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Neoadjuvant Treatment in Stage IIIA (N2) Non-Small Cell Lung Cancer: Evaluating Surgical Outcomes and Prognostic Impact of Induction Chemotherapy

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ABSTRACT

***Background*:** Non-small cell lung cancer (NSCLC) remains a leading cause of cancer-related mortality worldwide, with stage IIIA (N2) disease presenting a particularly complex therapeutic challenge. Historically, the management of potentially resectable stage IIIA (N2) NSCLC has evolved from surgery alone to a multidisciplinary approach involving neoadjuvant and induction therapies. Induction chemotherapy and induction chemoradiation represent the primary neoadjuvant modalities, each with distinct biological rationales and clinical implications. This review aims to synthesize current evidence regarding the impact of these strategies on surgical resectability, survival outcomes, and patient selection. We systematically examine published clinical trials, meta-analyses, and real-world data to provide a comparative analysis of induction chemotherapy versus chemoradiotherapy. The review also explores the evolving landscape of molecular profiling, immunotherapy, and targeted treatments as they pertain to neoadjuvant approaches in stage IIIA (N2) NSCLC. Special consideration is given to toxicity profiles, operative risks, and multidisciplinary decision-making. Our analysis highlights persistent gaps in optimal patient stratification and sequencing of therapy, with an emphasis on future directions, ongoing clinical trials, and the integration of personalized medicine. In conclusion, while both induction chemotherapy and chemoradiotherapy confer potential survival and downstaging benefits, individualized treatment selection and continued innovation are essential to improving long-term outcomes for patients with this challenging disease.

Keywords: Neoadjuvants, Non-Small Cell Lung Cancer, Chemotherapy

INTRODUCTION

Lung cancer is the most common cause of cancer death globally, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases[1]. Stage IIIA (N2) NSCLC is a particularly heterogeneous group characterized by ipsilateral mediastinal lymph node involvement, often representing a transition between potentially curable and inoperable disease[2]. Treatment paradigms for this subset have shifted from surgery alone to multidisciplinary regimens that include systemic therapy and radiotherapy. The integration of neoadjuvant or induction strategies prior to surgery aims to improve resectability and overall survival by targeting micrometastatic

disease and facilitating nodal downstaging[3].

Despite multiple randomized trials and meta-analyses, the optimal approach to induction therapy—chemotherapy alone versus concurrent chemoradiotherapy—remains controversial[4]. Chemoradiotherapy may enhance tumor response and increase the likelihood of complete resection but carries greater risks of perioperative morbidity[5]. The emergence of molecular diagnostics and immunotherapy further complicates treatment selection, demanding an individualized, patient-centric strategy. This review evaluates current evidence on the comparative effectiveness of induction chemotherapy versus chemoradiation in resectable stage IIIA (N2) NSCLC, highlights key factors influencing surgical and survival outcomes, and identifies knowledge gaps and future research directions.

The management of stage IIIA (N2) NSCLC has evolved significantly with the use of neoadjuvant or induction therapy prior to surgery. Multiple randomized clinical trials and meta-analyses have examined the impact of induction chemotherapy and chemoradiotherapy on resectability, pathologic response, and long-term survival. Induction chemotherapy, typically platinum-based doublets, has been shown to increase the rate of complete surgical resection and achieve nodal downstaging in a proportion of patients, which is associated with improved prognosis[6]. However, recurrence rates remain high, and survival benefits are modest.

Induction chemoradiotherapy was introduced with the rationale of increasing local control and potentially enhancing the eradication of micrometastatic disease. Trials such as the Intergroup 0139 and ESPATUE studies demonstrated that the addition of radiotherapy to chemotherapy before surgery can increase rates of mediastinal downstaging and pathological complete response, although the impact on overall survival has been less definitive[7,8]. Furthermore, combined-modality induction regimens may increase perioperative risks, including respiratory complications and treatment-related toxicity, raising important considerations for patient selection.

Several meta-analyses suggest that both induction chemotherapy and chemoradiotherapy improve surgical outcomes compared to surgery alone in stage IIIA (N2) NSCLC, but no clear superiority has been established between the two approaches in terms of overall survival[9,10]. The choice of regimen is often influenced by patient comorbidities, tumor characteristics, and institutional expertise. As treatment paradigms continue to evolve, the multidisciplinary team's role in tailoring induction strategies to individual patients is critical.

Surgical Outcomes and Resectability After Induction Therapy

The ultimate goal of induction therapy in stage IIIA (N2) NSCLC is to achieve tumor and nodal downstaging that enables complete surgical resection, which remains a key prognostic factor for long-term survival. Studies show that both induction chemotherapy and chemoradiotherapy can increase the rates of mediastinal nodal clearance, with pathological complete response rates ranging from 10% to 20% depending on the regimen[11]. Importantly, mediastinal downstaging after induction correlates strongly with improved survival outcomes, underscoring the importance of careful preoperative and intraoperative assessment[12].

Comparative trials such as the Intergroup 0139 have shown higher rates of mediastinal nodal clearance and pathological response with induction chemoradiotherapy compared to chemotherapy alone, but these advantages have not always translated into significantly higher rates of complete (R0) resection or improved overall survival[7,13]. Furthermore, pneumonectomy after chemoradiation is associated with increased perioperative morbidity and mortality compared to lobectomy, suggesting that surgical approach and patient selection are critical considerations when planning resection following induction therapy[14].

The decision to proceed with surgery following induction therapy should be individualized, integrating clinical response, radiological and pathological assessment, and careful evaluation by a multidisciplinary team. Ongoing research is focused on identifying biomarkers and response criteria that can better guide selection for surgery and predict which patients derive the greatest benefit from multimodality therapy[15].

Survival Outcomes and Prognostic Impact

Long-term survival in patients with stage IIIA (N2) NSCLC remains suboptimal despite multimodal treatment, with five-year overall survival rates typically ranging from 20% to 35%[16]. Induction chemotherapy and chemoradiotherapy have each demonstrated the potential to improve survival compared to surgery alone, largely by increasing the likelihood of achieving mediastinal downstaging and complete resection[9,17]. However, direct comparisons between the two induction approaches reveal only modest differences in overall survival, with some studies suggesting no statistically significant advantage for chemoradiotherapy over chemotherapy[10,18].

Key prognostic factors following induction therapy include the achievement of pathological complete response, nodal downstaging, and the ability to perform a lobectomy rather than a pneumonectomy, all of which are consistently associated with better survival[12,19]. The increased risk of perioperative mortality, especially after pneumonectomy following chemoradiation, may offset some of the survival benefits gained through more aggressive induction regimens[14,20].

Emerging data also indicate that molecular and immune markers, such as PD-L1 expression and driver mutations, may influence both response to induction therapy and long-term outcomes, suggesting a future role for biomarker-driven patient selection and novel therapeutic combinations in this setting[21].

Toxicity and Perioperative Risks

The choice between induction chemotherapy and chemoradiotherapy in stage IIIA (N2) NSCLC must carefully balance potential benefits with treatment-related toxicities and operative risks. Chemotherapy alone is generally associated with manageable hematologic toxicities such as neutropenia, anemia, and thrombocytopenia, while severe non-hematologic toxicities are relatively uncommon[22]. In contrast, the addition of radiotherapy increases the risk of esophagitis, pneumonitis, and pulmonary fibrosis, as well as cumulative hematologic toxicity[23].

One of the principal concerns with induction chemoradiotherapy is the heightened risk of perioperative complications, particularly when pneumonectomy is required. Studies have reported increased rates of

bronchopleural fistula, adult respiratory distress syndrome, and perioperative mortality in patients undergoing pneumonectomy after combined-modality therapy compared to lobectomy or surgery after chemotherapy alone[13,24]. Careful patient selection, avoidance of right-sided pneumonectomy when possible, and optimization of preoperative functional status are essential strategies to mitigate these risks[25].

Ultimately, the multidisciplinary team must weigh the potential for improved local control and downstaging against the risk of serious complications, tailoring the induction approach to each patient's comorbidities, tumor characteristics, and surgical candidacy[26].

Current Trends and Future Directions in Induction Therapy

The landscape of induction therapy for stage IIIA (N2) NSCLC is rapidly evolving with the integration of immunotherapy, targeted therapies, and molecular profiling into treatment algorithms. Recent trials have shown promising activity for immune checkpoint inhibitors, such as anti-PD-1/PD-L1 antibodies, as part of neoadjuvant or induction regimens, with reports of high rates of major pathological response and encouraging early survival outcomes[21,27]. Molecular testing for driver mutations (e.g., EGFR, ALK, ROS1, and BRAF) is increasingly guiding personalized approaches, allowing for targeted agents to be incorporated into multimodal protocols in select patient populations[28,29].

Combination strategies—such as concurrent immunotherapy with chemotherapy or chemoradiotherapy—are currently being evaluated in ongoing clinical trials, aiming to further enhance tumor downstaging, resectability, and survival while maintaining acceptable toxicity[30]. As data mature, these innovations may refine patient selection and optimize sequencing of therapy. Additionally, advances in radiological assessment, liquid biopsy, and minimal residual disease monitoring are expected to improve response evaluation and inform perioperative decision-making[31].

Continued collaboration between medical oncologists, thoracic surgeons, radiation oncologists, and molecular pathologists is vital to ensure evidence-based, individualized care. Future research should focus on identifying robust biomarkers of response, reducing treatment-related morbidity, and defining optimal strategies for integrating new systemic agents into neoadjuvant paradigms.

Conclusion

The management of resectable stage IIIA (N2) non-small cell lung cancer continues to evolve as new evidence and treatment modalities emerge. Both induction chemotherapy and chemoradiotherapy offer potential benefits in terms of tumor downstaging and increased rates of complete surgical resection. However, neither approach has demonstrated clear superiority in overall survival, and each presents unique challenges with respect to toxicity and perioperative risk. The recent integration of immunotherapy and targeted agents into induction regimens holds promise for further improving patient outcomes. Moving forward, individualized treatment decisions—based on patient comorbidities, tumor biology, and multidisciplinary evaluation—will remain the cornerstone of optimal care.

Ongoing research and clinical trials are anticipated to refine patient selection, define the best multimodality approaches, and ultimately enhance survival for this challenging population.

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