Title: A Case of Successful Surgical Resection of Locally Advanced (T4) Lung Cancer Utilizing a Multi-Disciplinary Approach Involving Previously Unresectable Structures

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Highlights:

- The importance of multi-disciplinary surgical planning before surgery.
- Surgical options for locally advanced lung cancer.
- The exclusion of organs such as the stomach and liver in the current T4 classification of lung cancer.

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Discussion Points:

Utilizing a multidisciplinary strategy for the surgical management of locally advanced (T4) lung cancer with invasion into the diaphragm, stomach, omentum and liver.

ABSTRACT. 191/250 words

Background: Lung cancer is the leading cause of cancer-related deaths worldwide and the second most prevalent cancer. Tumor-node-metastasis (TNM) staging remains the primary prognostic factor, with T4 disease traditionally deemed unresectable due to tumor invasion into critical structures. We report a case of a T4 non-small cell lung cancer that was initially deemed unresectable but successfully treated with radical surgical resection.

The Case: A 66-year-old asymptomatic male underwent a routine pre-operative chest X-ray, revealing an incidental lung nodule. Imaging identified a 6.1 cm mass with local extension to the stomach (excluded from TNM classification), diaphragm, and pericardium, rendering it initially unresectable. A multidisciplinary team pursued an aggressive surgical approach. The patient underwent a low left thoracoabdominal incision, left lower lobectomy, wedge liver resection, lymph node dissection, en bloc diaphragmatic resection, and omentum resection. Partial gastrectomy was unnecessary.

Histopathology confirmed non-small cell lung cancer, pT4 N0, M0, R0, stage IIIA, with omental and diaphragmatic involvement. At six months postoperatively, the patient remained well.

Conclusion: T4 disease exhibits heterogeneity, and although it is typically deemed unresectable, recent developments in surgery are challenging this conventional belief particularly where a radical dissection is anticipated.

Key Words (MeSH terms): *Neoplasms, Lung neoplasms, Pulmonary Surgical, Procedure, Neoplasm Staging*

INTRODUCTION:

Lung cancer is the most commonly diagnosed cancer worldwide and the leading cause of cancer-related deaths, with approximately 2 million new cases and 1.8 million fatalities annually.[1] In the United States, the 5-year survival rate for lung cancer patients diagnosed with localized disease (Stage I-II) is 59.0%. This declines to 31.7% for those with regional spread (Stage III) and further drops to 5.8% for metastatic disease (Stage IV). Additionally, 57% of lung cancer cases in the U.S. are diagnosed after metastasis. [1]

The tumor node metastasis (TNM) classification (9th edition) characterizes Tumor (T) 4 disease as a tumor exceeding 7 cm in its largest dimension or one that invades the mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, or spine, or represents a separate tumor in a different lobe of the ipsilateral lung.[2, 3] Typically, T3 and T4 tumors are locally advanced and associated with poor prognosis. T3 disease describes tumors that remain amenable to surgical resection, whereas T4 disease describes local invasion that traditionally precludes safe resection. Consequently, T4 disease is classified as stage IIIB and is deemed unresectable in most cases.

However, recent advancements in surgical techniques and perioperative management have expanded treatment options for select patients with T4 lung cancer. Technologies such as cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO) now enable the safe resection of tumors involving critical anatomy. Superior vena cava (SVC) invasion can be managed with SVC replacement, and right carinal pneumonectomy offers treatment for carinal invasion.[4]

Achieving a curative resection requires meticulous preoperative planning to assess the feasibility of removing all of the tumor remnants, including lymph node involvement. This planning often necessitates a multidisciplinary approach to optimize outcomes.

We present a case of T4 disease with local invasion of the diaphragm, pericardium, and omentum, which was successfully resected through a collaborative surgical approach. This case challenges the conventional perception of unresectability and highlights the potential for curative treatment in select patients with advanced lung cancer.

THE CASE:

An asymptomatic 66-year-old gentleman was referred to the lung cancer team with an incidental lung nodule found on a pre-operative chest x-ray before elective aortic Endovascular Aneurysm Repair (EVAR) (Fig. 1: A).

The patient had a history of laryngeal squamous cell carcinoma treated with chemoradiation, previous EVAR, ischemic heart disease, hypertension, previous stroke with residual left eye blindness and chronic renal function impairment. He is an ex-smoker of 20 years with a 40-pack-year smoking history and has a European Cooperative Oncology Group (ECOG) score of 1-2.

The lesion was initially assessed as radiologically benign. However, a subsequent CT Thorax demonstrated considerable enlargement of the nodule with diaphragmatic invasion (Fig 1: B). A PET-CT was then conducted. This revealed a 6.1cm intensely fluorodeoxyglucose (FDG) avid mass (standardized uptake value (SUV) max of 21) in the left lower lobe of the lung. (Fig 1: C-D). Additionally, an enlarged left hilum near the origin of the lingular bronchi showed mild FDG avidity (SUV max of 7) (Fig 1: E). Diffuse FDG uptake was seen throughout the stomach which was considered most likely benign. This was further investigated with an esophagogastroduodenoscopy which was normal. A diagnosis of presumed primary lung cancer was made. The tumor was radiologically staged as T4, primarily due to the possibility of invading the stomach and mesentery, and as N1 due to the presence of an ipsilateral hilar node.

Mediastinal staging with endobronchial ultrasound confirmed squamous cell carcinoma and staged as cT4 N0/1 M0. The case was discussed at the lung cancer tumor board. Due to the size and central location of the lesion radiotherapy ablation was not feasible. Immunotherapy was not a treatment option due to the exceedingly low levels of targets such as Programmed Death Ligand 1 (PD-L1). Hence, despite its T4 classification, surgery was considered. Thus, this case represents the first reported resection involving local invasion into the diaphragm, pericardium, omentum and onto the liver surface.

The patient was brought to theatre by both the cardiothoracic and the upper GI teams. Intra-operatively, a low left thoracoabdominal incision was used following induction of general anaesthesia, with double lumen intubation, central line monitoring and epidural catheter insertion.

Initial hilar dissection was performed to isolate the left lobe hilar structure. The pericardium was opened sparing the phrenic nerve and a margin was obtained. Then, the left lower lobe hilar structures were divided. Once the left lower lobe was freed from the hilum and mediastinum, the diaphragm and mediastinum were divided taking care to leave a margin

and a cuff of the remaining diaphragm. Tumor extension was found through the diaphragm and involving the pericardium (Fig 2: A shows the invasion of the tumor through the diaphragm). Where it was possible, large portions of the left hemidiaphragm were resected medially up to the arcuate ligament. This revealed no invasion into the stomach. However, there were suspicious adhesions of the lesion to the omentum and liver. These structures were resected (Fig 2: B demonstrates the total specimen sent to pathology).

Following the completion of resection, a full lymphadenectomy was performed. The diaphragmatic defect was then reconstructed with permacol bioprosthesis and the pericardial defect was reconstructed with bovine pericardium (Fig 2: C depicts the repaired pericardial defect). The thoracoabdominal incision was then closed in layers.

Post-operatively, the patient developed acute limb ischemia of the right lower limb. This was managed conservatively. There were no other post-operative complications. The patient was discharged on day 10 post-operation.

Histology confirmed non-small cell lung cancer (NSCLC) of squamous cell carcinoma subtype. Clear margins were obtained, and no lymph nodes were involved. The tumor was pathologically staged as T4 N0 M0, stage IIIA. The omentum, abdominal diaphragm and pericardium were also involved. The tumor was abutting the liver but the liver tissue itself was not involved.

Following discussion at the lung multi-disciplinary meeting adjuvant chemotherapy was recommended as the tumor was >4cm. However, adjuvant chemotherapy was offered and declined by the patient due to previous intolerance while undergoing treatment for laryngeal squamous cell cancer.

On post-operative review, the patient was doing well.

DISCUSSION.

Lung cancer is the leading cause of cancer death worldwide and the second most prevalent cancer in the world.[5] Tumor Node Metastasis (TNM) staging continues to serve as the primary prognostic factor for survival in lung cancer. Tumor (T) 3 and 4 disease describes locally advanced tumors which are associated with poor prognosis. T3 staging refers to invasion of anatomy which is amenable to resection whereas, T4 disease describes local invasion into anatomical structures which cannot be safely surgically resected. Consequently, T4 disease is classified as stage IIIB.[6] To pursue a curative resection, it is essential to pre-operatively assess the feasibility of eliminating all remnants of disease, including lymph node involvement.

T4 lung cancer is heterogenous.[7] For example, T4N0 cancers with multifocality often exhibit survival rates more akin to those of Stage IB or II non-small cell lung cancer (NSCLC). Although technically challenging, surgical resection of tumors involving the superior vena cava, carina, or thoracic inlet is considered feasible. Post-operative mortality rates vary across studies, with one study reporting rates between 4% and 13%.[4] Dartevelle et al. presented a 30-year review of extended surgical resections for T4 NSCLC focusing on resection techniques involving the superior vena cava and thoracic inlet.[4] They reported that 5-year survival rates for patients with N0–N1 disease exceeded 40%, demonstrating that surgery, in carefully selected cases, can provide significant survival benefits for locally advanced T4 NSCLC.[4]

This variability in prognosis within T4 disease has become increasingly evident, particularly with the change in T4 classification criteria between the 7th and 8th editions of the American Joint Committee on Cancer (AJCC) guidelines. In the 8th edition guidelines, tumors larger than 7cm are categorized as pT4 in the absence of invasion into adjacent organs.[8] Under the 7th edition, only tumors with extrapulmonary invasion were considered T4. This updated classification now encompasses a broader range of disease presentations, leading to a significant disparity in overall survival rates: rising from 35.5% under the 7th edition to 49.6% with the 8th edition.[9]

Tankel et al's study compared outcomes in patients with pT4 NSCLC classified under the AJCC 8th edition, with those classified as T4 under the 7th edition. Patients with extrapulmonary invasion exhibited higher disease burden, increased likelihood of requiring pneumonectomy, greater 90-day mortality, and a trend towards shorter overall survival.[10] The authors suggest that the expanded pT4 criteria in the 8th edition encompass a diverse patient population, necessitating a more tailored approach. However, The 9th edition of the TNM classification for lung cancer, which took effect in 2024, introduces some refinements, although the T (tumor) descriptors remain unchanged from the 8th edition.[3]

A study published in 2019 highlighted that the most significant prognostic factors for post-operative survival in T4 disease were achieving clear resection margins and nodal status.[11] To pursue a curative resection, it is essential to pre-operatively assess the feasibility of eliminating all remnants of the disease, including lymph node involvement. An international series involving 388 cases of surgery for T4 non-small cell lung cancer estimated a postoperative mortality rate of 4%.[4] An anticipated 5-year survival rate of 28% was expected in the R0 and N0-1 groups respectively.[12] However, notably for our case no studies have included patients with invasion into the stomach due to its exclusion from the T4 classification.

Rates of surgery in lung cancer are generally low, this is for a myriad of reasons. The 2008 National Lung Cancer audit revealed that lung cancer resection rates stand at just 11% with notable disparities among different medical centers, ranging from less than 5% to as high as 25%.[13] The patient's initial health status often serves as a common factor contributing to low rates of surgical intervention. Patients undergoing extensive surgical resection have an increased risk of morbidity and mortality.[6] These patients require assessment and optimization of their co-morbidities pre-operatively. Enhanced Recovery After Surgery (ERAS) plays a key role in patient optimization. Our patient had multiple co-morbidities which posed a significant surgical risk. ERAS is a multimodal and evidence-based approach to perioperative care that aims to optimize management and outcomes for patients.[14] ERAS protocols incorporate a wide range of preoperative, intraoperative, and postoperative strategies, all geared toward improving surgical outcomes and accelerating the recovery process.[14] By adhering to these principles, pain can be minimized, hospital stays reduced with a quicker return to patient's daily lives.[14]

To optimize the patient pre-operatively, a multidisciplinary approach was employed. Cardiovascular function was reviewed with an up-to-date pre-operative echocardiogram and electrocardiogram given the patient's history of ischemic heart disease. Hypertension management was optimized. Renal function was managed with maintenance intravenous hydration while fasting due to chronic renal impairment. The patient's history of smoking was addressed with pre-operative pulmonary rehabilitation. ERAS protocols were followed to improve postoperative recovery, focusing on nutrition, multimodal analgesia, and minimizing fasting to enhance outcomes.

Chemotherapy wasn't a viable option in this case due to patient preference. However, neoadjuvant therapy could potentially enhance the feasibility of surgical intervention for T4 cancer. A 1994 study involving twenty-three patients with stage IIB (T4) NSLCC, of which twelve also underwent radiation prior to surgery, found that complete eradication was observed in 13% of patients.[15] However, major post-operative complications occurred more commonly in those patients who received chemotherapy as well as radiotherapy compared to chemotherapy alone. This study did not include any patients with invasion through the diaphragm. The three-year survival was determined to be 54%.[15]

A study published in 2022 assessed the outcomes of extended resections in patients with stage III T3/T4 NSCLC following induction therapy.[16] Of 197 patients, 80% achieved R0 resection, including 36 extended resections, with no significant difference in mortality compared to standard resections. Extended resections showed promising survival rates, with 61% at 3 years and 29.5% at 10 years. R0 resection was associated with improved survival, but pretreatment N2 status had no significant impact. This highlights the potential for surgery post-induction therapy in selected patients with advanced T4 NSCLC.[16]

The LACE trial demonstrated that postoperative cisplatin-based chemotherapy significantly improves overall survival (OS) in patients with resected NSCLC. In a pooled analysis of five major trials with 4,584 patients, the median follow-up was 5.2 years, showing a 5-year absolute survival benefit of 5.4%. The benefit was more pronounced in stage II and III patients, with hazard ratios of 0.83 for both stages, compared to no benefit in stage IA. Chemotherapy was most effective in patients with better performance status, regardless of the associated drugs used..[17]

In summary, T4 disease exhibits heterogeneity, and although it is typically deemed unresectable, recent developments in surgery are challenging this conventional belief and demonstrating the potential benefits of surgical resection, particularly where a radical dissection is anticipated. Our case represents the first reported resection involving local invasion into the diaphragm, pericardium, omentum, and onto the liver surface. This case underscores the critical role of multidisciplinary collaboration and the need for consulting specialties not traditionally involved in lung cancer tumor boards when managing complex, challenging cases.

SUMMARY - ACCELERATING TRANSLATION

We present a case where a multidisciplinary approach enabled the complete surgical resection of locally advanced lung cancer that had invaded the diaphragm, pericardium, omentum and onto the liver surface.

FIGURES

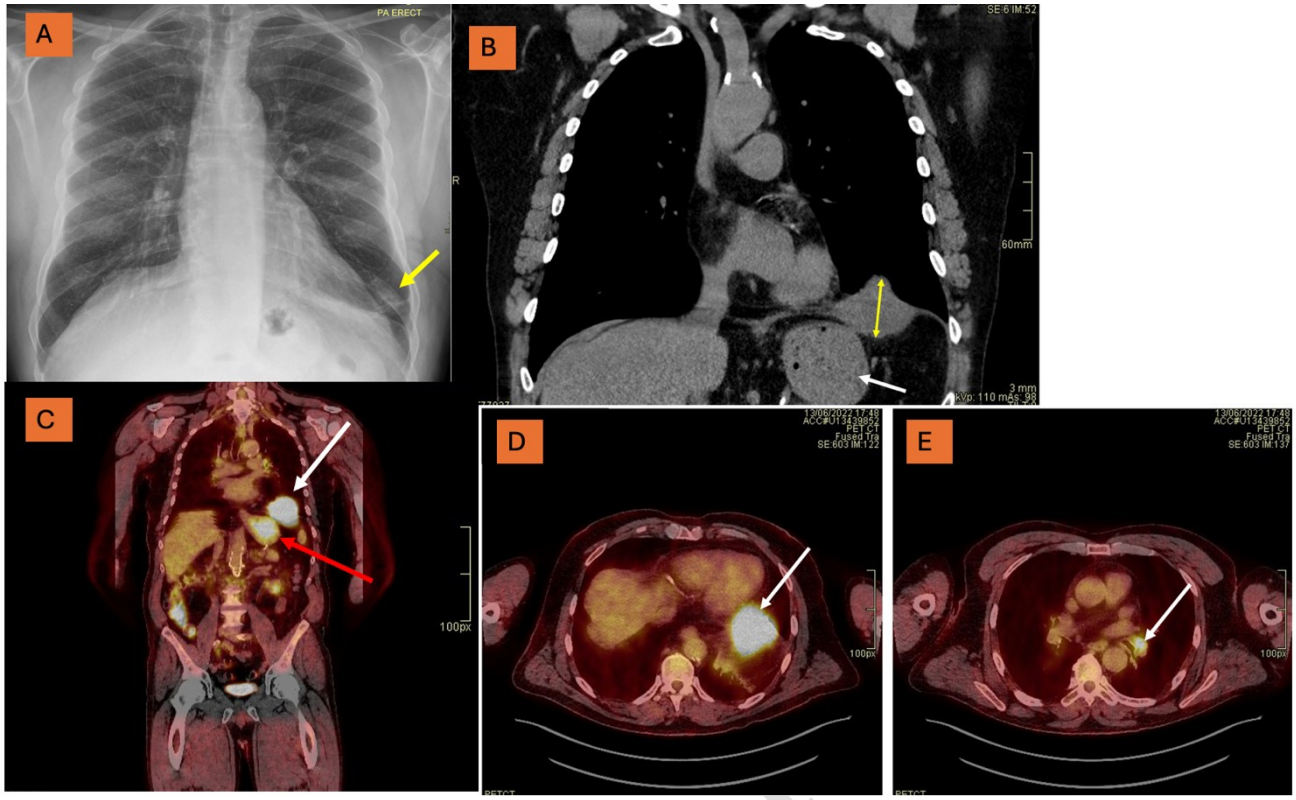

Figure 1: Diagnostic Imaging: A: Chest x-ray showing an approximately 2cm lesion in the left lower lobe (yellow arrow). **B:** Computed Tomography image demonstrating the left lower lobe lung mass (yellow arrow) extending beyond the diaphragm and potentially abutting the stomach (white arrow). **C:** PET CT scan showing 6.1cm intensely fluorodeoxyglucose (FDG) avid mass (standardized uptake value (SUV) max of 21) in the left lower lobe of the lung (white arrow) along with an approximately 1cm mildly FDG avid lymph node in the left intrahilar region adjacent to the origin of the lingular bronchi (SUV max of 7) (red arrow). There was diffuse FDG uptake seen throughout the stomach which was considered most likely benign. This was confirmed using esophagogastroduodenoscopy. **D:** PET CT demonstrating on the left an approximately 6.1cm intensely FDG avid pulmonary mass at the left lung base (SUV max 21). **E:** PET CT demonstrating an approximately 1cm mildly FDG avid lymph node in the left intrahilar region adjacent to the origin of lingular bronchi (SUV max 7). This was found to be benign on endobronchial node biopsy.

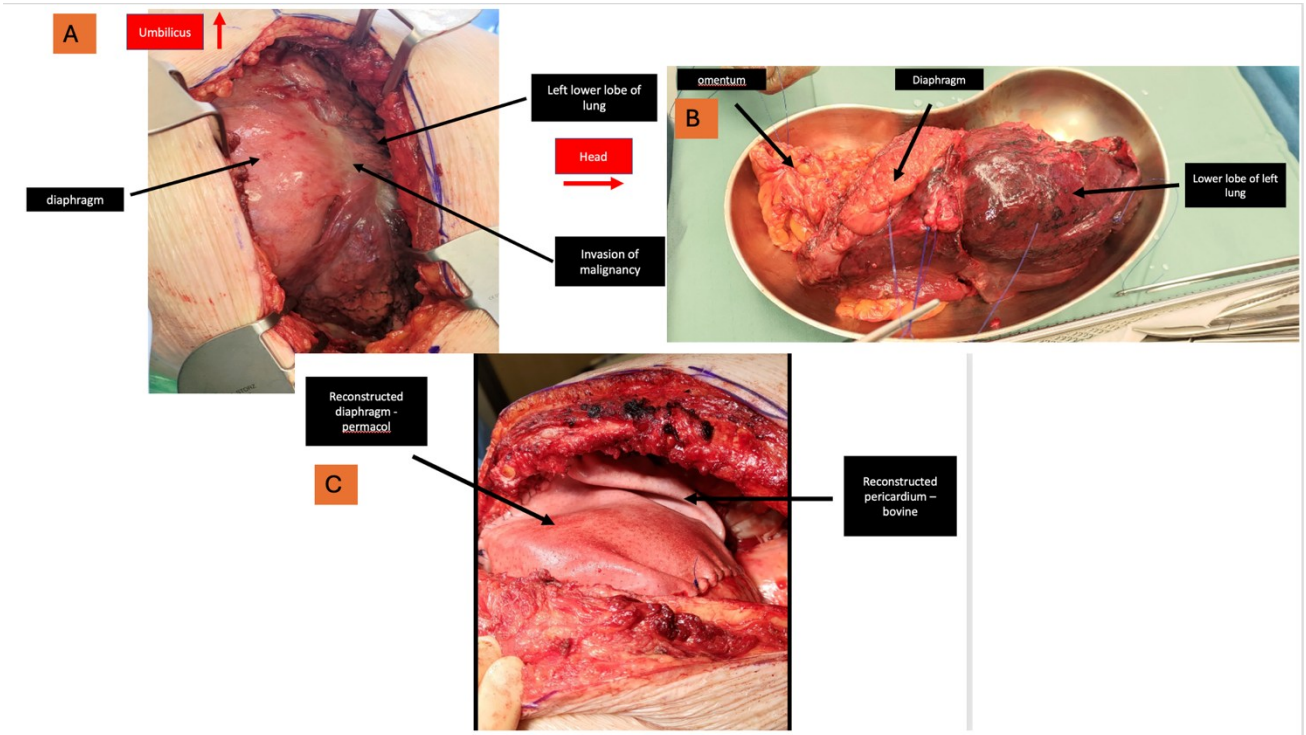

Figure 2: Intra-operative Imaging: A: An intra-operative image showing invasion of the malignancy into the diaphragm. Local invasion of the central tendon extended both medially and posteriorly. The diaphragm was resected en bloc with a small sleeve of greater omentum. **B:** This image depicts the specimen sent for histopathology. It included the left lower lobe lung, aspect of the left hemidiaphragm, peritoneum and left lobe of the liver. **C:** This intra-operative image demonstrates the diaphragm reconstructed with Permacol prosthesis and the pericardium reconstructed with bovine pericardium.

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