Review Article

The evolving landscape of adjuvant therapy in T1-T2N0 resected non-small cell lung cancer: a narrative review

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Background and Objective: Lung cancer recurrence after complete surgical resection of early-stage T1-T2N0 non-small cell lung cancer (NSCLC) remains a problem due to unrecognized micrometastatic disease. The objective of this review is to present and summarize data from major randomized trials in which have studied the survival benefit of adjuvant therapy for early-stage NSCLC.

Methods: Information used to write this paper was collected from PubMed and the National Clinical Trial registry from the National Library of Medicine.

Key Content and findings: Clinical trials that explored the use of adjuvant platinum-based chemotherapy historically have failed to show a benefit to giving adjuvant therapy in this early-stage patient population. Specifically, no survival benefit has been shown in stage IA (T1N0) tumors and stage IB tumors (T2aN0), less than 4 cm in size. As a result, adjuvant chemotherapy is currently recommended for only stage IB (pT2aN0) and IIA (pT2bN0) which are greater than 4 cm in size or have high-risk pathologic features. Newer and more effective treatments including targeted therapy against tumors with epidermal growth factor receptor (EGFR) driver mutants, tumors with anaplastic lymphoma kinase (ALK) rearrangements and immunotherapy have renewed interest in exploring the role of adjuvant therapy among early-stage patients. Three years of adjuvant osimertinib with or without adjuvant chemotherapy has been shown to improve overall survival (OS) in a trial population of IB–IIIA NSCLC patients and is approved for adjuvant use in EGFR mutant early-stage NSCLC.

Conclusions: In the future, appropriate patient selection for adjuvant therapy, driven by molecular high-risk features, circulating tumor DNA, or blood-based biomarkers will be important as the majority of early-stage patients are cured with surgical resection alone.

Keywords: Non-small cell lung cancer (NSCLC); adjuvant chemotherapy; immunotherapy; targeted therapy; early-stage

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Introduction

Surgical resection for early-stage non-small cell lung cancer (NSCLC) offers the best chance at long-term survival, however, disease recurrence remains a challenge even in stage I disease. Treating micrometastatic disease that may be present around the time of resection has become a major focus of efforts to improve cure rates in resected early-stage NSCLC. Over the past two decades, clinical trials have demonstrated survival benefits with neoadjuvant and adjuvant systemic therapies including chemotherapy, targeted therapy, and immunotherapy. As real-world experience and long-term data accumulates, the clinical challenge becomes understanding this evolving landscape of systemic therapies to select the most suitable strategy based on patient and tumor factors. The objective of this article is to review the current data supporting the use of these adjuvant therapies for completely resected T1-2N0 by 8th edition staging criteria, early-stage NSCLC. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-245/rc).

Methods

Information used to write this paper was collected from PubMed and the National Clinical Trial registry from the National Library of Medicine (*Table 1*).

Discussion

Adjuvant chemotherapy

Early clinical trials demonstrated trends toward overall survival (OS) benefit when adjuvant chemotherapy was used following surgical resection for early-stage NSCLC, though without statistical significance. The Non-Small Cell Lung Cancer Collaborative Group in 1995 published a meta-analysis of 52 randomized clinical trials and found a combined hazard ratio (HR) of 1.15 (P=0.005) for patients who underwent adjuvant chemotherapy with alkylating agents following surgical resection (1). The Adjuvant Lung Project Italy (ALPI) randomized stage I, II, and IIIA NSCLC to adjuvant mitomycin, cisplatin, and vindesine versus observation after surgical resection and found no statistically significant survival benefit for patients in any NSCLC stage (2). Similarly, Big Lung Trial (BLT), which randomized 381 patients to either 3 weeks of chemotherapy or no chemotherapy, found no benefit in OS to the chemotherapy group [HR 1.02, 95% confidence interval (CI): 0.77–1.35] (3).

The first trial to show real evidence of the benefit of adjuvant chemotherapy was the International Adjuvant Lung Cancer Trial (IALT) in 2003. IALT randomly assigned 1,867 patients to either three or four cycles of cisplatin-based chemotherapy or observation and compared OS following surgical resection of NSCLC. Patients assigned to chemotherapy had a significantly higher disease-free survival at 5 years compared to observation (39.4% *vs.* 34.3%, P<0.003) and adjuvant cisplatin-based chemotherapy was only found to improve 5-year survival from 40.4% to 44.5% (P<0.03) (4).

Following IALT, subsequent clinical trial results started to suggest promising benefits of the use of adjuvant chemotherapy. The JBR.10 North American Intergroup phase III clinical trial compared the outcomes of adjuvant vinorelbine/cisplatin versus observation following resection in stage IB and stage II NSCLC. Compared to patients in the observation group, patients treated with adjuvant vinorelbine/cisplatin were found to have lower recurrence rates (36.0%) versus in the observation cohort (49.6%, P=0.003). In addition, an absolute survival advantage at 5-year was found in patients treated with adjuvant chemotherapy (69%) compared to the observation group (54%) (P=0.03). However, no statistical survival benefit was observed among stage IB patients at 5 years. To date, JBR.10 is the trial which has demonstrated the greatest survival advantage to adjuvant chemotherapy in stage II NSCLC (5).

The Adjuvant Navelbine International Trialist Association (ANITA) trial was a phase III trial of stage IB, II, and IIIA NSCLC patients comparing benefits of vinorelbine/cisplatin versus observation with or without adjuvant radiation (6). Similar to results found in JBR.10, the ANITA trial demonstrated no benefit of adjuvant chemotherapy in stage IB patients, with patient survival found to be 62% following adjuvant chemotherapy and 64% with observation. Results from this trial found that NSCLC patients treated with adjuvant chemotherapy had an 8.6% improvement in OS after 5 years (P=0.02). However, again the benefit was not seen in the earliest stage patients and in the ANITA trial N0 patients obtained no survival benefit from adjuvant platinum-based chemotherapy with 5-year survival being 58% (95% CI: 51–56%) compared to 61% (95% CI: 53–68%) in the observation group (6).

Cancer and Leukemia Group B (CALGB) 9633 evaluated the use of adjuvant paclitaxel/carboplatin in stage

Table 1 The search strategy summary

Items	Specification
Date of search	September 5, 2023
Databases and other sources searched	PubMed, National Clinical Trials Registry
Search terms used	"Non-small cell lung cancer", "adjuvant chemotherapy"
Timeframe	1995–2023
Inclusion and exclusion criteria	Inclusion: studies published in English language, primary studies only, randomized trials, included stage IA, stage IB or stage II patients
	Exclusion: studies <100 patients
Selection process	All authors discussed trials which were of high relevance to this topic which should be included in the summary. Consensus was obtained on the pivotal trials to be discussed in detail
Additional considerations	Major trials in this space are the focus of this review

IB NSCLC, with preliminary analysis showing improved survival. However, the final analysis in 2008 revealed a median survival time of 95 months for stage IB NSCLC treated with adjuvant paclitaxel/carboplatin and 78 months in the observation group (P=0.13, HR 0.83). While the lack of statistical significance was related to the study being underpowered, a sub-group analysis of the data results found that tumors greater than 4 cm in size benefitted from adjuvant paclitaxel/carboplatin. This size criteria of greater than 4 cm has since been included in National Cancer Center Network treatment guidelines (7).

With several trials now showing significant OS benefits from adjuvant chemotherapy, the Lung Adjuvant Cisplatin Evaluation (LACE) trial performed a meta-analysis to identify which groups of patients benefited from postoperative chemotherapy (8). Patient data was collected using the five largest trials (4,584 patients) of cisplatin-based chemotherapy following complete resection, which included stage I NSCLC patients. LACE estimated a 11% reduction in the risk of death and a 5.4% absolute survival benefit of adjuvant chemotherapy (P=0.005, HR: 0.89) after 5 years from 40.4% to 44.5% for all resected stage IB through III patients (8). However, no benefit was seen for stage IA patients and the small benefits seen in the stage IB patients were not significant.

In 2017 an American Society of Clinical Oncology (ASCO) panel performed a systematic review of literature to update the guidelines for using adjuvant therapy in resected NSCLC (9). After reviewing five clinical trials, it was found that surgery without adjuvant chemotherapy offered a greater survival benefit for patients with stage IB disease compared to patients with adjuvant chemotherapy following complete resection (9,10). Ultimately the ASCO Practice Guideline Update in 2017 did not recommend routine adjuvant chemotherapy for patients with stage IA and IB NSCLC (9).

Despite data that there is a 5–6% survival advantage if adjuvant platinum-based chemotherapy is given to patients with stage II–III NSCLC, certain sub-populations of patients that otherwise qualify for adjuvant chemotherapy do not receive it (11). These disparities in use of adjuvant chemotherapy are found to be more pronounced in patients with multiple comorbidities, advanced age, and vulnerable groups such as rural or underinsured patients with one possible assumption being that postoperative chemotherapy would only provide a modest survival benefit in these groups (11). As a result, a post-hoc analysis evaluating the impact of adjuvant therapy on overall and recurrence-free survival among pN1 NSCLC patients enrolled in the JBR10 trial was performed with results published in 2022. Prior to this study, the same group previously evaluated adjuvant chemotherapy outcomes in patients with pN1 NSCLC using the National Cancer Database and found a 14% 5-year survival advantage in this group compared to surgery along (12). The JBR10 trial was selected to enable a more streamlined comparison with the study completed earlier because it enrolled North American patients with similar demographics (12). The post-hoc analysis revealed that adjuvant therapy improved 5-year OS (61.4%) compared to observation alone (41.0%, P=0.008) (11). The data suggested that pN1 NSCLC patients may have greater clinical benefits from adjuvant therapy than the LACE

meta-analysis had previously suggested (11,13).

The Japan Lung Cancer Research Group (JLCRG) is the only randomized clinical trial to demonstrate a survival benefit in stage I adenocarcinoma treated with adjuvant uracil-tegafur following surgical resection (14). When comparing OS in a subset of patients with pT2N0 disease, a survival advantage of 85% was seen in the adjuvant therapy group compared to 74% in the observation group (14).

In 2020, a retrospective cohort study emerged investigating data from over 50,000 patients diagnosed with early-stage NSCLC using the National Cancer Database to assess the association of high-risk pathologic features with survival after adjuvant chemotherapy versus observation (15). In this cohort, tumor size alone was not associated with improved efficacy of adjuvant chemotherapy in early-stage NSCLC. The authors suggested that rather, tumor size and high-risk pathologic features should be viewed in combination when deciding the utility of adjuvant chemotherapy for early-stage NSCLC (15).

Adjuvant chemotherapy current guidelines

The National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant chemotherapy for patients with completely resected pathologic stage IIA (pT2bN0) NSCLC and in stage IB (pT2aN0) tumors with "high-risk" features. High-risk features suggested in the guidelines include: tumors greater than 4 cm, poorly differentiated tumors, visceral pleural involvement, vascular invasion, wedge resection, and unknown lymph node status (16). Adjuvant therapy is not currently recommended for stage IA tumors, classified as less than 3 cm by the NCCN eighth edition staging system (16). In addition to adjuvant platinum-based chemotherapy, stage IB and greater tumors with epidermal growth factor receptor (EGFR) mutations are candidates for 3 years of adjuvant osimertinib after the completion of adjuvant chemotherapy.

Targeted therapy in adjuvant setting

Early studies on the adjuvant use of EGFR tyrosine kinase inhibitors (TKIs) did not show a survival advantage. The initial study, the RADIANT trial, examined the benefit of the first generation of TKI, erlotinib, in the adjuvant setting for EGFR-positive, IB to IIIA NSCLC following complete surgical resection (17). The RADIANT trial was a phase III, placebo-controlled study comparing disease-free survival for patients treated with erlotinib versus placebo. The RADIANT trial was ultimately negative and failed to show a disease-free survival benefit for adjuvant erlotinib in patients with EGFR-expressing NSCLC or in patients with EGFR-activating mutations (median, 50.5 months for erlotinib and 48.2 months for placebo; HR 0.90, P=0.32) (17).

Newer generations of EGFR TKI are more effective than the first generation drugs with improved penetration of the blood brain barrier. The FLAURA study established osimertinib as the first line treatment for advanced NSCLC with an EGFR mutation (exon 19 deletion or L858R allele) (18). This trial renewed interest in the potential use of EGFR TKI in the adjuvant setting. The ADAURA trial therefore examined the survival benefit of osimertinib in patients with completely resected stage IB to IIIA EGFR mutation-positive NSCLC (19). This double-blind, phase 3 trial of 682 patients found that in the overall population (stage IB to IIIA) the 5-year OS of 88% in the osimertinib group and 78% in the placebo group (HR for death, 0.49; 95% CI: 0.34–0.70; P<0.001). The OS benefit of adjuvant osimertinib was consistent among across disease stage. For patients diagnosed with stage IB disease, the 5-year OS was 94% in the osimertinib group and 88% in the placebo group (95% CI: 0.17–1.02). Among stage II NSCLC patients with EGFR mutations, 5-year OS was 78% whereas those in the osimertinib group were found to have 85% 5-year OS (HR for death, 0.63; 95% CI: 0.34–1.12). Patients diagnosed with stage IIIA disease had a 5-year OS of 85% in the osimertinib group and 67% in the placebo group (HR for death, 0.37; 95% CI: 0.20–0.64). Other benefits of ADAURA included the superior control of cranial metastasis among patients treated with adjuvant osimertinib. The ADAURA trial investigators are continuing to follow the trial cohort and as the data continues to mature the stage IB and IIA survival differences may become statistically significant with more time.

Following the success of ADURA, two additional trials of adjuvant osimertinib are underway. ADAURA was designed to study 3 years of daily, adjuvant osimertinib (80 mg) but it is unknown if more time on therapy would provide an even greater benefit. The TARGET study is a phase 2 trial that will evaluate the safety and efficacy of giving daily, adjuvant osimertinib for 5 years to 180 patients with stage II–IIIB resected NSCLC (20). ADAURA2 will study the benefit of 3 years of adjuvant Osimertinib in stage IA2–IA3 NSCLC patients following complete tumor resection (21). Aside from measuring disease-free survival and OS, ADAURA2 evaluates the safety of using osimertinib in the overall population and assesses central nervous system disease-free

survival. In addition, ADAURA2 secondarily aims to assess the impact of treatment with osimertinib on patient quality of life by investigating physical functioning using SF-36 V2 health survey results in comparison to a placebo group (21).

The ALINA trial compared the efficacy of adjuvant alectinib to platinum-based chemotherapy among patients with anaplastic lymphoma kinase (ALK) positive resectable NSCLC (22). In this phase 3 trial randomizing 257 patients, it was found that 93.8% of ALK positive stage II or IIIA NSCLC patients treated with adjuvant alectinib remained disease-free at 2 years compared to 63% in the platinum-based chemotherapy group (HR 0.24; 95% CI: 0.13–0.45; P<0.001).

Adjuvant immunotherapy

Immunotherapy has dramatically changed the treatment of NSCLC and has an expanding role in the perioperative setting. Impower010 was an international, phase 3 trial of stage IB to IIIA NSCLC that randomized patients to 1 year of adjuvant atezolizumab after complete surgical resection followed by adjuvant chemotherapy. It compared the survival benefit of atezolizumab versus supportive care after adjuvant chemotherapy and found improved disease-free survival with tumors that expressed PD-L1 on 1% or more of tumor cells (HR 0.66, P=0.004) (23).

Following this study, similar evidence emerged supporting the use of adjuvant pembrolizumab for stage IB-IIIA NSCLC following complete resection, in the PEARLS/KEYNOTE-091 trial (24). While pembrolizumab is currently used for advanced NSCLC, results from PEARLS/KEYNOTE-091 found significantly improved disease-free survival of 53.6 months for stage IB-IIIA NSCLC after complete resection regardless of PD-L1 expression when compared to a placebo group which reached a median disease-free survival of 42 months (P=0.001) (25).

Historically, the utility of targeting immune checkpoint inhibitors to improve disease-free survival has been unclear. The MAGRIT trial, a large international phase III clinical trial published in 2016, found no benefit in adding MAGE-A3 cancer immunotherapy to adjuvant chemotherapy regimens (26). The placebo-control, randomized trial evaluated patients diagnosed with stage IB, II, and IIIA MAGE-A3-positive NSCLC who did or did not receive adjuvant chemotherapy. The results showed no benefit in disease-free survival when compared with a placebo (HR 1.02, P=0.74) (26).

Given the success of immunotherapy in the adjuvant setting, trials have incorporated its use in the neoadjuvant setting. CheckMate-816 was an international phase 3 trial enrolling patients with stage IB to IIIA resectable NSCLC, found significantly longer event-free survival and pathological complete response for patients given neoadjuvant nivolumab plus platinum-doublet chemotherapy in comparison to platinum-doublet chemotherapy alone for three cycles before undergoing definitive surgery. Those treated with neoadjuvant nivolumab plus chemotherapy were found to have a median event-free survival of 31.6 months in comparison to 20.8 months with chemotherapy alone (HR 9.63; CI 0.43–0.91, P=0.005). Of note, the addition of immunotherapy with neoadjuvant chemotherapy was not found to preclude patients from also undergoing surgery (27). Newer trials including KEYNOTE-617, NADIM II, and AEGEAN are utilizing treatment regimens of both neoadjuvant and adjuvant immunotherapy. While pT1-2N0 patients are not included in the current trials, the success of these regimens in locally advanced disease is likely to foster interest in expanding future trials to include more early-stage NSCLC.

The importance of personalized medicine in lung cancer: a look forward

As driver mutation targeted therapies and immunotherapy move in the adjuvant therapy space for early-stage NSCLC, proper patient selection will become increasingly important. Though these therapies are generally less toxic than traditional chemotherapy, they are not without risk, morbidity, and cost. Proper patient selection should be used instead of a broad application of more advanced therapies in the adjuvant setting for stage I patients where the majority of patients are cured with surgical resection alone. Strategies to identify patients most at risk of recurrence include tumor characteristics and circulating tumor DNA at the time of surgery or immediately following surgery.

Incorporating molecular prognostic classification has improved survival prediction models while also identifying high-risk patients more accurately compared to TNM staging alone for patients diagnosed with NSCLC (28). In recent years, the validation of protein-based signatures (BRCA1, QKI, and SLC2A1) for early-stage adenocarcinoma was found to not only predict 5-year disease-free survival but also OS (P<0.001). The novel molecular signatures provided results that supported the use of adjuvant chemotherapy for stage I–IIA adenocarcinoma

patients identified as high-risk when combined with information from TNM staging (29). Identifying circulating messenger ribonucleic acid (mRNA) lung-specific X protein (LUNX) expression in peripheral blood for patients with NSCLC has become a non-invasive, and yet, highly specific and sensitive detection method for tumor micrometastases to guide chemotherapy treatment. It was found that patients identified as LUNX-positive who became LUNX-negative following adjuvant chemotherapy had improved 5-year survival compared to patients who remained LUNX-positive (P=0.03) (30).

A 14-gene quantitative polymerase chain reaction (PCR)-based expression profile (DetermaRx™, OncoCyte Corporation) was validated to identify NSCLC patients at high-risk of 5-year mortality following surgical resection due to micrometastatic, undetectable disease (31). Evidence now suggests that use of this molecular assay, in addition to standard staging methods, improves identification of high-risk patients with early stage NSCLC after surgery to reduce recurrence rates and improve survival and has been validated prospectively, even stage 1A patients (32-34).

Tumor DNA found in the blood, also known as cell-free circulating DNA (cfDNA) has become a convenient and minimally invasive method of testing tumor markers (35). cfDNA has potential applications both as a diagnostic tool and as a measure of treatment response and recurrence. Additionally, it has been found that patients with high cfDNA at the time of diagnosis of NSCLC had poorer OS compared to those with low cfDNA concentration, thereby depicting its role as a prognostic biomarker (36). The utility of cfDNA has been particularly beneficial when insufficient quantity of tissue from biopsy is present or repeat invasive testing is too high of a risk for the patient to undergo. One single-institution retrospective study tested cfDNA from plasma blood of patients diagnosed with NSCLC found an 81% concordance between the Guardant360 panel at the time of diagnosis and tissue samples obtained 12 weeks later (37). The accessibility of cfDNA to aid with the molecular diagnosis of NSCLC and guide treatment options may also improve follow-up detection of residual disease or for selecting high-risk, early-stage patients who need adjuvant therapy.

Conclusions

Traditional platinum-based adjuvant chemotherapy following complete surgical resection has been shown to have a small survival benefit in select T1-T2N0, early-stage NSCLC patients. The development of more targeted and effective therapeutics such as targeted therapies or immunotherapy will likely have a more dramatic impact on outcomes. The strong OS benefit seen in the ADAURA trial is the first of many trials of targeted therapies to probe this space in early-stage disease.

Proper patient selection for adjuvant therapy, driven by molecular high-risk features, circulating tumor DNA, or blood-based biomarkers will become an even more important part of adjuvant therapy in early-stage NSCLC as the vast majority of early-stage patients are cured with surgical resection alone.

The use of adjuvant chemotherapy following surgical resection for patients with early-stage NSCLC remains a debate in the scientific community and is a challenging decision for clinicians. Based on current literature and guidelines, stage IB and IIA patients with high-risk pathologic features may benefit from adjuvant chemotherapy (38). However, additional research is needed to identify the scope of genomic testing in the adjuvant treatment of NSCLC. With rapidly changing advancements in medicine, oncologic care of early-stage NSCLC is becoming more dependent on patient individual characteristics, thus establishing a more defined role for personalized medicine. Understanding the current clinical literature as a multidisciplinary team is crucial to advance knowledge in the field and ultimately improve patient survival.

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Footnote

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