Evolving role for surgery in stage IIIA-N2 lung cancer

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When IASLC was founded, treatment for stage IIIA non–small-cell lung cancer (NSCLC) was primarily single modality (surgery or radiation therapy), the staging system was less refined with each stage very heterogeneous, and preoperative staging was inaccurate. In highly selected patients, surgery at best could obtain a 20% five-year survival. Today there are 2.21 million new cases of lung cancer yearly worldwide (1). Among those with newly diagnosed NSCLC, it is estimated that about 20% of patients present with stage IIIA disease (2). Although five-year survival has improved to 40% with multimodality treatment, outcomes remain unsatisfactory for the majority of patients.

The recognition of poor outcomes from stage IIIA NSCLC and the heterogeneity of this group was dependent on development of an accurate clinical and pathologic staging system. In 1964, Dr. Clifton Mountain, a surgeon at the University of Texas MD Anderson Cancer Center (MDACC) and Dr. David Carr, a medical oncologist at the Mayo Clinic realized the importance of a staging system for lung cancer. No such system existed at that time for lung cancer, although the TNM system was already being used in Europe for other organs. Together, Dr. Mountain and Dr. Carr developed the first TNM staging system for lung cancer, supported by a large database of collected clinical material. This work was undertaken under the auspices of the Task Force on Lung Cancer of the American Joint Committee on Cancer Staging and End Results Reporting (AJCC) and was subsequently adopted by the AJCC. Dr. Mountain continued to refine this system throughout the rest of his career, and his staging system became the standard worldwide in the management of lung cancer. Recognizing the need to coordinate international efforts in lung cancer research, Dr. Mountain was one of the founders of the International Association for the Study of Lung cancer (IASLC) in 1973. He carried the message of the multidisciplinary care for lung cancer developed at MD Anderson to physicians and researchers worldwide seeding the framework for national guidelines to come and establishing the foundation for the IASLC Staging Committee.
Despite refinement of the staging system for NSCLC, now in its 8th edition, stage IIIA is one of the most heterogeneous stages with T descriptors ranging from T1-T4 and nodal descriptions ranging from N0-N2 with single or multiple stations. Most clinical trials have focused on “classic” IIIA which would be primarily T1-T2 N2. However, this is a small group making completion of such trials difficult and many of the subsequently discussed clinical trials failed to meet accrual goals.

Converging clinical advances in the 1980s set the stage for the development of the multimodality treatment of stage IIIA NSCLC. Preoperative staging improved with wider use of more accurate CT scans and mediastinoscopy. Clinical trials with cisplatin in NSCLC lung cancer began in the 1970s with a 21% single agent response rate (3). This was the highest response rate achieved for a single agent in NSCLC up to that time and

additional trials, many led by IASLC members, showed that responses to combination drug treatment (e.g. etoposide) were higher. This stimulated the hypothesis that the addition of systemic drug treatment either pre- (neoadjuvant) or post- (adjuvant) surgical resection could improve long-term survival. It was possible that more drug could be delivered prior to surgery than afterward with deterioration of the patient's performance status. A second benefit of induction therapy would be a more accurate assessment of the tumor response to chemotherapy which could influence post-operative treatment. Based on this rationale, the first neoadjuvant chemotherapy clinical trial in NSCLC was initiated (4). Patients with stage IIIA NSCLC were randomized to receive either up to 3 cycles of cisplatin combination chemotherapy followed by surgery followed by up to 3 cycles of chemotherapy if the tumor was initially stable or responded or immediate surgery.The trial showed a highly significant difference in overall survival in favor of the induction chemotherapy group. The results were first presented at an IASLC Symposium in Brussels in 1993. A second clinical trial, also lead by IASLC members and begun 3 years later, confirmed these findings (5). The publication of a large randomized adjuvant chemotherapy trial for stages I-III, again lead by IASLC members, showing a modest survival benefit with adjuvant chemotherapy shifted interest away from induction trials (6).Adjuvant chemotherapy has its greatest survival benefit in Stage III patients. The overall magnitude of the benefit is similar to that of induction chemotherapy when compared to adjuvant chemotherapy. However, it is more likely that full dose chemotherapy will be given pre-operatively compared to post-operatively. Brandt and colleagues showed that patients who received neoadjuvant chemotherapy compared to adjuvant chemotherapy were more likely to receive the full dose (78% vs. 63%) and full cycle regimen (91% vs. 78%) (7). Patients receiving adjuvant chemotherapy were more than twice as likely to have an adverse event compared to patients who had neoadjuvant therapy (38% vs. 15%). These findings are similar to the NATCH trial, where 97% of neoadjuvant chemotherapy patients began their planned course of treatment compared to only 66.2% of adjuvant therapy patients (8).

During this period developments in the treatment of lung cancer with radiation therapy combined with chemotherapy showed that concurrent chemo-radiation was more effective than sequential administration (9). This observation stimulated a large number of randomized clinical trials attempting to define the benefits of surgery compared to non-surgical chemo-radiation in Stage III patients with IASLC members taking a leading role. In the Intergroup (INT) 0139 trial, patients were treated with induction chemoradiation and subsequently randomized between surgery or further radiotherapy (10). Overall survival did not differ between both arms although progression-free survival was better in the surgical resection group. Mortality following pneumonectomy was very high, emphasizing the high morbidity of induction chemo-radiation in this group and likely neutralizing any survival advantage for surgery. An unplanned subset analysis was done by matching patients having lobectomy after induction chemoradiation to a matched group treated by chemoradiation alone. There was a highly significant difference in survival favoring the surgical group.

In the ESPATUE trial, patients with IIIA(N2) and selected patients with IIIB received induction chemotherapy, as well as concurrent chemoradiotherapy. Patients were then

randomly assigned to receive a chemoradiotherapy boost or undergo surgery (11). No difference in overall survival was observed between the two arms. In the European Organization for Research and Treatment of Cancer (EORTC) 08941 trial, only induction chemotherapy was given followed by surgery or radiotherapy in case of response to chemotherapy, also randomizing those patients with a minor response (12). Once again overall and progression free survival did not differ between the two randomized groups. These trials were completed at a time when mediastinal staging by positron emission tomography and endobronchial ultrasound guided biopsies was not routinely available. Today surgical mortality and morbidity have decreased dramatically due to more widespread use of minimally invasive techniques and enhanced recovery protocols (13). Despite the number of trials and large numbers of patients, definitive answers to the optimal management of stage IIIA are lacking due to the heterogeneity of patients entered and continuing advances in radiation, surgical, and staging technology.

Other recent trials have attempted to fill the gaps. The Swiss Cooperative Group, SAKK,study compares induction chemotherapy and surgery vs. induction chemoradiation and surgery for stage IIIA-N2 NSCLC (14). No differences were found in overall or event free survival suggesting that in future clinical trials the appropriate control group is induction chemotherapy and surgery. Before this study, there was only one completed randomized trial comparing induction chemotherapy to induction chemoradiation by the German Lung Cancer Cooperative Group (GLCCG) (15). Although an important study, it had limitations. Many patients were included who would be considered unresectable (including those with T4 tumors, and 44% of the patients did not have surgery. No survival difference was observed between the two arms.

A recent excellent review of the surgical management of Stage IIIA NSCLC, authored by IASLC members, summarized the results of five meta-analyses of stage IIIA clinical trials to date (16). In none of the five studies was the surgical arm superior to definitive chemo-radiotherapy. The authors concluded that “after induction therapy for preoperative N2 involvement, best surgical results are obtained with proven mediastinal downstaging when a lobectomy is feasible to obtain a microscopic complete resection. However, no definite, universally accepted guidelines exist.” These findings emphasize that all patients with Stage IIIA should undergo multidisciplinary management and treatment.

The emergence of targeted drug therapy and immunotherapy has greatly improved outcomes for patients with Stage IV NSCLC. These include osimertinib, which targets mutations in the epidermal growth factor, and monoclonal antibodies (e.g. nivolumab, pembrolizumab) which block the immune checkpoint protein PD1, an inhibitory receptor that is expressed by all T cells during activation and stimulates T cells to kill neo-antigen expressing tumor cells. In a recent randomized trial, durvalumab (anti-PD-L1 monoclonal antibody that binds to the PD1 ligand) was evaluated as an adjuvant therapy following definitive chemo-radiotherapy. Patients with unresectable stage III NSCLC who had no evidence of disease progression after two or more cycles of platinum-based chemo-radiotherapy received either durvalumab or the placebo (17). Progression-free survival was significantly longer for durvalumab compared to the placebo.

Many investigators are moving these agents into earlier disease settings including neoadjuvant treatment, once again with IASLC members leading the way. In the Checkmate 816 clinical trial neoadjuvant chemotherapy with nivolumab plus platinum-doublet chemotherapy significantly improved pathologic complete response rate and event-free survival compared with chemotherapy alone in patients with resectable stage IB to IIIA non–small cell lung cancer (NSCLC) (18). Cascone and co-workers reported the results of the phase 2 randomized NEOSTAR trial (NCT03158129) of neoadjuvant nivolumab or nivolumab + ipilimumab (a monoclonal antibody that blocks the CTLA4 checkpoint) followed by surgery in 44 patients with operable NSCLC, using major pathologic response (MPR) as the primary endpoint (19). The nivolumab + ipilimumab arm met the prespecified primary endpoint threshold of 6 MPRs in 21 patients, with a 38% MPR rate (8/21). In the 37 patients resected on trial, nivolumab + ipilimumab had an MPR rates of 50%. The authors concluded that nivolumab + ipilimumab resulted in higher pathologic complete response rates (10% versus 38%), less viable tumor (median 50% versus 9%), and greater frequencies of effector, tissue-resident memory and effector memory T cells. They evaluated the gut micro biome and found increased abundance of gut Ruminococcus and Akkermansia spp. was associated with MPR to dual therapy. They concluded that neoadjuvant nivolumab + ipilimumab-based therapy enhances pathologic responses, tumor immune infiltrates and immunologic memory, and merits further investigation in operable NSCLC. Although no definitive conclusions can be made, the results are promising, and larger randomized trials are in progress to evaluate the effects on overall survival. It has been an honor and privilege for me to be associated with the IASLC and participate in clinical trials over the past 35 years from the first induction chemotherapy trial to the latest studies of induction checkpoint blockade.

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