Editorial

Recent randomized trials on stage III lung cancer treatment

Chi-Fu Jeffrey Yang, Thomas A. D'Amico

Division of Cardiovascular and Thoracic Surgery, Department of Surgery, Duke University Medical Center, Durham, North Carolina, USA

Correspondence to: Thomas A. D'Amico, MD. Division of Cardiovascular and Thoracic Surgery, Department of Surgery, Duke University Medical Center, DUMC 3496, Duke South Room 3589, Durham, NC 27710, USA. Email: thomas.damico@duke.edu.

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The optimal strategy for patients with stage III non-small cell lung cancer (NSCLC) is not well-established and significant variation in practice exists across the United States and Europe (1,2). In the U.S., the majority of National Comprehensive Cancer Network (NCCN) member institutions consider surgery to be indicated in stage IIIA patients with involvement of a single N2 lymph node station smaller than 3 cm who have undergone induction chemotherapy (1). However, there is no agreement among institutions regarding treatment for other manifestations of stage IIIA-N2 involvement (e.g., multi-station or bulky disease) and both NCCN and European Society of Medical Oncology (ESMO) guidelines recommend that the role of surgery be discussed in a multidisciplinary tumor board setting (2,3). The lack of consensus regarding treatment strategies for stage III NSCLC is in part due to the paucity of randomized studies available to guide decision-making (4). Recently, though, there have been two randomized controlled trials published that attempt to better elucidate the role of induction therapy regimens and the role of surgery for stage III NSCLC.

Induction chemotherapy *vs.* induction chemoradiation for stage IIIA-N2 NSCLC

The first of these randomized studies was performed by the Swiss Cooperative Group, SAKK, and evaluated the outcomes of induction chemotherapy and surgery *vs.* induction chemoradiation and surgery for stage IIIA-N2 NSCLC (5). After randomization, 115 patients were allocated to the chemotherapy group and 117 patients to the chemoradiation group. The chemotherapy regimen consisted of three preoperative cycles of cisplatin (100 mg/m^2) and docetaxel (85 mg/m^2). The chemoradiation regimen consisted of three cycles of cisplatin and docetaxel followed by radiotherapy with 44 Gy (22 fractions over 3 weeks). Patients were randomized by center, mediastinal bulk (less than 5 cm *vs.* 5 cm or more), and weight loss (less than 5% *vs.* 5% or more in the previous 6 months), and the groups were similar in preoperative baseline characteristics. Of note, patients with bulky, multi-level mediastinal disease were eligible for enrollment, but 93% of patients in both groups had mediastinal disease <5 cm. The primary outcome was event-free survival. The investigators found no significant differences in event-free survival between the induction chemotherapy group [12.8 (95% CI, 9.7–22.9) months] and the induction chemoradiation group [11.6 (95% CI, 8.4–15.2) months]. There were also no significant differences in overall survival between the two groups.

Prior to this study, there had only been one completed randomized trial comparing induction chemotherapy to induction chemoradiation by the German Lung Cancer Cooperative Group (GLCCG). Two other trials, the Japanese (WJTOG9903) (6) and French (IFTC-0101) (7) trials, were both closed prior to completion due to low accrual. In the GLCCG trial, 558 patients with stage IIIA and IIIB NSCLC were randomized to either preoperative chemotherapy followed by surgery followed by radiation or preoperative chemotherapy followed by concurrent carboplatin, vindesine, and twice-daily radiation followed by surgery (1,8). This study, while important, had several limitations. First, the study included many patients who

would be considered unresectable according to current practice (including those with T4 tumors and mediastinal nodal involvement or any T stage and N3 involvement) and 44% of patients never underwent surgical resection (1). There were also significant differences in chemotherapy and radiation treatment regimens between the groups (1).

The SAKK trial addresses limitations of the GLCCG trial by including only pathologically proven T1–3 N2 M0 NSCLC (and did not include T4 or N3 disease). Another strength of this trial is that over 80% of patients in both groups underwent surgical resection. There are some limitations to the SAKK trial though. First, the trial was not designed to show a small survival benefit although it has about twice as many T1–3 N2 M0 patients as in the GLCCG trial (5). Second, radiation was delivered sequentially rather than concurrently with chemotherapy, and in trials that have assessed definitive chemotherapy and radiotherapy without surgery, concomitant chemoradiation has been shown to be superior to sequential chemoradiation (5). Still, the SAKK trial findings are consistent with many retrospective studies performed in the U.S., where induction chemoradiation is given concurrently (9), including a population-based analysis we performed that found no significant differences in overall survival between induction chemotherapy and chemoradiation (10). A third limitation is that the patient population consisted mostly of patients with limited N2 disease, with 93% of patients in both groups having mediastinal bulk less than 5 cm, and the findings of the SAKK trial may not be generalizable to all stage IIIA-N2 NSCLC.

Despite its limitations, the SAKK trial offers the strongest evidence to date that induction chemotherapy should be considered the superior induction regimen for patients with potentially resectable N2 disease. Although the investigators found no significant differences in overall survival between induction chemotherapy and induction chemoradiation, induction chemotherapy has several potential advantages over induction chemoradiation, which include: (I) a higher delivery of preoperative chemotherapy which may contribute to improved survival (11); (II) a more accurate assessment of the tumor's response to chemotherapy (11); (III) a lower perioperative complication rate (11); (IV) reduced toxicity (3); and (V) reduced cost (12). Future investigation regarding induction regimens should consider studying the differences between induction chemotherapy *vs.* concurrent (as opposed to sequential) chemoradiation and evaluating the impact of induction therapy on bulkier N2 disease.

Surgery *vs.* definitive chemoradiation for stage III NSCLC

The second of the two recent randomized trials on stage III lung cancer was published by the Essen-Paris-Tübingen (ESPATUE)/Arbeitsgemeinschaft Internistische Onkologie (AIO)/Arbeitsgemeinschaft Radiologische Onkologie (ARO)/Clinical Trial group of the German Cancer Society (13). Patients with biopsy-proven IIIA N2 NSCLC and selected patients with IIIB NSCLC received induction chemoradiation, and if felt to have resectable disease by a tumor board, were randomly assigned to either a chemoradiation boost or to surgery. Overall survival was the primary end point. After induction therapy, 161 (65%) of 246 patients were felt to have resectable tumors and 81 patients underwent surgery and 80 underwent chemoradiation boost. There were no significant differences in 5-year overall survival between the surgery arm (44%) and the chemoradiation arm (40%) (P=0.34). There were also no significant differences found in progression-free survival between the two groups.

Prior to this study, there have been two other large randomized controlled trials that have compared surgery *vs.* optimal non-operative management following induction therapy for stage III NSCLC. The first study was European Organization for Research and Treatment of Cancer (EORTC) 8941, which compared surgery *vs.* radiation in patients with stage IIIA-N2 NSCLC who had complete, partial or minor response to three cycles of induction platinum-based chemotherapy (14). In the surgery group, only 50% had complete resection and 47% underwent pneumonectomy. The study reported no significant difference in survival between the two arms. In EORTC 8941, a key limitation was that integrated positron emission tomography/computed tomography (PET/CT) and brain imaging were not performed in the initial staging, and given that PET/CT has been shown to detect occult metastases in up to 25% of patients with clinical stage III disease, the study likely included patients with stage IV disease (1).

The second study was the North American Intergroup 0139 trial, where patients with stage IIIA-N2 NSCLC were randomized to surgery *vs.* radiation following concomitant induction chemotherapy (two cycles of cisplatin and etoposide) and radiation (45 Gy) (9). Both groups were also scheduled to receive two more cycles of cisplatin and etoposide following surgery or radiation. There were no significant differences in overall survival between the two groups (5-year survival of 27% for the surgery group *vs.* 20% for the radiation group, P=0.10) although in an unplanned exploratory analysis, patients who underwent

lobectomy had improved survival when compared to the chemotherapy plus radiation group (median survival of 33.6 months for the surgery group *vs.* 21.7 months for the radiation group, P=0.002).

The ESPATUE study builds on Intergroup 0139 and EORTC 8941 by reporting the outcomes of more contemporary treatment strategies for stage III NSCLC. The Intergroup 0139 trial had an accrual period from 1994–2001 while EORTC 8941 had an accrual period from 1994–2002 whereas the ESPATUE trial accrual period was from 2004–2013. The notable finding of the ESPATUE trial was that in patients with resectable disease, both surgery and definitive chemoradiation following induction therapy were associated with excellent 5-year survival rates of 40% or greater. In comparison, Intergroup 0139 reports 5-year survival rates of 20–27% while the EORTC 8941 reports 5-year survival rates of 14–15.7%.

ESPATUE raises interesting points for discussion. First, should more patients with stage IIIB disease be considered for surgery after induction therapy given the excellent survival outcomes reported by this study? ESPATUE does not report the overall survival of the subgroup of stage IIIB patients in the study and it would be helpful to have this data available for clinicians. Second, the study also helps clarify the role of pneumonectomy in stage III disease. Of the patients who underwent surgery, a significant percentage of patients (32%) underwent pneumonectomy. In the pneumonectomy group, there were no perioperative deaths. This is in contrast to the findings from the Intergroup 0139 trial, which reported that 26% of patients who underwent a pneumonectomy had a treatment-related death (9). The use of pneumonectomy after induction therapy remains controversial and should be considered for well-selected patients and in centers with extensive experience.

There are important limitations to the ESPATUE study. First, the trial was stopped early due to slow accrual. In the original power calculation, the trial needed 300 patients, for a type I error of α=0.05 and a type II error of β=0.20, for a power of 80%. Second, the study included patients with both stage IIIA and stage IIIB. Approximately one-third of patients had T4, N0 or N1 disease, another third had T1–3 N2 disease, and another third had T1–4, N3 or T4, N2. The inclusion of heterogeneous sub-stages makes it difficult to draw specific conclusions regarding treatment. Third, there are differences in chemoradiation regimens used between the ESPATUE trial and those used in the U.S., which make the findings less generalizable. In most North American centers, when chemotherapy and radiation are given in the pre-operative setting, patients typically receive 45–54 Gy over 5 weeks, concurrently with 2–3 cycles of chemotherapy (3). In the ESPATUE trial, patients received 1.5 Gy fractions twice a day (accelerated radiation) with a single cycle of chemotherapy. The approach seen in the ESPATUE trial is more aggressive than the US approach with regards to the radiation regimen (the 45 Gy is given in 3 weeks, as opposed to 5 weeks). However, the chemotherapy regimen is less aggressive (only one cycle *vs.* two cycles).

Conclusions

The SAKK and ESPATUE trials are important additions to the literature regarding stage III lung cancer treatment. The SAKK trial demonstrated that there were no significant differences in survival using induction chemotherapy alone *vs.* induction chemoradiation for patients with resectable stage IIIA-N2 disease. Given inherent advantages of induction chemotherapy over induction chemoradiation, the SAKK findings suggest that for N2 disease that is microscopic or <5 cm in burden, induction chemotherapy is the preferred induction regimen. ESPATUE found no differences between surgery and definitive chemoradiation for stage IIIA and IIIB lung cancer and report that both treatment strategies are associated with excellent 5-year survival of greater than 40%. Both SAKK and ESPATUE trials were underpowered and unable to detect small but clinically meaningful differences in survival between control and comparator arms and both trials were done in Europe with chemotherapy and radiation regimens different from those used in the United States. While SAKK and ESPATUE have contributed to a better understanding of stage III NSCLC treatment strategies, there is a continued need for future trials to be done, given the overall poor prognosis of patients with advanced NSCLC and the questions that remain regarding treatment. Future trials may consider evaluating differences between induction chemotherapy and chemoradiation for bulky, macroscopic, multistation N2 disease. Studies should investigate whether there are difference in outcomes between the timing of chemotherapy and radiation for N2 disease (i.e., whether chemotherapy should be given before or after surgery for resectable stage III NSCLC). In addition, given the outcomes of ESPATUE, investigators may also consider evaluating whether surgery is superior to definitive chemoradiation for selected stage IIIB disease. Finally, because SAKK and ESPATUE reflect European regimens that are not typically used in the U.S. or Asia, there is a pressing need for trials to be performed in North America and Asia that evaluate treatment practices common to those regions.

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