

Complete Response in Inoperable Stage IIB Squamous Cell Lung Carcinoma after Sequential Radiotherapy and Chemotherapy: A Case Report and Review of the Literature

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Abstract

Background: This manuscript reports a stage IIB (cT3N0M0) squamous NSCLC case deemed inoperable and treated with definitive radiotherapy followed by carboplatin/paclitaxel, achieving complete metabolic response on PET/CT. The paper then reviews standard management options for stage II NSCLC, emphasizing multidisciplinary decision-making. The main message is that selected inoperable stage II patients may achieve durable control with sequential or concurrent chemoradiation. **Patients and Methods:** I present a case report of complete therapeutic response in inoperable stage IIB non-small cell lung carcinoma after sequential radiotherapy and chemotherapy and a review of literature. **Results:** Surgical resection is the cornerstone of treatment and the best option for achieving cure in patients with clinically operable Non-Small Cell Lung Cancer (NSCLC). In circumstances where surgical resection may not be feasible, patients may be presented at a Multidisciplinary Tumour Board for further discussion between surgery, medical oncology, radiation oncology, and palliative care. Whenever possible, patients should be considered for enrollment in clinical trials. **Conclusions:** Patients with stage II NSCLC who are inoperable or refuse surgery can also have long survival with concurrent or sequential radiotherapy and chemotherapy.

Keywords

Non-Small Cell Lung Cancer, Chemotherapy, Radiotherapy

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, accounting

for the highest mortality rates among both men and women. Smoking is the leading cause of lung cancer, responsible for approximately 85% of all cases. Lung cancer is often diagnosed at advanced stages when treatment options are limited. Screening high-risk individuals has the potential to allow early detection and to dramatically improve survival rates. Primary prevention (such as tobacco control measures and reducing exposure to environmental risk factors) can reduce the incidence of lung cancer and save lives. A stage II non-small cell lung cancer is located in one lung and may involve lymph nodes on the same side of the chest that do not include lymph nodes in the mediastinum. The purpose of receiving cancer treatment may be to improve symptoms through local control of the cancer, increase a patient's chance of cure, or prolong a patient's survival. Treatment may consist of surgery, radiation, chemotherapy, or a combination of these treatment techniques. The potential benefits of receiving cancer treatment must be carefully balanced with the potential risks of receiving cancer treatment. Administration of chemotherapy after surgery, referred to as adjuvant therapy improves survival for patients with NSCLC when compared to treatment with surgery alone and is now considered standard of care [1]. Efforts are underway to evaluate new precision or targeted therapies to further improve the outcome of individuals with early-stage lung cancer. A variety of factors ultimately influence a patient's decision to receive treatment for cancer. Some patients with lung cancer are not able to undergo the surgery to remove their cancer. Two studies have demonstrated that patients with stages I-II NSCLC who are not able to, or do not wish to undergo surgery may be treated with radiation therapy and chemotherapy.

2. Case Report

A 55-year-old man with complaints of cough with sputum, shortness of breath during physical activity, fatigue and loss of appetite for about 2 months and hemoptysis for about 10 days was admitted to the pulmonology department in September 2024. The patient was a long-term smoker and had a family history of head and neck cancer. Chest computed tomography showed tumor in the right hemithorax parahilar with dimensions of 55/46mm in the axial plan, pulmonary thromboembolism of the lower segment branches of the right a. pulmonalis. D-dimer tested—0.25 mg/L. Bronchoscopy was performed in September 2024—complete obstruction of the main bronchus on the right by a tumor with a heterogeneous surface, bleeding spontaneously and during manipulations was established, and the distance from carina to the tumor was 1 cm. A biopsy was taken from the tumor, histologically proven to be high-grade non-small cell lung cancer—squamous cell carcinoma. NGS genetic testing was performed—no activating predictive aberrations were found in the studied genes—EGFR, ALK, ROS1, RET, BRAF, KRAS, MET, ERBB2, NTRK1, NTRK2, NTRK3. PDL-1-TPS < 50%. FDG PET/CT showed central tumor in the right hemithorax 56/45 mm SUX_{max} 10.6 and no evidence of enlarged regional lymph nodes and distant metastases.

Stage cT3cN0cM0, IIB. Discussed on multidisciplinary tumor board. It is discussed that pneumonectomy is associated with high mortality and morbidity and the procedure is typically reserved for centrally located tumors where a lobectomy is not possible. Right pneumonectomy is generally associated with poorer long-term survival and higher risks compared to left pneumonectomy and patients should have adequate lung function. Due to the fact that the distance from the carina to the tumor was 1 cm, the patient was a long-time smoker, right lung was affected and did not have adequate cardiopulmonary reserve (after spirometry—FEV1 < 2 L and predicted postoperative FEV1 e < 40%), the patient was assessed as inappropriate for pulmonectomy—medically inoperable and a decision was made to conduct definitive radiotherapy and chemotherapy. Invasive mediastinal staging such as EBUS/EUS/mediastinoscopy for additional N0 staging was not performed because the patient was considered inoperable due to the tumor being very close to the carina and the patient would not have adequate lung function after surgery. Definitive radiotherapy of lung carcinoma, total dose 55 Gy, fraction size 2.5 Gy was performed. Technique used was IMRT (Intensity-Modulated Radiotherapy). IMRT is preferred technique, because it's superior conformity and Organ-At-Risk (OAR) sparing compared with 3D-CRT, reduced mean lung dose and heart dose, recommended in modern thoracic RT guidelines (e.g., NCCN, ASTRO). Target volume used: GTV (Gross Tumor Volume)—primary tumor + regional nodes (contrast-enhanced CT guided), CTV (Clinical Target Volume)—GTV + 5 mm margin for microscopic spread. The regimen of 55 Gy in 2.5 Gy fractions provides modest biological dose escalation over conventional 2 Gy fractionation while maintaining acceptable lung and esophageal toxicity, and has been used in UK hypofractionated schedules for locally advanced NSCLC with comparable tumor control and acceptable safety profiles.

CT scan performed in November 2024 showed persistence of central carcinoma of the right lung measuring 32/38mm. Tumor response was assessed using standardized, auditable criteria. On contrast-enhanced CT, response was evaluated per RECIST v1.1, demonstrating a partial response with a change in the sum of target lesion diameters from 32 cm at baseline to 56 cm at best response, corresponding to a 42% decrease. Six cycles of chemotherapy with Paclitaxel (175 mg/m² = 350 mg) in combination with Carboplatin (5AUC = 700 mg) every 21 days were performed. Premedication with dexamethasone 20 mg, chlorpyramine hydrochloride and ondansetron was also prescribed. There were no adverse grade events from the therapy and the patient underwent full-dose chemotherapy without any delays. Sequential not concurrent chemotherapy was performed in this patient, because of the bleeding and hemoptysis before starting the treatment and generally chemotherapy may increase the thrombocytopenia and subsequently the bleeding risk. Anticoagulation for the incidental pulmonary thromboembolism (PE) of the lower segment branches of the right a. pulmonalis was not initiated, because of the bleeding risk and low D-dimer value. The incidental PE was assessed as

chronic condition and did not affect radiotherapy and chemotherapy timing.

Metabolic response was assessed on FDG PET/CT according to PERCIST 1.0 criteria. The target lesion demonstrated a reduction in SUV_{max} from 10.6 at baseline to 2.2 post-treatment, consistent with complete metabolic response as defined by PERCIST. Bronchoscopy was not repeated to document endobronchial response, because of the patient's refusal. Active surveillance of the patient has been initiated. On subsequent imaging techniques—PET/CT every 6 months there were no data for disease progression in the next two years.

Written informed consent for publication of this case report was obtained from the patient prior to manuscript submission. All identifying information has been removed and anonymized to protect patient privacy, and no details that could reasonably lead to patient identification are included in this publication.

2.1. Diagnosis and Staging

Pathological diagnosis is required in all patients with suspected lung cancer if feasible. Feasibility and diagnostic method should be determined by a Multidisciplinary Team (MDT) based on patient and tumour characteristics. Biomarker testing is also essential for treatment decision-making in patients with stage IB-III NSCLC [2]. Staging is based on the ninth edition of the Union for International Cancer Control TNM (tumour-node-metastasis) Classification of Malignant Tumours (TNM9) [3] and the third edition of the International Association for the Study of Lung Cancer (IASLC) Staging Manual [4]. IASLC has also provided recommendations on tumour measurement using CT [5] [6]. Contrast-enhanced CT and PET or PET-contrast-enhanced CT are recommended for assessment of mediastinal and hilar Lymph Nodes (LNs), for patients with abnormal mediastinal and/or hilar LNs on CT and/or PET-CT. Invasive mediastinal and hilar staging by representative endosonography is recommended [2]. A PET-CT is indicated for all patients with suspected stage II NSCLC. Surgical candidates should also receive a pulmonary function test to ensure adequate lung function for resection. NSCLC accounts for 80 percent of all lung cancer cases, and is categorized using the ninth edition TNM staging system [3].

2.2. Surgery

For patients with NSCLC who have cancer that is limited to the chest surgical resection is not only an important therapeutic modality, but in many cases, the most effective method of controlling the disease. Patients with stages I-II localized cancer without spread to lymph nodes are considered to have early-stage lung cancer and are almost always treated with surgery. Systematic mediastinal lymph node sampling or dissection should be performed for accurate pathological staging of patients undergoing resection for stage II NSCLC. In a pooled analysis of three studies comparing mediastinal lymph node dissection to systematic sampling, Manser and colleagues reported a significant reduction in the risk of death in pa-

tients with stages I to IIIA NSCLC undergoing dissection, with a pooled Hazard Ratio (HR) of 0.63 (95% CI 0.51 - 0.78; $p < 0.0001$) [7]. Similarly, in a case series involving 100 consecutive patients, Lardinois *et al.* reported that mediastinal lymph node dissection was associated with longer disease-free survival and better local tumour control rates compared to mediastinal lymph node sampling after complete resection for N0-1 disease, with no increase in morbidity [8]. In a prospective randomized trial completed by the American College of Surgery Oncology Group (ACOSOG Z0030 trial), the investigators also reported that morbidity is not increased with complete lymph node dissection, and recommended that the number of lymph nodes resected during mediastinal lymph node dissection be 12 or more, with nodes removed from stations 2R, 4R, 7, 8, 9 and 10R for right-sided cancers, and stations 4L, 5, 6, 7, 8, 9 and 10L for left-sided cancers [9] [10]. Published data from the ACOSOG study showed little difference in median survival between patients in the mediastinal lymph node sampling group compared to the dissection group (8.1 years vs. 8.5 years, $p = 0.25$) [11]. Five-year disease-free survival rates were also similar (69% vs. 68%, $p = 0.92$), and there were no differences in local, regional, or distant recurrences between the two groups [11]. The investigators concluded that, for patients undergoing resection for N0 or nonhilar N1, T1, or T2 NSCLC, and for whom systematic and thorough presection sampling of the mediastinal and hilar lymph nodes is negative, mediastinal lymph node dissection does not improve survival in patients with early stage disease. Surgical resection is the treatment of choice for patients with early stage NSCLC, and offers the best potential for long-term survival and cure [12] [13]. Five-year survival rates ranging from approximately 29 to 51 percent have been reported for patients with stage II disease who undergo surgical resection, with more favourable results for individuals with single node involvement and smaller (<3 cm) lesions [14]-[16]. All patients with early stage disease should be evaluated by a thoracic surgeon to determine whether they are an appropriate candidate for surgery [12]. A lobectomy, the surgical removal of a single lobe, is the optimal procedure for the management of early stage disease because it preserves pulmonary function [13]. Although conclusions about the efficacy of different surgical methods for patients with local or locoregional NSCLC are limited by both the small number of included participants in trials and methodological weaknesses of published trials, there is agreement among current published guidelines that a lobectomy is preferred over a sublobar resection for patients who are medically fit for surgery. This recommendation has been adopted from recommendations made by the American College of Chest Physicians (ACCP) and the National Comprehensive Cancer Network (NCCN) [12] [13]. A systematic review by the Cochrane Collaboration reported the results of 13 trials involving 2290 patients who underwent surgery for stages I to IIIA NSCLC [7]. A pooled analysis of three relevant trials included in this review showed that overall survival was superior in patients who underwent surgical resection (lobectomy or pneumonectomy) and complete mediastinal lymph node

dissection compared with those who underwent surgical resection and lymph node sampling (Hazard Ratio (HR) = 0.63; 95% CI 0.51 - 0.78, $p < 0.0001$) [7]. The surgical procedure used will depend on the extent of the disease, location of the tumour, and cardiopulmonary reserve of the patient. Recommendations from both the NCCN and ACCP state that for patients with an anatomically appropriate tumour, a sleeve lobectomy is the preferred alternative to pneumonectomy, in order to conserve lung function [12] [13]. In addition, for patients with T3 NSCLC with chest wall involvement, complete resection of the tumour should be the aim by either extrapleural or en bloc chest wall resection. Several retrospective series and comprehensive reviews have concluded that Video-Assisted Thoracic Surgery (VATS) lobectomy for early stage NSCLC is safe, and is associated with fewer complications, less pain, and more rapid return to normal functioning when compared to open thoracotomy [17]-[19]. There are a few randomized trials comparing the two procedures and, consequently, evidence for a survival difference is limited. Where facilities exist, Video-Assisted Thoracic Surgery (VATS), by experienced surgeons, or open thoracotomy are both appropriate resection techniques for either lobectomy or segmentectomy for patients with stage II NSCLC who are appropriate surgical candidates.

2.3. Chemotherapy

The results of several large randomized controlled trials have established a clear benefit for adjuvant chemotherapy following surgery in patients with stage II NSCLC. The JBR.10 trial, conducted by the National Cancer Institute of Canada Clinical Trials Group, reported the most striking survival benefit for their subset of 263 patients with stage II disease treated with chemotherapy compared to observation (80 months vs. 41 months; HR = 0.59; 95% CI 0.42 - 0.85, $p = 0.004$) [20]. In an updated analysis from this trial, Butts and colleagues reported that, at a median follow-up of 9.3 years, patients with stage II disease treated with chemotherapy versus observation continued to show a significant survival benefit (median survival = 6.8 vs. 3.6 years; HR = 0.68; 95% CI 0.50 - 0.92, $p = 0.01$), corresponding to an absolute benefit of 20 percent at five years [21]. Similarly, the ANITA clinical trial reported five-year survival rates of 52 and 39 percent for patients with stage II disease treated with chemotherapy or observation, respectively (HR = 0.71; 95% CI 0.49 - 1.03, $p = 0.07$), corresponding to an absolute benefit of 13 percent at 5 years [22]. The survival benefits associated with adjuvant chemotherapy were further examined in a large review by the LACE Collaborative Group [23]. In this meta-analysis based on individual patient data, the investigators used pooled data from five clinical trials representing 4584 patients, 1616 of whom had stage II disease [23]. With a median follow-up of 5.2 years, the HR for death was 0.83 (95% CI 0.73 - 0.95, $p = 0.04$), corresponding to an absolute survival benefit of 10 percent at five years [23]. Based on the results of these clinical trials and meta-analysis, ESMO and NCCN recommend

the use of platinum-based chemotherapy regimens as post-operative adjuvant therapy in the management of patients with completely resected stage II NSCLC. The combination of carboplatin and paclitaxel, such as was used in the CALGB 9633 trial, is an acceptable alternative for individuals with a contraindication to cisplatin [24]. Chemotherapy should ideally start 6 to 8 weeks post-surgery, but certainly before 12 weeks.

2.4. Radiotherapy

Patients with stage II NSCLC who are medically inoperable or who refuse surgery should be assessed for the appropriateness of radical radiotherapy. In one randomized trial of 169 patients with stages I and II disease, continuous hyperfractionated accelerated radiotherapy (CHART; 1.5 Gy three times daily/12 days) resulted in superior survival rates when compared to conventionally fractionated radiotherapy (60 Gy/30 fractions over 6 weeks) [25]. However, CHART is often not a feasible option, due to lack of equipment and manpower, as well as low patient compliance. In a systematic review of one randomized and 26 non-randomized studies, Rowell and colleagues concluded that when CHART is not available, patients with early stage NSCLC who are medically inoperable but suitable for radical radiotherapy should be offered conventional fractionated radiotherapy [26]. Techniques such as hypofractionated conformal 3D radiotherapy have also been associated with favorable overall survival rates, high rates of local control, and low toxicity in inoperable patients with early stage disease. Patients with stage II NSCLC who are medically inoperable but not suitable for radical radiotherapy should be offered palliative radiation for symptom management, when appropriate [27]. There is no significant role for Stereotactic Body Radiation Therapy (SBRT) in stage II NSCLC. In very rare T3N0 cases, it may be appropriate to treat with SBRT if the patient is medically inoperable. The National Comprehensive Cancer Network recommends concurrent chemoradiation for inoperable, node-positive stage II NSCLC patients [13]. A systematic review of over 3700 stage I to III NSCLC patients treated within a randomized controlled trial demonstrated a survival benefit for concurrent chemoradiation [28]. However, the study authors did note that of the 25 trials included in the review, only four included patients with stage I and II disease; therefore, patient selection is an important consideration due to added toxicity. Concurrent chemoradiation may be considered for selected medically inoperable stage II NSCLC patients, especially if they are node positive, have a large tumour (≥ 5 cm), and are reasonably fit. The incidence of local recurrence following surgical resection of early stage NSCLC was documented in an 11-year study of 975 consecutive patients treated at a single institution [29]. In this study, a local failure was defined as a recurrence at the surgical margin, in the ipsilateral hilum, or in the mediastinum. The 5-year incidence of any local recurrence after surgery was 23 percent, with a median time to recurrence of 14 months [29]. In addition, the 5-year risk of any treatment failure, including local or distant relapses and second primary lung can-

cers, was 42 percent. First sites of recurrence were local only in 25 percent of cases, local and distant in 29 percent of cases, and distant only in 46 percent of cases.

2.5. Follow-Up and Surveillance

Due to high rates of post-treatment recurrence, long-term follow-up and surveillance are recommended for patients with early stage NSCLC. To date there are no randomized trials assessing different surveillance strategies in patients with stage I NSCLC. One prospective study examined the feasibility and impact on patient survival of an intensive surveillance program of 192 NSCLC patients [30]. The follow-up consisted of physical examination and chest roentgenogram every 3 months and bronchoscopy and thoracic CT scan with sections of the liver and adrenal glands every 6 months. Seventy-one percent of patients developed a recurrence; 26 percent were asymptomatic of which all but one were detected by a scheduled follow-up procedure. From the date of recurrence, 3-year survival was 13 percent in all patients and 31 percent in asymptomatic patients whose recurrence was detected by a scheduled follow-up procedure. The study authors concluded that intensive follow-up and surveillance may improve survival through early detection of potentially curable recurrences [30].

3. Discussion

It is important to realize that patients with Stage II NSCLC may already have small amounts of cancer that have spread outside the lung and cannot be detected with any of the currently available tests. Undetectable areas of cancer are referred to as micrometastases. The presence of micrometastases causes the 40% of relapses that follow treatment with surgery or radiation alone. Patients with stage II NSCLC who are medically inoperable should be assessed for the appropriateness of radical radiotherapy. Chemotherapy after surgery and radiotherapy is considered standard treatment for stage IB and II NSCLC: A National Cancer Institute of Canada clinical trial showed that adjuvant chemotherapy increased the number of patients who lived 5 years or more from 54% to 69%, and US researchers have demonstrated that adjuvant chemotherapy increased the number of patients who survived 3 years or more from 69% to 82% [6]. The development of more effective treatment for NSCLC requires that new and innovative therapies be evaluated with cancer patients. Future progress in treatment will result from the continued evaluation of new treatments in clinical trials. Patients may gain access to better treatments by participating in a clinical trial. Participation in a clinical trial also contributes to the cancer community's understanding of optimal cancer care and may lead to better standard treatments.

4. Conclusion

In circumstances where patients with stage II NSCLC are inoperable or refuse surgery concurrent or sequential radiotherapy and chemotherapy may increase a pa-

tient's chance of cure, or prolong a patient's survival. Patients need to be presented at a Multidisciplinary Tumour Board for discussion and treatment decision. Due to high rates of post-treatment recurrence, long-term follow-up and surveillance are needed for patients with early stage NSCLC.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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