operable, pathologically proven stage IIIA/N2 non-small cell lung cancer (NSCLC). This encompasses 2 scenarios: (*1*) microscopic IIIA/N2 NSCLC found after resection of NSCLC: in this setting, there is now agreement that fit patients should receive some type of adjuvant chemotherapy, but little consensus otherwise; and (*2*) clinically diagnosed stage IIIA/N2 NSCLC, in which there is general agreement that patients should not proceed to surgery immediately, but little consensus otherwise.

There is a striking lack of level I evidence on the value of RT in these 2 settings. This is at least true with respect to the endpoint of overall survival. Ultimately, the decision regarding whether to offer these patients RT is based on one's opinion on the importance of other endpoints.

Wisnivesky et al. Postoperative radiotherapy for elderly patients with stage III lung cancer. *Cancer* 2012. (1)

Summary: This is a detailed analysis of the Surveillance, Epidemiology, and End Results (SEER)/Medicare databases, attempting to determine the value of postoperative RT (PORT) in resected stage IIIA/N2 NSCLC in elderly patients. It included patients $\geq$65 years old with stage IIIA/N2 NSCLC who had definitive surgery (lobectomy or pneumonectomy) between the years 1992 and 2005. Patients who had preoperative chemotherapy and patients who died within 30 days after surgery were excluded. The final sample size was 1307 patients, of whom 714 received PORT. Overall survival was the primary endpoint (SEER/Medicare does not have data on local control or event-free survival).

In an effort to minimize bias in their analysis, the authors used the statistical technique of propensity score analysis. This is a method to compare treatments while adjusting for imbalances between the PORT and no-PORT groups. Furthermore, they used an "instrumental variable" (IV) technique to control for unmeasured confounders; this is claimed to simulate a randomized controlled trial.

Raw survival data for the PORT or no-PORT groups were not presented. Patterns of failure, local control, and progression-free survival data are also unavailable. After adjustment for propensity score analysis, there seemed to be no difference in survival (hazard ratio 1.11; 95% confidence interval [CI] 0.97-1.27). Adjusting for the use of adjuvant chemotherapy did not change the results.

Comments: The role of PORT remains one of the most controversial issues in thoracic radiation oncology. This study does not settle this controversy. The results here differ from a previous SEER study by Lally et al (2), which suggested a benefit from PORT. They also differ from other retrospective reports, including the secondary analysis of the Adjuvant Navelbine International Trialist Association (ANITA) trial (3) and several recent Chinese studies (4, 5). Wisnivesky et al (1) stated that their approach is superior to other retrospective reports, because of the use of the propensity score and IV analyses to "control" for potential biases in who receives PORT and who does not.

A detailed critique of these advanced statistical techniques is beyond the scope of this commentary. However, a basic assumption of propensity score matching is that important confounding factors are available and utilized. Unfortunately, the SEER/Medicare database has a great deal of missing data on important prognostic factors and surgical (or radiotherapeutic) quality. The authors have used statistical techniques to correct for one bias (the presumed bias that fitter patients are more likely to receive PORT) but have not (and cannot using techniques such as propensity score) corrected for the likelihood that patients with "worse" tumors and/or "worse" surgery are referred for PORT. We think the most pertinent missing data relate to adequacy of tumor resection margins and proximity of the tumor to central structures, but other factors may include size of involved lymph node(s), uni- versus multilevel N2 disease, location of N2 disease, extracapsular extension, and the process and procedure of surgical resection (ie, how the surgeon felt about the completeness of resection). The IV analysis approach is capable of adjusting for such unmeasured confounders if an appropriate instrument is available and certain other assumptions are met. It is impossible to ascertain from the limited data in the IV analysis whether this is the case. For example, serious bias can occur if the instrument used (in this case, regional variation in PORT use) is only weakly correlated with treatment. For an accessible and conceptual discussion of these analysis approaches, see Pizer et al (6). There is also no information regarding how patients were staged, including proper ruling out

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of N3 and/or M1 disease before surgery and/or in the interval between surgery and start of PORT. In fact, it is possible that some patients included in the PORT group may have actually received early salvage or palliative RT, because the methodology for assigning patients to the PORT group was based in part on simple Medicare coding.

Another shortcoming of the SEER/Medicare database is lack of RT dose and quality assurance data—a major difference from papers coming from cooperative groups and/or academic medical centers. It has been suggested that high-dose PORT is dangerous and could overshadow its potential benefits (7, 8). Finally, it is important to recall that the Wisnivesky analysis was limited to the Medicare (age $\geq$65 years) population, and results may differ in a younger population.

In summary, we do agree with the conclusion that the ongoing LungArt randomized trial in Europe is valid and should be supported. Future vigorous research should be performed to identify biomarkers that may identify patients at elevated risk for local–regional recurrence and thus more likely to benefit from PORT. We do not, however, agree with the authors' opinion that PORT should not be used for stage IIIA/N2 disease outside of a randomized trial. SEER/Medicare databases have come a long way from the old accusations of "garbage-in, garbage-out," but they are far from sparkling clean.

Shah et al. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. *Annals of Thoracic Surgery* 2012. (9)

Katakami et al. Phase 3 study of induction treatment with concurrent chemoradiotherapy versus chemotherapy before surgery in patients with pathologically confirmed N2 stage IIIA NSCLC (WJTOG9903). *Cancer* 2012. (10)

Summary: In the *Annals of Thoracic Surgery*, Shah et al (9) report on a meta-analysis of randomized clinical trials and retrospective studies in which neoadjuvant (induction) chemoradiation therapy (chemoRT) was compared with chemotherapy alone for potentially operable stage III NSCLC. After screening over 3000 papers, 4 randomized trials were identified; 2 were published as full-text articles (the other 2 were old American Society of Clinical Oncology abstracts that were never published as full manuscripts). One of these 2 trials had 125 evaluable patients, and the other had 46 patients in 3 arms, of which 31 patients from 2 arms were evaluable. The former (125 patients) is a subset from the well-known German Lung Cancer Cooperative Group trial by Thomas et al (11). The latter is a small French trial that compared neoadjuvant chemotherapy alone with RT/cisplatin/vindesine or RT/carboplatin/paclitaxel (12). Feasibility quantitative meta-analysis of these 156 patients showed no benefit to chemoRT over chemotherapy alone with respect to overall survival (hazard ratio 0.93; 95% CI 0.54-1.62; $P = .81$). A qualitative review of the other small randomized trials and several retrospective papers was subsequently done. The authors concluded that chemotherapy followed by surgery should be the preferred treatment for these patients.

Coincidentally, a small randomized trial on this topic was published in *Cancer* by Katakami et al (10). Unfortunately, only 58 evaluable patients were randomized, and the study was closed early because of slow accrual. Chemotherapy included carboplatin/docetaxel and was the same in both arms. In the RT arm, the dose was 40 Gy over 4 weeks.

Results showed that overall survival at 3 years was 39.3% with chemotherapy alone and 51.7% with chemoRT ($P = .397$); the corresponding progression-free survival rates were 17.9% and 34.5%, respectively ($P = .187$). More patients had pathologic downstaging with chemoRT (40% vs 20.8%; $P = .215$). Local–regional failure occurred in 12 patients in the chemotherapy alone arm and 5 patients in the chemoRT arm ($P = .0435$). The authors summarized their work by noting that there were trends toward better outcomes with chemoRT, but the underpowered sample size prevents meaningful conclusions except with respect to local control.

Comments: The management of patients with stage IIIA with N2 NSCLC represents the most controversial issue in the therapy of NSCLC. These 2 articles on neoadjuvant chemotherapy alone versus neoadjuvant chemoRT do not resolve this issue but are important reading for thoracic radiation oncologists. The Radiation Therapy Oncology Group (RTOG)/Intergroup trial (13) and the European Organization for Research and Treatment of Cancer trial (14) showed similar outcomes for chemoRT alone versus neoadjuvant therapy followed by surgery. Nonetheless, some physicians, tumor boards, patients, advocates, and their families will continue to desire surgery as part of treatment in highly selected stage IIIA cases, and we agree that surgery may be considered for healthy patients with nonbulky resectable disease when a lobectomy is planned.

The meta-analysis by Shah et al (9) has some very serious flaws. It is hard to understand how a group of 156 patients from 2 trials justifies a formal, quantitative meta-analysis. The 2 trials making up this meta-analysis had suboptimal design to answer questions about modern neoadjuvant therapy. The chemoRT arm of the German trial used 3 cycles of induction chemotherapy, before a very aggressive concurrent chemoRT schedule (1.5 Gy b.i.d. to 45 Gy, with concurrent carboplatin/vindesine) (11). It also had a very heterogeneous patient population, including patients with bulky IIIA disease and IIIB disease, who might more commonly be treated with chemoRT alone. Shah et al should be commended for isolating the N2/IIIA subpopulation. Also of note, its chemotherapy-alone arm encouraged the use of PORT—thus the German trial can more accurately be described as a study of the timing of RT rather than a study of its utility. The other published randomized trial was designed as a phase 2 randomized study, to assess feasibility, and thus was small; the third arm (RT/carboplatin/paclitaxel) was not included in the meta-analysis because survival data were not available (median survival not reached) (12).

It is interesting to note that 5 of the 6 studies in Shah et al's meta-analysis (including retrospective studies) that report 3-year survival data displayed a trend toward improved survival with chemoRT. We do not have access to individual patient-level data, but the tables suggest an absolute difference in 3-year survival of approximately 5.5% (estimated 95% CI 0.5%-10.5%). This estimate would be even more in favor of chemoRT if it were to be weighted by number of patients from each study. Of course, it is difficult to mix randomized and retrospective studies into a single quantitative meta-analysis, but given such limited data available