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Optimizing Preoperative Strategies for Stage IIIA (N2) Non-Small Cell Lung Cancer: Combined Chemoradiotherapy and Chemotherapy Alone

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ABSTRACT

Background: Stage IIIA (N2) non-small cell lung cancer (NSCLC) presents substantial therapeutic challenges due to its intermediate status between resectable early-stage and unresectable advanced disease. The optimal induction approach remains controversial, primarily between induction chemotherapy (IC) alone and induction chemoradiotherapy (CRT). While IC aims to reduce tumor burden and eradicate micrometastases, induction CRT combines chemotherapy with radiation to enhance local control and potentially increase surgical resection rates. This systematic review aims to critically evaluate existing literature comparing these two strategies, focusing on clinical outcomes such as surgical resectability, pathological complete response rates, survival advantages, toxicity profiles, and quality of life post-treatment. By examining clinical trials, observational studies, and meta-analyses, the review highlights evidence-based strengths and limitations of both induction therapies. Findings indicate induction CRT may enhance local tumor control and complete response rates, yet it can also escalate toxicity and complicate subsequent surgical intervention. Conversely, IC alone generally demonstrates lower toxicity but may be associated with less robust local control. This review underscores the importance of personalized medicine, advocating treatment strategies tailored to individual patient profiles, tumor characteristics, and institutional expertise. The review concludes that while CRT offers advantages in specific patient populations, careful patient selection, based on comprehensive clinical and molecular profiling, is crucial to achieving optimal outcomes and minimizing toxicity.

Keywords*: Stage IIIA (N2), Non-Small Cell Lung Cancer,Combined Chemoradiotherapy , Chemotherapy Alone*

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) representing approximately 85% of cases. Despite therapeutic advances, prognosis

10.48047/jocaaa.2024.33.06.82

remains modest, especially for stage IIIA (N2) disease, characterized by mediastinal lymph node involvement without distant metastases. The heterogeneity of stage IIIA (N2) disease complicates treatment strategies, with controversies surrounding optimal induction therapies to maximize surgical resection and long-term survival outcomes [1,2].

Epidemiologically, stage IIIA NSCLC constitutes about 15-20% of NSCLC diagnoses. Clinical outcomes vary significantly depending on the therapeutic strategy selected, with multimodality approaches becoming the standard. Historically, surgical resection alone demonstrated inadequate outcomes due to high recurrence rates, prompting the exploration of induction therapies such as chemotherapy and chemoradiotherapy [3-5].

Induction chemotherapy (IC) reduces systemic micrometastatic disease, potentially enhancing surgical resectability. Conversely, induction chemoradiotherapy (CRT) combines systemic and local treatments, aiming to enhance local control, pathological complete responses, and possibly survival outcomes. Nevertheless, the enhanced efficacy of CRT may accompany increased treatment-related toxicity, impacting overall patient tolerance and surgical morbidity [6,7].

The research gap identified pertains to uncertainty regarding optimal patient selection criteria for IC versus CRT, including molecular predictors of response, optimal radiotherapy dosage, and timing of surgical interventions. Thus, this systematic review critically analyzes evidence comparing IC and CRT to establish a comprehensive understanding of their relative clinical benefits and toxicities, aiming to guide clinicians toward personalized, evidence-based therapeutic decision-making for patients with stage IIIA (N2) NSCLC.

Lung cancer is a heterogeneous disease with diverse histopathological subtypes, molecular characteristics, and clinical presentations. NSCLC, comprising adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, dominates the global incidence landscape. Risk factors include tobacco exposure, environmental pollutants, and genetic predispositions, with smoking accounting for over 85% of lung cancer-related deaths. Advances in molecular biology have elucidated driver mutations that influence prognosis and therapeutic responsiveness, forming the basis for targeted interventions [8,9]. The disease burden remains substantial, with late-stage presentation in the majority of patients underscoring the importance of early detection, optimal staging, and multimodal therapeutic strategies.

Epidemiology

Globally, lung cancer accounts for approximately 11.4% of all cancer cases and 18% of cancer-related deaths, with NSCLC representing the predominant subtype [10]. Stage IIIA (N2) disease accounts for nearly one-fifth of newly diagnosed NSCLC cases, with incidence rates varying across regions depending on smoking prevalence, environmental exposures, and access to early detection programs

10.48047/jocaaa.2024.33.06.82

[11]. Developed nations tend to have more stable or declining lung cancer incidence due to successful tobacco control, whereas low- and middle-income countries are experiencing a rising burden due to increasing tobacco use and limited screening infrastructure [12]. The median age at diagnosis for stage IIIA NSCLC is typically between 65 and 70 years, with a slight male predominance historically; however, the incidence in females is rising, particularly among non-smokers, often associated with oncogenic driver mutations [13]. Survival outcomes remain poor, with five-year survival rates for stage IIIA NSCLC ranging between 20–30%, underscoring the need for effective multimodal treatment strategies tailored to patient and tumor-specific characteristics [14].

Clinical Picture

Patients with stage IIIA (N2) NSCLC often present with non-specific respiratory and systemic symptoms, which may delay diagnosis. Common respiratory manifestations include persistent cough, hemoptysis, dyspnea, and chest pain, while systemic features can include weight loss, anorexia, fatigue, and malaise [15]. Mediastinal lymph node involvement may lead to additional signs such as hoarseness due to recurrent laryngeal nerve compression, superior vena cava syndrome, or dysphagia from esophageal compression [16]. Some patients remain asymptomatic, with incidental diagnosis occurring during imaging for unrelated conditions. The presentation is influenced by tumor location, extent of local invasion, and comorbid conditions. Early recognition of symptom patterns and prompt referral for diagnostic workup are essential, as delays can reduce the potential for curative intervention [17].

Pathology

Non-small cell lung cancer encompasses a diverse group of histological subtypes, with adenocarcinoma, squamous cell carcinoma, and large cell carcinoma being the most prevalent. In stage IIIA (N2) disease, pathological examination of mediastinal lymph nodes is crucial to confirm metastatic involvement and guide treatment planning [18]. Adenocarcinoma remains the most common subtype, particularly among non-smokers, while squamous cell carcinoma is more frequently associated with heavy tobacco exposure [19]. Histological features, including degree of differentiation, presence of lymphovascular invasion, and tumor necrosis, provide prognostic insights and can influence therapeutic decision-making. Immunohistochemistry and molecular profiling further refine diagnosis by detecting biomarkers such as EGFR mutations, ALK rearrangements, and PD-L1 expression, which can guide targeted therapy integration into multimodal treatment regimens [20]. Accurate pathological classification ensures optimal staging, prognostication, and selection of appropriate induction strategies for resectable stage IIIA NSCLC.

Diagnosis

10.48047/jocaaa.2024.33.06.82

The diagnosis of stage IIIA (N2) NSCLC requires a combination of clinical evaluation, imaging, and invasive procedures to establish both tumor histology and the extent of disease. Initial assessment typically begins with chest radiography, followed by high-resolution computed tomography (CT) to define tumor size, location, and mediastinal involvement [21]. Positron emission tomography-computed tomography (PET-CT) plays a pivotal role in identifying metabolically active nodal disease and excluding distant metastases, thereby refining staging accuracy [22]. Invasive mediastinal staging via endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) or mediastinoscopy is essential for histopathologic confirmation of N2 disease [23]. Magnetic resonance imaging (MRI) of the brain may be performed to rule out intracranial metastases in higher-risk patients. The integration of imaging and tissue sampling ensures precise staging, enabling selection of appropriate candidates for induction therapy followed by surgical resection. Early and accurate diagnosis remains critical for optimizing treatment outcomes and reducing the risk of futile thoracotomies in this patient population [24].

Clinical Assessment

Clinical assessment in stage IIIA (N2) NSCLC involves a comprehensive evaluation of the patient's overall health status, comorbidities, and performance status to determine suitability for multimodal therapy. The Eastern Cooperative Oncology Group (ECOG) or Karnofsky performance scales are routinely used to gauge functional capacity and predict treatment tolerance [25]. A thorough cardiopulmonary assessment, including spirometry and diffusion capacity testing, is essential to evaluate operability, particularly in candidates for surgical resection after induction therapy [26]. Cardiovascular evaluation, often incorporating echocardiography or stress testing, is indicated to identify underlying ischemic disease or heart failure that may complicate surgery or chemoradiotherapy. Nutritional status, frailty indices, and psychosocial factors should also be assessed, as they influence treatment compliance and recovery potential [27]. Multidisciplinary team discussions incorporating thoracic surgeons, medical oncologists, radiation oncologists, pulmonologists, and radiologists are critical in tailoring individualized treatment plans for patients with stage IIIA (N2) NSCLC [28].

Radiological and Pathology Assessment

Radiological evaluation is a cornerstone in the staging and management planning of stage IIIA (N2) NSCLC. High-resolution computed tomography (CT) of the chest provides detailed anatomical information about tumor size, location, and potential invasion into surrounding structures [29]. Positron emission tomography-computed tomography (PET-CT) offers functional imaging that improves the detection of metabolically active mediastinal nodes and distant metastases, thereby enhancing staging accuracy and avoiding unnecessary surgical interventions [30]. For central tumors

10.48047/jocaaa.2024.33.06.82

or those with suspected local extension, contrast-enhanced magnetic resonance imaging (MRI) can be valuable in delineating tumor margins and involvement of mediastinal structures [31].

Pathological assessment is equally critical, requiring tissue sampling to confirm histology and molecular characterization. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy are standard modalities for obtaining nodal tissue [32]. Immunohistochemistry and molecular profiling, including EGFR mutation testing, ALK and ROS1 rearrangements, and PD-L1 expression analysis, provide essential predictive and prognostic information [33]. Integration of radiologic findings with pathological results allows precise staging and guides the choice between induction chemotherapy, chemoradiotherapy, and definitive surgical strategies, ensuring a personalized approach to patient management [34].

Treatment Modalities in NSCLC

Management of non-small cell lung cancer involves a range of therapeutic approaches tailored to disease stage, tumor biology, and patient performance status. For early-stage disease, surgical resection remains the standard of care, while locally advanced stages, including IIIA (N2), often require multimodal strategies incorporating systemic therapy and radiotherapy [35]. Chemotherapy, typically platinum-based doublets, serves as the backbone of systemic treatment and can be used in neoadjuvant, adjuvant, or palliative settings [36]. Radiotherapy offers effective locoregional control, particularly when integrated with chemotherapy as concurrent chemoradiotherapy in patients with unresectable disease [37].

In potentially resectable stage IIIA NSCLC, induction chemotherapy aims to address micrometastatic disease and improve operability, while induction chemoradiotherapy may enhance pathological complete response rates and local control [38]. Immunotherapy with immune checkpoint inhibitors has emerged as an important adjunct, especially in advanced stages, and is under investigation in earlier-stage disease [39]. Targeted therapies directed against specific oncogenic mutations, such as EGFR or ALK, have revolutionized treatment for select patient populations and are increasingly considered in the perioperative setting [40]. Optimal outcomes often require multidisciplinary collaboration to balance efficacy, toxicity, and patient-specific factors in designing the treatment plan.

Surgical Indication by Stage

Surgical candidacy in NSCLC is determined by a combination of tumor stage, anatomical resectability, and patient fitness for surgery. In **Stage I** disease, surgery is the primary treatment modality, typically via lobectomy with systematic lymph node dissection or sampling, offering high cure rates when complete resection is achieved [41]. For **Stage II** NSCLC, surgery remains the mainstay, but adjuvant platinum-based chemotherapy is often recommended to address micrometastatic disease and improve survival outcomes [42]. In **Stage IIIA (N2)** disease, surgical indication becomes more complex.

10.48047/jocaaa.2024.33.06.82

Patients with single-station, non-bulky mediastinal nodal involvement may be considered for surgical resection following induction therapy, particularly if restaging demonstrates nodal downstaging [43]. Conversely, bulky or multi-station N2 disease is generally managed with definitive concurrent chemoradiotherapy, with surgery reserved for select cases in specialized centers [44]. Multimodal evaluation, incorporating thoracic surgery, oncology, radiology, and radiation oncology input, is essential in determining the role of surgery for each patient. Surgical intervention should be pursued only if it is likely to achieve complete resection with acceptable morbidity and mortality [45].

Stage I

Stage I NSCLC is characterized by localized tumors without lymph node involvement or distant metastasis, typically classified as T1 or T2aN0M0. Surgical resection is the gold standard, with lobectomy being the preferred approach due to superior long-term survival compared to sublobar resections [46]. Segmentectomy or wedge resection may be considered in patients with limited cardiopulmonary reserve or significant comorbidities, though these are generally associated with slightly higher recurrence rates [47]. Systematic lymph node dissection or sampling during surgery is critical for accurate staging and prognosis. The five-year survival rate for completely resected Stage I disease exceeds 70%, making timely diagnosis and surgical intervention crucial [48]. Adjuvant therapy is generally not required unless adverse pathological features, such as vascular invasion or poor differentiation, are present [49].

Stage II

Stage II NSCLC typically involves larger primary tumors (T2b or T3) and/or regional lymph node involvement limited to ipsilateral peribronchial or hilar nodes (N1), without mediastinal involvement. The primary treatment remains surgical resection, preferably lobectomy or pneumonectomy, combined with systematic lymph node dissection [50]. Adjuvant platinum-based chemotherapy is generally recommended for all patients with completely resected Stage II disease, as it has been shown to improve overall survival by reducing the risk of systemic relapse [51]. Selected patients with incomplete resection margins may benefit from postoperative radiotherapy, although this must be balanced against potential pulmonary toxicity [52]. The prognosis for Stage II NSCLC is less favorable than Stage I, with five-year survival rates ranging from 40–55%, but outcomes can be improved with effective multimodal therapy [53].

Novel Complementary Therapies for Resectable Stage II and III NSCLC

In recent years, several novel therapeutic strategies have emerged to complement standard surgical and chemoradiotherapy regimens in resectable Stage II and III NSCLC. Neoadjuvant immunotherapy, particularly immune checkpoint inhibitors targeting PD-1/PD-L1, has shown promise in enhancing

10.48047/jocaaa.2024.33.06.82

pathological complete response rates and potentially improving long-term survival [54]. Early-phase clinical trials integrating targeted therapies, such as EGFR inhibitors for mutation-positive tumors, into the perioperative period have also demonstrated encouraging results [55]. Vaccine-based approaches, oncolytic viruses, and adoptive T-cell therapies are under investigation for their potential to stimulate anti-tumor immunity in the preoperative setting [56]. These novel modalities aim to reduce recurrence risk and address micrometastatic disease more effectively, with the ultimate goal of translating biological advances into tangible survival benefits for patients with resectable NSCLC [57].

Stage III

Stage III NSCLC represents a heterogeneous group with variable tumor sizes, nodal involvement, and resectability. Stage IIIA (N2) disease is particularly challenging due to involvement of ipsilateral mediastinal lymph nodes, often requiring a combination of systemic and local therapies. Management strategies depend on tumor bulk, nodal extent, and patient operability. For potentially resectable IIIA (N2) cases, induction chemotherapy or chemoradiotherapy followed by surgery may be considered, especially if nodal downstaging is achieved [58]. Bulky or multi-station N2 disease is generally treated with definitive concurrent chemoradiotherapy, with surgery reserved for highly selected cases in experienced centers [59]. Stage IIIB and IIIC disease, involving contralateral mediastinal or supraclavicular nodes, or unresectable primary tumors, are typically managed with concurrent chemoradiotherapy followed by consolidation immunotherapy when indicated [60]. Multidisciplinary evaluation is essential to optimize outcomes, balancing the potential benefits of surgical resection against risks of morbidity and mortality.

Stage III Resectable Disease

Resectable Stage IIIA (N2) NSCLC represents a subset of patients with ipsilateral mediastinal lymph node involvement who are suitable candidates for surgery after careful selection. The determination of resectability hinges on the extent of nodal disease, tumor location, and patient fitness for surgery. Single-station, non-bulky N2 disease offers the best potential for favorable outcomes following induction therapy and surgical resection [61]. Induction chemotherapy, with or without concurrent radiotherapy, aims to achieve nodal downstaging and reduce tumor volume, thereby increasing the likelihood of complete resection (R0) [62]. Post-induction restaging with PET-CT and invasive nodal assessment is critical to confirm response before proceeding to surgery [63]. Surgical options typically include lobectomy or pneumonectomy, with systematic mediastinal lymph node dissection to ensure thorough clearance and accurate staging. While randomized trials have shown mixed survival benefits of adding surgery to multimodal regimens, selected patients can achieve five-year survival rates approaching 35–40% when complete resection and effective systemic control are achieved [64].

Stage IV

10.48047/jocaaa.2024.33.06.82

Stage IV NSCLC is defined by the presence of distant metastases, including contralateral lung involvement, pleural or pericardial effusions with malignant cytology, or spread to extrathoracic organs such as the brain, bone, liver, or adrenal glands [65]. The primary goal of treatment in Stage IV disease is palliative, focusing on prolonging survival, controlling symptoms, and maintaining quality of life. Systemic therapy forms the cornerstone of management, with treatment choice driven by molecular and immunologic profiling [66]. Targeted therapies are preferred in patients harboring actionable mutations such as EGFR, ALK, ROS1, or KRAS G12C, while immune checkpoint inhibitors, alone or in combination with chemotherapy, have shown significant survival benefits in patients with high PD-L1 expression and no driver mutations [67]. Local treatments, including stereotactic body radiotherapy (SBRT) or surgery, may be considered for patients with oligometastatic disease to achieve durable control in select cases [68]. Optimal management requires an individualized, multidisciplinary approach that integrates systemic therapy, symptom control, and supportive care measures to improve patient outcomes [69].

Special Considerations

Certain clinical scenarios within NSCLC require tailored management approaches due to unique tumor locations or patterns of spread. **Pancoast (Superior Sulcus) tumors**, located at the lung apex, frequently invade adjacent structures such as the brachial plexus, subclavian vessels, and vertebral bodies, leading to symptoms including shoulder pain, arm weakness, and Horner's syndrome [70]. These tumors often necessitate induction chemoradiotherapy to achieve tumor shrinkage and facilitate complete surgical resection, typically via posterior or anterior thoracotomy approaches [71]. Outcomes have improved significantly with multimodal therapy, with five-year survival rates reaching 30–50% in selected patients [72].

Other special considerations include tumors with endobronchial obstruction, which may require bronchoscopic debulking or stent placement prior to definitive therapy, and NSCLC with synchronous malignancies, where treatment sequencing must be carefully planned [73]. The presence of comorbidities, advanced age, or compromised pulmonary reserve may also necessitate modification of treatment intensity to balance efficacy with safety [74]. Multidisciplinary coordination is crucial in these cases to optimize both oncologic control and patient quality of life.

Salvage Surgical Management

Salvage surgery refers to resection performed after definitive chemoradiotherapy or other non-surgical modalities have failed to achieve local control or in cases of locoregional recurrence without distant metastasis. In stage IIIA (N2) NSCLC, salvage procedures are technically challenging due to radiation-induced fibrosis, altered anatomy, and reduced tissue pliability [75]. Careful preoperative assessment is required, including restaging with PET-CT, invasive nodal sampling, and cardiopulmonary

10.48047/jocaaa.2024.33.06.82

evaluation, to confirm operability and exclude systemic progression [76]. While associated with higher morbidity and mortality rates compared to planned primary resections, salvage surgery can offer prolonged survival and symptomatic relief in highly selected patients [77]. Optimal outcomes are achieved in experienced centers with multidisciplinary expertise, where meticulous surgical technique and perioperative care can mitigate the risks associated with post-radiation thoracic surgery [78].

Concurrent Chemoradiotherapy (CRT)

Concurrent chemoradiotherapy remains a cornerstone in the treatment of unresectable stage III NSCLC and is increasingly used as an induction strategy for select resectable stage IIIA (N2) cases. The combination of systemic chemotherapy and high-dose radiotherapy aims to achieve both locoregional control and eradication of micrometastatic disease [79]. Concurrent administration enhances radiosensitization, leading to improved tumor response rates compared to sequential approaches, albeit at the cost of increased acute toxicities such as esophagitis and pneumonitis [80]. Standard regimens typically involve a platinum-based doublet combined with radiotherapy delivered at 60–66 Gy over 6–7 weeks [81]. Careful patient selection is critical, as treatment intensity can pose significant risks for those with poor performance status or comorbidities. Advances in radiotherapy techniques, including intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), have improved dose conformity and reduced exposure to surrounding healthy tissues, thereby mitigating toxicity while preserving efficacy [82].

Trimodality Therapy

Trimodality therapy, combining induction chemoradiotherapy followed by surgical resection, has been explored as a treatment strategy for select patients with stage IIIA (N2) NSCLC. The rationale is to integrate the systemic and locoregional control benefits of concurrent CRT with the definitive removal of residual disease through surgery [83]. Clinical trials have demonstrated that this approach can achieve high pathological complete response rates and improved mediastinal downstaging, which are both associated with better survival outcomes [84]. However, the potential benefits must be weighed against increased perioperative morbidity, particularly after high-dose radiation, which can complicate surgical dissection and wound healing [85]. Candidate selection is paramount—patients must have adequate cardiopulmonary reserve, good performance status, and disease characteristics favorable for complete resection. Multidisciplinary coordination is essential to optimize timing, manage toxicities, and ensure that surgery is performed in centers with expertise in post-radiation thoracic procedures [86].

Targeted Therapies

Targeted therapies have transformed the management of NSCLC by allowing treatment to be tailored to the molecular profile of each tumor. In the context of stage IIIA (N2) disease, their role is evolving,

10.48047/jocaaa.2024.33.06.82

particularly in the neoadjuvant and adjuvant settings. **ALK rearrangements** respond well to ALK inhibitors such as alectinib and brigatinib, which are under investigation for perioperative use [87]. **ROS1 rearrangements**, though less common, are highly sensitive to crizotinib and entrectinib [88]. **MET exon 14 skipping mutations** can be targeted with agents such as capmatinib and tepotinib, offering promising disease control [89]. Similarly, **BRAF V600E mutations** respond to combined BRAF/MEK inhibition, while **KRAS G12C mutations** are now targetable with sotorasib and adagrasib [90]. For **EGFR exon 20 insertions**, novel agents like mobocertinib and amivantamab have shown efficacy [91]. **HER2 mutations** are emerging targets for therapies such as trastuzumab deruxtecan, and **NRG1 rearrangements** are being explored as candidates for ERBB-targeted treatments [92]. The integration of these agents into multimodal treatment strategies may enhance response rates, facilitate surgical resection, and reduce recurrence risk in genetically defined patient subsets.

Targeted Therapy: Future Direction

The future of targeted therapy in resectable stage IIIA (N2) NSCLC lies in early integration with existing multimodal strategies. Ongoing trials are evaluating the potential of perioperative targeted therapy to downstage tumors and improve surgical outcomes [93]. Liquid biopsy techniques, including circulating tumor DNA (ctDNA) analysis, are emerging as tools to monitor minimal residual disease and guide postoperative treatment adjustments [94]. Adaptive trial designs are enabling rapid assessment of novel targeted agents, expediting their transition from advanced-stage use to curative-intent settings [95]. Furthermore, combining targeted therapy with immunotherapy is an area of intense investigation, aiming to exploit synergistic effects on the tumor microenvironment [96]. Personalized therapy based on comprehensive genomic profiling will likely become standard, ensuring that treatment selection is informed by a tumor's complete molecular signature rather than single-gene alterations [97].

Immune Checkpoints: CTLA4, TIGIT, and Others

Immunotherapy targeting immune checkpoints has revolutionized NSCLC treatment, and its role in resectable stage IIIA (N2) disease is expanding. Agents targeting PD-1 and PD-L1 have already demonstrated survival benefits in advanced disease and are now being evaluated in the neoadjuvant setting, often showing increased pathological complete response rates [98]. Beyond PD-1/PD-L1, novel checkpoints such as CTLA4, TIGIT, LAG3, and TIM3 are under active investigation for their potential to further enhance anti-tumor immune activity [99]. CTLA4 inhibitors, when combined with PD-1 blockade, may amplify T-cell activation, while TIGIT inhibition has shown synergy with PD-1/PD-L1 inhibitors in early trials [100]. Combination strategies involving checkpoint inhibitors with chemotherapy, targeted therapy, or radiotherapy are also being explored to achieve more durable and

10.48047/jocaaa.2024.33.06.82

complete responses [101]. As biomarker-driven patient selection improves, these agents may become integral components of multimodal regimens aimed at maximizing cure rates in resectable NSCLC.

Combination with anti-VEGF

The combination of immune checkpoint inhibitors with anti-vascular endothelial growth factor (anti-VEGF) therapy represents a promising approach in NSCLC management, including in the resectable stage IIIA (N2) setting. VEGF plays a key role in tumor angiogenesis and immune evasion, and its inhibition can normalize tumor vasculature, enhance immune cell infiltration, and potentially improve the efficacy of immunotherapy [102]. Bevacizumab, the most extensively studied anti-VEGF antibody, has demonstrated survival benefits when combined with chemotherapy in advanced NSCLC, and early-phase trials are now evaluating its integration with PD-1/PD-L1 inhibitors in neoadjuvant regimens [103]. Preclinical data suggest that VEGF blockade may also reduce myeloid-derived suppressor cells and regulatory T cells in the tumor microenvironment, further augmenting anti-tumor immunity [104]. These synergistic effects may translate into improved pathological response rates and long-term outcomes when incorporated into multimodal treatment strategies for resectable disease, although careful patient selection is critical to balance efficacy with the risk of vascular and bleeding complications [105].

Adoptive Cellular Therapy

Adoptive cellular therapy (ACT) harnesses autologous or allogeneic immune cells, such as tumor-infiltrating lymphocytes (TILs), genetically engineered T cells, or natural killer (NK) cells, to target and destroy cancer cells. In NSCLC, ACT is still largely investigational, but early studies suggest potential benefits in both metastatic and locally advanced settings, including stage IIIA (N2) disease [106]. TIL therapy involves harvesting and expanding tumor-specific lymphocytes from resected tumor tissue, followed by reinfusion after lymphodepleting chemotherapy to enhance engraftment [107]. Chimeric antigen receptor (CAR) T-cell therapy, widely used in hematologic malignancies, is being adapted to target NSCLC-associated antigens such as MUC1 and mesothelin [108]. NK cell-based therapies, including cytokine-induced NK cell infusions, may provide an off-the-shelf immunotherapeutic option. Combining ACT with immune checkpoint blockade or targeted therapy could further enhance efficacy by overcoming tumor immune evasion mechanisms [109]. Although promising, ACT requires specialized facilities, rigorous patient selection, and further validation in randomized clinical trials before routine application in resectable NSCLC can be recommended.

Taxanes in Non-Small Cell Lung Cancer

Taxanes, including paclitaxel and docetaxel, are microtubule-stabilizing agents that disrupt mitotic spindle formation, leading to cell cycle arrest and apoptosis. In NSCLC, they are commonly used in combination with platinum compounds as part of induction or concurrent chemoradiotherapy

10.48047/jocaaa.2024.33.06.82

regimens, especially in stage IIIA (N2) disease [110]. Weekly paclitaxel with carboplatin has shown favorable tolerability and radiosensitizing properties, making it a preferred option in certain induction CRT protocols [111]. Docetaxel, administered postoperatively or as part of sequential chemotherapy, has demonstrated survival benefits in advanced disease and remains an important option in salvage settings [112]. The integration of taxanes into multimodal treatment for resectable stage IIIA NSCLC aims to maximize tumor shrinkage, improve pathological response rates, and facilitate complete surgical resection, while balancing the risk of cumulative toxicity [113]

Toxicity

The use of multimodal therapy in stage IIIA (N2) NSCLC carries the risk of both acute and long-term toxicities, which can influence treatment selection and patient outcomes. **Haematological toxicity**, including neutropenia, anemia, and thrombocytopenia, is common with platinum-based chemotherapy and taxanes, often requiring dose modifications or growth factor support [114]. **Neurotoxicity**, typically manifesting as peripheral neuropathy, is most frequently associated with taxanes and can be cumulative, potentially impacting quality of life and functional recovery post-treatment [115]. **Other adverse events** include esophagitis and pneumonitis from thoracic radiotherapy, fatigue, mucositis, nausea, and treatment-related cardiopulmonary complications [116]. Early recognition and proactive management of toxicities through supportive measures, dose adjustments, and multidisciplinary care are essential to maintaining treatment intensity while safeguarding patient well-being [117].

Prognosis

Prognosis in stage IIIA (N2) NSCLC is influenced by multiple factors, including tumor burden, number of involved nodal stations, pathological response to induction therapy, and completeness of surgical resection. Patients who achieve mediastinal nodal downstaging and undergo complete (R0) resection generally have better long-term outcomes, with five-year survival rates approaching 35–40% in selected cases [118]. Conversely, persistent N2 disease after induction therapy is associated with a significantly higher risk of recurrence and poorer survival [119]. Molecular features, such as the presence of actionable mutations, PD-L1 expression, and tumor mutational burden, may also influence prognosis and guide the selection of targeted or immunotherapeutic strategies [120]. The integration of advanced imaging, precise pathological assessment, and biomarker-driven treatment selection offers the potential to refine prognostication and improve individualized care for patients with resectable stage IIIA NSCLC [121].

Conclusion

The management of potentially resectable stage IIIA (N2) NSCLC remains one of the most complex areas in thoracic oncology. While induction chemotherapy and induction chemoradiotherapy both have established roles, their optimal selection depends on careful assessment of patient fitness, tumor

10.48047/jocaaa.2024.33.06.82

biology, and institutional expertise. Induction chemoradiotherapy may offer improved local control and higher pathological complete response rates, but at the cost of greater treatment-related morbidity. Induction chemotherapy alone remains a viable approach for patients in whom toxicity risks outweigh potential benefits of combined modality treatment. The integration of targeted therapies, immunotherapies, and novel treatment combinations into multimodal regimens offers hope for improving survival and quality of life in this challenging patient group. Moving forward, advances in molecular profiling, imaging technologies, and minimally invasive surgical techniques will likely refine patient selection and further personalize treatment, ultimately improving long-term outcomes for patients with resectable stage IIIA (N2) NSCLC.

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