Commentary: Surgery for N3 non–small cell lung cancer—utopia or future reality?

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With the exception of highly selected cases, surgical resection of N2 or N3 non–small cell lung cancer (NSCLC) has historically been associated with similar survival compared with concomitant chemoradiation alone.^{1,2} The presence of cancer in mediastinal nodes powerfully predicts future metastatic disease and therefore in the setting of N3 disease the effectiveness of systemic therapy is particularly important. Locoregional control is generally achieved with chemoradiation albeit with 30% to 45% 2-year recurrence.^{3,4} Two major phase III trials failed to show survival benefit of surgery compared with chemoradiation in this setting.^{1,2} As such, surgery for N3 NSCLC is not recommended in any currently available guidelines.⁵

Despite these facts, Raman and colleagues queried the National Cancer Database to study the “Outcomes of surgery versus chemoradiotherapy in patients with clinical or pathologic N3 non–small cell lung cancer.”⁶ After the customary propensity matching analysis, the authors found that long-term survival in surgically resected patients is improved compared with chemoradiation alone, and concluded that randomized trials are needed to further study this paradigm. Although the study and conclusions are compelling, the inherent weakness of the baseline National Cancer Database data make the interpretation and application of these results difficult. Of 1173 surgical patients only 616 (53%) received perioperative therapy for clinical N3, and only 209 (18%) received neoadjuvant therapy. This fact highlights either gross mistakes in staging or documentation, misunderstanding of what N3 disease means, or blatant deviation from the National Comprehensive Cancer Network guidelines⁵ in many cases. The authors therefore further focused on a pathologically confirmed N3 group of patients, but even in this group only 11% (31/283) received neoadjuvant therapy and 34% (96/283) did not have documented any perioperative chemotherapy. Even in the propensity matched pathologic N3 group, 26% (58/221) of surgically managed

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Central Message

Surgery for N3 NSCLC is not recommended in any current treatment guidelines. However, locoregional control with chemoradiation in this setting ranges between 60% and 70%. The additional use of 1 year of durvalumab treatment with chemoradiation significantly improved progression-free and overall survival, but it is unknown whether it also improved locoregional disease control. Additional use of surgical therapy in well selected patients might provide further survival benefit to selected patients suitable for dual locoregional NSCLC control in the era of immunotherapy. Whether surgery should be used in a salvage or planned setting after chemoradiation is not clear. Careful patient selection and excellent perioperative outcomes are of utmost importance to show benefit of surgical therapy in this setting.

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patients did not receive additional therapy. It should also be highlighted that 90-day mortality in the surgery arm was a very high 9% (24/283). Despite of the apparent benefit of surgery in propensity matched cohorts, the inherent weakness of the data used in this study make its findings extremely difficult to interpret and will not convince any of our oncology colleagues that surgical therapy is superior to chemoradiation in N3 disease. Especially when a phase III randomized trial using 1 year of anti-programmed death ligand 1 checkpoint blockade durvalumab in unresectable but responding patients to definitive chemoradiation showed an 83% 1-year and 66% 2-year survival, without a 9% 90-day mortality.⁷

However, there might be a hypothesis-generating finding in this study after all. And it is that maximal locoregional disease control aided by surgical therapy in selected patients with regionally advanced disease might translate

into prolonged survival, especially now that distant disease control is significantly improved with adjuvant durvalumab. In the A Global Study to Assess the Effects of MEDI4736 Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non-Small Cell Lung Cancer (PACIFIC) NCT02125461 trial, the benefit of durvalumab extended across all groups regardless of histology, smoking, programmed death ligand 1, or epidermal growth factor receptor status, and was mainly in decreasing the incidence of new metastatic disease.⁷ Unfortunately, data on locoregional control in the PACIFIC trial are not available, but historically 2-year local failure after chemoradiation ranges between 30% and 45%.^{3,4} Herein lies the opportunity of the addition of surgery to multimodality treatment in patients with regionally advanced NSCLC. However, patients for such therapy need to be carefully selected to avoid 9% 90-day mortality. The influence of maximal locoregional control on survival is evident from oligometastatic NSCLC and intuitively this paradigm should extend to N3 NSCLC.⁸

For now, the PACIFIC trial established level I evidence and a long-awaited step forward in the management of advanced mediastinal N2 and N3 nodal NSCLC. For well selected patients, the additional use of surgical therapy in this setting might provide further survival benefit, but it is highly unlikely that the effect of surgical

locoregional disease control will be studied in a randomized trial.

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