Induction therapy for non–small cell lung cancer

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At present, fewer than one half of all cases of lung cancer are diagnosed at a localized or regional state (stage I to III).1 The recent emphasis on improving the detection of and screening for lung cancer promises to identify disease at earlier stages and improve prognoses. Yet even when patients are diagnosed with early-stage lung cancer, recurrence-free survival and overall survival (OS) remain poor. During the last decade, efforts have been made to advance the multidisciplinary management of stage I to III non–small cell lung cancer (NSCLC). In this review, we discuss the historical context for multimodality therapy for NSCLC, present data on the currently evolving standards of care, and explore future directions to improve the prognoses of patients with resectable lung cancer.

RATIONALE FOR PREOPERATIVE TREATMENT

Before the addition of systemic therapy to the treatment regimen for patients with early-stage lung cancer, the risk of recurrence with surgical resection alone was as high as 50% in patients with node-negative disease,2 with increasing pathologic stage associated with increasing risk of recurrence.3 The discovery that cisplatin-based doublet chemotherapy in the adjuvant setting was associated with a lower risk of recurrence and death from lung cancer resulted in a treatment paradigm shift.4-6 In the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis, a pooled analysis demonstrated that adjuvant cisplatin-based doublet chemotherapy was associated with an absolute improvement in disease-free survival (DFS) of 5.8% and in OS of 5.4% at 5 years. A subsequent subset analysis of patients with stage IB disease demonstrated that this approach was also associated with a survival benefit in patients with tumors ≥4 cm.7 Although this analysis was underpowered, the recommendation to administer chemotherapy to patients with node-positive disease or with tumors ≥4 cm has persisted and remains standard clinical practice. The National Comprehensive Cancer Network guidelines list cisplatin combined with pemetrexed, docetaxel, or gemcitabine as the preferred regimen for patients whose tumors meet these characteristics. However, given that the reduction in absolute risk is modest, clinicians must individualize the application of these guidelines to their patients. The decision-making for this approach takes into consideration concerns for treatment-related death (generally accepted as 1%) or for permanent morbidity from cisplatin, such as kidney injury or hearing loss, in this typically older population with medical comorbidities.

When the results of the initial trials that investigated adjuvant chemotherapy were reported, contemporaneous trials of neoadjuvant chemotherapy were halted; subsequent meta-analyses revealed that absolute benefit in OS was similar between the adjuvant and the neoadjuvant approach, at 5%.9,10 Despite similar observed benefits in OS, the neoadjuvant approach offers multiple potential advantages over the adjuvant approach. The delivery of adjuvant systemic therapy can be more difficult to achieve; in the LACE meta-analysis, 24% of patients received partial courses of adjuvant chemotherapy, and 9% of patients received no adjuvant chemotherapy at all.5 In addition, a
IMMUNOTHERAPY AND COMBINATION CHEMOIMMUNOTHERAPY

In the years after the publication of these studies on perioperative chemotherapy, T-cell checkpoint inhibition, either alone or in combination with chemotherapy, has become an important treatment option for patients with metastatic NSCLC. Approval of these drugs in the metastatic setting prompted several trials with the purpose of evaluating these agents in patients with resectable disease. Initial phase 1 and 2 trials were open-label, single-arm studies that investigated drugs such as nivolumab and atezolizumab in patients with stage IB to IIIB disease. These trials observed a major pathologic response (<10% viable tumor remaining) in approximately 20% to 45% of selected patients. Furthermore, surgical resection after the use of these regimens appeared to be comparable with resection after the use of other induction strategies. The results of additional phase 2 trials that evaluated combination strategies—either dual-agent checkpoint inhibition or combinations of immunotherapy and traditional cytotoxic chemotherapy—provided further evidence in support of this approach. Once again, rates of pathologic response and event-free survival were better than those in historical studies that used chemotherapy, with comparable rates of surgical morbidity and mortality.

The results from the first phase 3 randomized clinical trial to investigate combination checkpoint inhibition with chemotherapy versus chemotherapy alone were published in 2021. This study, Checkmate 816, randomized 358 patients with stage IB to IIIA (American Joint Committee on Cancer 7th edition) NSCLC to receive 3 cycles of either platinum-based chemotherapy plus nivolumab or chemotherapy alone. Combination chemoimmunotherapy was associated with significantly better event-free survival (31.6 vs 20.8 months; \( P = .005 \)) and rate of pathologic complete response (24% vs 2.2%; \( P < .001 \)). The trial was quickly followed by data from similar studies that used chemoimmunotherapy preoperatively for 4 cycles and immunotherapy in the adjuvant setting for up to 1 year in the form of pembrolizumab (KEYNOTE-671), atezolizumab (AEGEAN), and nivolumab (CheckMate 77T). These studies also demonstrated that patients treated with combination therapy had better outcomes, and these results established chemoimmunotherapy as the preferred induction regimen for patients whose tumors do not harbor actionable driver gene alterations in EGFR or ALK. It is worth noting that, for patients with these driver gene–positive molecular subtypes, induction chemotherapy alone remains the standard of care, pending data from ongoing trials (as discussed in subsequent sections). Furthermore, this paradigm of tailored induction therapy based on genotype has made early molecular testing paramount in cases of locally advanced NSCLC.

With regard to patients who do not receive induction therapy, randomized phase 3 studies have also demonstrated the efficacy of T-cell checkpoint inhibition administered in the adjuvant setting for patients with stage II to III NSCLC. These findings have renewed the debate concerning whether these agents should be administered in the neoadjuvant or the adjuvant setting. Proponents of the adjuvant approach cite the advantage of earlier removal of the primary tumor, particularly in situations in which disease progression or treatment-related morbidity during induction therapy may jeopardize the possibility of complete resection. These concerns are highlighted by data from trials of neoadjuvant chemoimmunotherapy that observed approximately 20% of patients do not proceed to surgery after treatment. Conversely, neoadjuvant immunotherapy appears to have several advantages in addition to the benefits of preoperative chemotherapy discussed in previous sections. Given that the efficacy of T-cell checkpoint inhibition is related to the induction of immune reactivity to tumor neoantigens, the initiation of this reactivity while the primary tumor (and associated neoantigens) is in situ may allow for a more robust antitumor response. Similarly, engaging immune priming in the setting of an intact lymphatic network and uninhibited trafficking of immune cells may offer similar benefits. Although such benefits are mostly still conceptual, accumulating data on other tumor types, such as melanoma, suggest that these mechanistic insights are clinically relevant. However, if ongoing trials investigating a perioperative approach (ie, combined neoadjuvant and adjuvant therapy) observe superior long-term outcomes, the debate regarding pre- versus postoperative therapy may ultimately become irrelevant.

TARGETED THERAPY

Whereas some of the pivotal immunotherapy trials included patients with oncogene-driven NSCLC, such as EGFR-mutant and ALK-rearranged cancers, others
excluded these patients. Current treatment guidelines recommend preoperative chemoimmunotherapy only in the absence of these molecularly targetable alterations. Patients with these molecular subtypes are instead recommended to receive preoperative chemotherapy alone. Therefore, early biomarker testing is paramount to ensure timely and appropriate treatment decisions are made for patients whose disease harbors targetable oncogenes.

However, the perioperative management of this subset of patients with targetable alterations is also rapidly evolving. The initial results of the ADAURA trial, in which patients with stage IB to IIA (American Joint Committee on Cancer 7th edition) EGFR-mutant NSCLC were treated with up to 3 years of daily osimertinib after resection, demonstrated that the use of osimertinib was associated with better DFS (hazard ratio, 0.20; 99.12% confidence interval, 0.14-0.30; P < .001), which led to the adoption of this regimen as the standard of care. The updated analysis of OS observed an impressive hazard ratio of 0.49 (95.03% confidence interval, 0.33-0.73; P < .001) and thereby confirmed the use of targeted therapy in the adjuvant setting for patients with EGFR-mutant NSCLC. In patients with stage IB to IIA ALK+ NSCLC, adjuvant alectinib was compared with chemotherapy: patients who received alectinib had better DFS (hazard ratio, 0.24; 95% confidence interval, 0.13-0.43; P < .0001). Also underway is LIBRETTO-432, a trial of adjuvant selpercatinib for patients with RET fusion-positive NSCLC.

The use of targeted therapy in the neoadjuvant setting is also an area of interest. Preliminary studies have observed that neoadjuvant osimertinib has only modest efficacy; its use is under further exploration in the phase 3 study NeoADAURA (NCT04351555), which is investigating neoadjuvant osimertinib with or without chemotherapy versus chemotherapy alone. In addition, NAUTIKA1 (NCT04302025), a multicenter study of multiple matched targeted therapies in biomarker-selected patients with resectable lung cancer, is currently ongoing, and numerous other trials of neoadjuvant targeted therapy have been reported or are currently accruing patients.

NEoadjuvant CHEMORADIATION

The role of preoperative chemoradiation in these patients remains another area of relative uncertainty. The INT0139 trial previously established that concurrent chemoradiotherapy followed by surgery is an effective treatment option for patients with stage IIIA (N2) NSCLC. However, more recent trials that compared chemoradiation versus chemotherapy alone have suggested that the use of radiotherapy in these patients may result in additional toxicity without a demonstrable improvement in survival. As a result, at many institutions, treatment for resectable patients has evolved to comprise chemotherapy alone, and this strategy was recently endorsed in the American Association for Thoracic Surgery 2023 Expert Consensus Document: Staging and Multidisciplinary Management of Patients with Early-Stage Non-Small Cell Lung Cancer.

Although the routine use of radiotherapy for locally advanced NSCLC is declining, radiotherapy may be relevant for particular subsets of patients. For instance, preoperative radiation may still be useful in patients with superior sulcus tumors, in whom complete resection can be challenging because of anatomic considerations and in whom rapid tumor response may aid in palliation of tumor-related pain. Whether the benefits of preoperative chemoimmunotherapy can be extrapolated to this patient population (particularly those without N2 nodal involvement) remains unclear, and appropriately powered randomized trials will be difficult to complete given the rarity of this situation.

PERIOPERATIVE CARE CONSIDERATIONS

As 3 to 4 cycles of chemoimmunotherapy is now the standard induction regimen for most patients with resectable NSCLC, it is essential for surgeons to be familiar with treatment-related risks relevant to the perioperative period. Unlike the predictable side effects of chemotherapy, immune-mediated adverse events are more sporadic in onset. Endocrinopathies are among the most prevalent perioperative immune-mediated adverse events, and preoperative endocrine laboratories, such as thyroid function tests and those related to adrenal function, should be routinely performed. Cases of otherwise-unexplained hemodynamic instability or electrolyte derangement in the postoperative period should be reviewed with the multidisciplinary team to determine potential associations with immunotherapy and to guide management.

STAGE-SPECIFIC RECOMMENDATIONS

The American Association for Thoracic Surgery expert consensus recommendations regarding the use of neoadjuvant therapy for NSCLC were recently published and will be briefly summarized by stage.

Stage IIIA/Resectable IIIB (T3/T4 N2)

Patients with N2-positive or other variants of stage III disease (ie, T3N1) should routinely receive neoadjuvant treatment before surgical resection. For patients who lack actionable driver alterations, such as EGFR or ALK, and do not have medical contraindications to immunotherapy, neoadjuvant treatment should include preoperative or perioperative chemoimmunotherapy, as outlined previously. For patients who possess driver gene mutations or are not candidates for immunotherapy, preoperative chemotherapy remains the standard of care. Chemoradiotherapy can be considered in cases of superior sulcus tumors, for the reasons mentioned previously.
Stage II
Expert consensus also favors induction therapy for patients with stage II tumors—either those with hilar lymph node involvement (N1) or those >4 cm in size (T2b or higher). Although, in clinical practice, preoperative therapy may be used more variably in these patients than in patients with N2-positive disease mentioned previously, the advantages of preoperative treatment, particularly in the setting of chemoinmunotherapy, may tip the balance toward neoadjuvant treatment.

Stage I
There are few data to support the use of preoperative therapy in patients with stage I lung cancer. Although trials conducted in Asia suggest that adjuvant therapy has a benefit in patients with resected stage I disease, similar results have not been reproduced elsewhere. In contrast, the LACE meta-analysis suggested that adjuvant therapy has detrimental effects on survival in patients with stage IA disease.
However, National Comprehensive Cancer Network guidelines do allow for the use of systemic therapy in patients with resected stage I disease with high-risk features, such as visceral pleural invasion, solid or micropapillary histologic profile, and lymphovascular invasion. It is worthwhile to note that many of these features are identified upon examination of the surgical specimen, limiting their utility for treatment guidance in the neoadjuvant period. However, genomic biomarker testing is still recommended for patients with stage IB tumors, as patients with EGFR-mutant tumors >3 cm may be appropriate for adjuvant osimertinib.

CONCLUSIONS
Multimodality therapy remains an important treatment paradigm for patients with locally advanced NSCLC. Recent studies regarding the utility of immunotherapy and targeted therapy have redefined the standard of care in this patient population, and indeed, to not consider the use of multimodality therapy for patients with early-stage resectable disease risks delivering substandard care. However, in the face of pioneering paradigm changes, it is critical to emphasize that many patients across the country currently receive inadequate management of early-stage lung cancer, including insufficient lymph node dissection and lack of appropriate biomarker testing. Continued education for surgical and medical oncologists is paramount in order to improve the implementation of standard care for all patients. Future directions for these continuously evolving treatment paradigms include the optimal management of patients who do not have a pathologic complete response, the role of additional surveillance tools (such as cell-free DNA) in postoperative patients, and the use of additional biomarkers to escalate or de-escalate therapy as needed. With further trials ongoing, it is critical for surgeons to remain informed of the evolving evidence and to collaborate with colleagues across disciplines to determine optimal care pathways for these patients.

Conflict of Interest Statement
A.C. has received honoraria from MJH Life Sciences and serves as a consultant for Gilead. J.E.C. is a consultant for AstraZeneca, Bristol Myers Squibb, Genentech, Arcus Biosciences, Flame Biosciences, Regeneron-Sanoﬁ, Merck, Guardant Health, Lilly, and Janssen and receives research funding to Memorial Sloan Kettering Cancer Center from Bristol-Myers Squibb, Merck, Genentech, BeiGene, Novartis, and AstraZeneca. M.J.B. is a consultant for AstraZeneca Pharmaceuticals, Iovance Biotherapeutics, and Intuitive Surgical and receives research support from Obsidian Therapeutics.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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monotherapy in untreated melanoma; combined nivolumab and ipilimumab or monotherapy in untreated melanoma; nivolumab and ipilimumab versus ipilimumab in untreated melanoma; rapid eradication of a bulky melanoma mass with one dose of immunotherapy; genetic basis for clinical response to CTLA-4 blockade; genetic basis for clinical response to CTLA-4 blockade in melanoma; nivolumab plus ipilimumab in advanced melanoma; safety and tumor responses with lambrolizumab (Anti-PD-1) in melanoma; hepatotoxicity with combination of vemurafenib and ipilimumab. *N Engl J Med*. 2018;379:2185.


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**Key Words:** non–small cell lung cancer, induction therapy, chemotherapy, immunotherapy, surgical resection, locoregional disease
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