Commentary: Surgery for N3 disease: Next frontier or has this ship already sailed?

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Every year at either the American Association for Thoracic Surgery or Society of Thoracic Surgeons annual meetings, we as a specialty still host lively debates over whether surgery is indicated for N2-positive non-small cell lung cancer. Inevitably, the crux of the arguments boils down to the fundamental idea that not all N2 patients are necessarily the same. A difference in both the biology and clinical behavior is thought to exist between patients with bulky multistation N2 disease and non-bulky single-station disease with respect to the risk of systemic recurrence. There may also be a difference in the efficacy of surgery as applied to either scenario in terms of both the ability to adequately clear the disease and the morbidity related to more extensive and complex resections. Response to neoadjuvant therapy, regardless of regimen, factors critically into this equation as well, since the probability of complete eradication of disease is undoubtedly enhanced. So, when are we going to start having debates on the role of surgery in N3 disease?

By the American Joint Commission on Cancer 8th edition, N3 disease includes all patients with either supraclavicular or scalene and/or contralateral mediastinal or hilar lymph node involvement.¹ Guidelines from the National Comprehensive Cancer Network before 2018 recommended concurrent definitive chemoradiotherapy with a 5-year survival in the 5% to 25% range.² The literature on surgery for stage IIIB non-small cell lung cancer is sparse and limited to mostly retrospective and small prospective phase II studies. Patients with actual N3 disease comprise even-smaller subsets of these cohorts, and patients with supraclavicular nodal involvement are frequently excluded altogether. Thus, with no randomized data evaluating chemoradiation alone versus chemoradiation plus surgery for patients with N3 disease, what conclusions can we draw from this study among the others?

After an in-depth review, I believe that there are a few common threads that are worth examining and may guide us in the way forward. None of these represent truly novel insights and all relate back conceptually to our initial observations in patients with N2 disease. Although a complete pathologic response in the tumor bed or complete

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Central Message

Based on this report and others, aggressive local therapy in selected patients with N3 disease may represent the next frontier of improving outcomes in this patient population.

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sterilization of mediastinal lymph nodes is a relatively rare event (5%-15%) following any regimen of neoadjuvant chemotherapy and/or radiotherapy in this patient population, nodal downstaging consistently occurs in roughly one-third of patients and portends a significantly improved prognosis. In fact, DeCamp and colleagues³ found that the most important predictor of long-term survival was pathologic nodal status. One-half of patients who were successfully down-staged with neoadjuvant therapy survived more than 5 years, whereas patients with persistent N3 disease were not likely to survive even 2 years. Similarly, in the study of Grunenwald and colleagues,⁴ surgery was only offered to patients who demonstrated a response to systemic therapy, and those with sterilization of the mediastinal lymph nodes achieved a 5-year survival of 42%. Overall, across the board, rates of eligibility for surgery ranged from approximately 60% to 85%, as did rates of complete resection thereafter. The results of the Southwest Oncology Group Trials on stage IIIB disease highlighted the need for appropriate patient selection by suggesting criteria for consideration of and extent of surgical resection.⁵ For example, 18 patients included in this trial had biopsy-proven supraclavicular nodal involvement at enrollment, but only patients without persistent evidence of supraclavicular disease following neoadjuvant chemoradiotherapy actually proceeded to surgery. The intent of thoracotomy, therefore, was strictly to remove the primary tumor only.

The current study,⁶ based on the National Cancer Database, reports an extraordinarily high incidence of nodal downstaging in their clinical N3 population (>80%), either by way of induction therapy or invasive pathologic nodal assessment. It is not surprising, therefore, that a long-term survival benefit is seen in patients treated with chemoradiotherapy plus surgery versus chemoradiation alone, since the surgery group appears to include a high proportion of patients that either had an excellent response to induction therapy or never had N3 disease in the first place. What is surprising, however, is that a survival benefit is still seen with surgery after 6 months in the pathologic N3 population, although to a much lesser extent.

This is the first study to my knowledge to suggest that surgery may be beneficial in patients with persistent N3 disease, but we are left wondering about the specifics of these patients. For example, the implication of the subgroup comparisons is that an R0 resection via lobectomy contributed to the improved survival observed in this population. It is hard to imagine, however, how an R0 resection can truly be achieved in a patient with persistent N3 disease via lobectomy, unless we are missing some key information. Many of us are all too well-aware of the myriad and unfortunate shortcomings of the National Cancer Database. Missing variables, lack of operative details or indications for surgery, and unclear staging methodologies plague all manuscripts that rely on this data source, and this study is certainly no exception. The authors appropriately make note of these Achilles' heels, and so my intention is not to persevere on it here. In a related study on surgery for stage IIIB disease overall using the same data source (we can expect some overlap here but not entirely), Bott and colleagues⁷ similarly detected a survival advantage in patients with stage IIIB who were treated with chemoradiation plus surgery versus chemoradiation alone with a median survival ranging from 25 to 30 months in the surgery group. Of note, Raman and colleagues⁶ observe median survival rates exceeding 30 months, possibly reflecting greater heterogeneity in this analysis.

While response to neoadjuvant therapy is impossible to predict a priori based on currently available tools, serial computed tomography and positron emission tomography imaging can identify patients with limited mediastinal/supraclavicular nodal disease that responds or stabilizes with systemic therapy who may then benefit from aggressive local therapy. In further support of this approach, we can turn to the latest in the oligometastatic lung cancer literature. A few months ago, Gomez and collaborators⁸ published the results of a multicenter phase II clinical trial that randomized nearly 50 patients without progression of disease after 3 months of front-line systemic therapy to either continued maintenance systemic therapy versus local consolidative therapy including surgery and/or radiotherapy

to all sites of disease. Eligibility was limited to patients with 3 or fewer metastatic sites, and one half of patients in each group had either N2 or N3 disease. While a dedicated subgroup analysis was not performed for stage IIIB patients, accrual was closed early due to a compelling benefit in both overall and progression-free survival seen in the local consolidative therapy group.

Therefore, although the evidence does not meet Level 1 criteria, I think the trend is apparent: selected patients with limited N3 disease that responds durably to systemic therapy probably deserve a shot at aggressive local therapy, including surgery, or at least the consideration of a multidisciplinary tumor board. Will we ever have randomized data to prove this? Naysayers may quote the results of the recent PACIFIC (A Global Study to Assess the Effects of MEDI4736 Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non-Small Cell Lung Cancer) trial, which thus far demonstrates prolonged overall survival with the addition of durvalumab to definitive chemoradiation for stage III non-small cell lung carcinoma, and the 2018 National Comprehensive Cancer Network guidelines have already been updated to reflect these data.⁹ Median survival rates with this regimen mirror closely with those seen with existing multimodality therapy and surgery, thereby raising the question of whether the addition of an immune checkpoint inhibitor may eventually obviate the need for surgery. However, large database studies, such as this one, provide the justification and inspiration for us to explore new frontiers. If our goal is to push the envelope, we may hypothesize that perhaps the best outcomes will be achieved with a combination of all 4 available modalities: chemotherapy, radiation, immunotherapy, and surgery. Future prospective clinical trials with collaborative leadership from the thoracic surgery community will be paramount to uncovering this answer.

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