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Commentary: Why does neoadjuvant therapy suddenly make sense for early stage non–small cell lung cancer?

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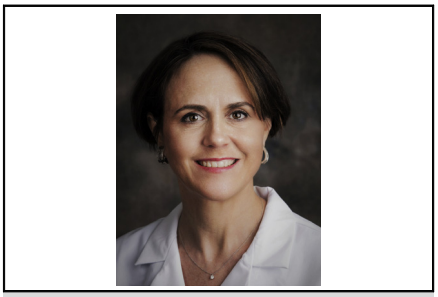

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CENTRAL MESSAGE

Trials of neoadjuvant immune checkpoint inhibitors have generated great enthusiasm, but we must be cognizant of the potential for negative influence on short-term surgical outcomes in early-stage patients.

Immune checkpoint inhibitors (ICIs) have dramatically altered systemic therapy in non–small cell lung cancer (NSCLC) by revolutionizing stage IV treatment and improving survival for unresectable stage III disease. They are now under investigation in resectable stage III and early-stage disease. They might represent the next big breakthrough in early-stage NSCLC and provide a similar stepwise survival improvement as seen with the introduction of adjuvant therapy, minimally invasive resection, and stereotactic radiotherapy into routine care. Along with the excitement come many questions and concerns. Trials of ICIs in the adjuvant and neoadjuvant setting are completed, but survival outcomes are many years away. Adjuvant ICI cannot degrade short-term surgical outcomes and biomarkers in resected tumors can help guide use, but their utility may be limited by the absence of the primary tumor for immune priming. Therefore, neoadjuvant strategies are being investigated with great enthusiasm, but preoperative ICIs carry some potential to influence short-term surgical outcomes and reports to date have been sparse, which makes the work from Stiles and colleagues[1] timely and important. It combines expertise from surgical teams that led the early ICI induction trials and focuses on surgery-specific outcomes, including attrition, delays to resection, rate of open procedures, degree of hilar and mediastinal fibrosis, and perioperative complications. These outcomes tend to be overlooked by medical oncologists who have focused primarily on treatment-related immune toxicity and major pathologic response in their early reports. In the prospective trials reported to date, ICIs appear safe in the preoperative setting with rates of attrition, significant delays, perioperative complications, and intraoperative technical difficulty similar to what has been previously reported for induction chemotherapy alone and with some early evidence for increased tumor response.

An important aspects of these trials that should be noted is the inclusion of stage IB, II, and N2-negative stage IIIA patients, whereas the trials used for historical comparison were typically limited to N2-positive IIIA disease. Outside of a clinical trial, patient with earlier-stage disease are recommended for resection and adjuvant chemotherapy based on a series of large prospective trials and the Lung Adjuvant Cisplatin Evaluation meta-analysis.[2] We have never had similar prospective evidence supporting neoadjuvant regimens. Therefore, upfront systemic therapy is a major change in treatment strategy for early-stage patients. The induction ICI trials reported to date have been too small to tease out stage-specific surgical outcomes. Although thoracic surgeons tolerate increased rates of attrition, delay, open procedures, and intraoperative complexity when treating stage III disease due to the high risk of systemic relapse,

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there may be less acceptance for similar issues in patients with stage I and II disease, where resection and local control are the cornerstone of curative therapy. If 5% to 10% of patients with early-stage disease are made ineligible for surgery or experience perioperative complication due induction ICI, there is significant potential to negate any benefits achieved by immune priming. The answers to such concerns are several years away, but they highlight the importance of keeping surgeons integrated in trial conception and design.

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