

Virtual Tumor Board

A Multidisciplinary Approach to Cancer Treatment

Edited by Keith A. Delman, MD

Locally Advanced Lung Cancer

Arafat H. Tfayli, MD ¹; Pierre M. Sfeir, MD²; Bassem Y. Youssef, MD³; Fadlo R. Khuri, MD⁴

Case Presentation and Overview

Mrs. GG is a 76-year-old woman who presented in March 2020 with a 4-month history of middle back pain radiating to the right chest wall. A magnetic resonance image of the thoracic spine on March 11, 2020, revealed the presence of 4.4-cm right posterior mediastinal lung mass in close contact with the T8 and T9 vertebral bodies. A computed tomography (CT) scan of the chest on April 3, 2020, revealed a 4.3-cm x 4.7-cm mass with central necrosis in the posterior segment of the right lower lobe with close proximity to the descending thoracic aorta and esophagus. CT-guided biopsy of the mass confirmed the presence of a poorly differentiated squamous cell cancer with PD-L1 expression in 50% of cells. A positron emission tomography/CT scan showed significant (18) F-fluorodeoxyglucose uptake in the right lower lobe with a standardized uptake value of 13.6 and a small focus of uptake in the right lung hilum with a standardized uptake value of 3.5 (Fig. 1). A magnetic resonance image of the brain was negative for metastasis, and endobronchial ultrasound and sampling of the mediastinal lymph nodes revealed no mediastinal node involvement. The patient was very functional, with an Eastern Cooperative Oncology Group performance status of 1.

The patient's case was discussed in our thoracic tumor board in April 2020, and it was debated whether surgery was an option in this case. It was decided to give the patient neoadjuvant therapy and assess her response after that. It was appreciated that a good response was needed in this patient if

we were to consider surgical excision at all. Given the consistently higher response rates with a combination of chemotherapy and immunotherapy compared with chemotherapy alone and the strong PD-L1 expression of this patient's tumor, we gave the patient 3 cycles of carboplatin/gemcitabine and pembrolizumab.

Repeat imaging in June 2020 showed a minor response in the tumor (Fig. 2). However, the patient's initial complaints of severe back pain completely resolved after the first cycle of therapy. The patient's case was discussed again in the thoracic tumor board, and it was decided to proceed with surgical excision given the significant necrosis seen on imaging and the resolution of the patient's back pain.

The patient underwent right lower lobe lobectomy and osteotomy of the T8 and T9 vertebral bodies on June 25, 2020. A complete resection with negative margins (R0 resection) was achieved. Microscopic evaluation revealed 98% necrosis in the tumor specimen with only a small focus of residual squamous cell cancer, negative surgical margins, and negative hilar and mediastinal lymph nodes (Fig. 3). There was no evidence of therapy effect in the hilar lymph node that had mild activity on the baseline positron emission tomography scan. Postoperatively, the patient received intensity-modulated radiation therapy (IMRT) to the tumor bed (50.4 grays in 28 fractions) and was maintained on pembrolizumab.

A follow-up CT scan in October 2020 revealed postoperative changes with no evidence of disease recurrence. Unfortunately, the patient caught COVID-19 infection in December 2020 complicated by bacterial pneumonia, necessitating a prolonged hospital stay

¹Department of Internal Medicine, Division of Hematology/Oncology, American University of Beirut, Beirut, Lebanon

²Department of Surgery, American University of Beirut, Beirut, Lebanon

³Department of Radiation Oncology, American University of Beirut, Beirut, Lebanon

⁴President, American University of Beirut, Beirut, Lebanon.

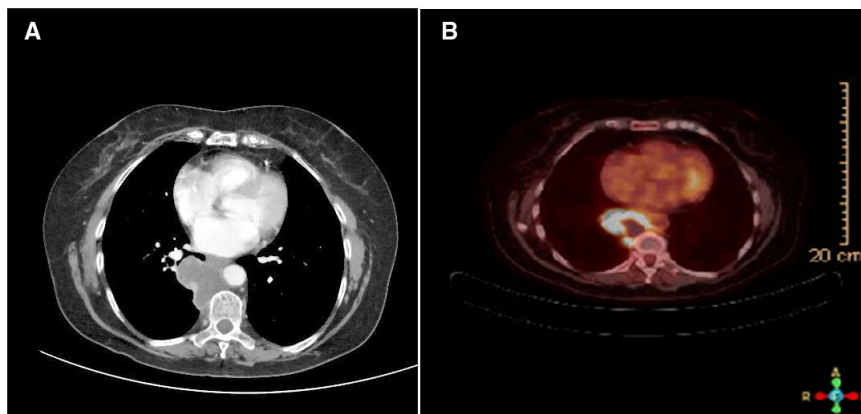


FIGURE 1. (A) Computed Tomography and (B) Positron Emission Tomography Scan Images at Presentation Showing the Central Mass With Mediastinal Invasion.



FIGURE 2. Computed Tomography Scan After Neoadjuvant Therapy Showing Tumor Shrinkage and Necrosis.

and interruption of her therapy with pembrolizumab. The patient had 2 small metastatic brain lesions in February 2021 that were treated with stereotactic radiation therapy (RT). After her COVID-19 infection, the patient never recovered adequately and had multiple hospital admissions for respiratory failure. She is currently at home receiving supportive care, including continuous oxygen supplementation.

Medical Oncology Perspective: Systemic Therapy Decision Making

This case is that of a woman with a locally advanced tumor for which surgical excision was being contemplated. Neoadjuvant chemotherapy with or without RT is considered the standard of care. Several points of decision needed to be addressed regarding the choice of preoperative therapy in this patient. The first decision was whether to give systemic chemotherapy alone or combined with RT. This issue has not been resolved in large, randomized trials, and large variations between different centers remain. In

a prospective, randomized study of 232 patients, the Swiss Group for Clinical Cancer Research showed that sequential chemoradiation therapy did not provide an additional benefit over chemotherapy alone.¹ The second point of decision is the choice between either neoadjuvant chemotherapy alone or combination chemoimmunotherapy. Although chemotherapy remains the standard of care to date, data on neoadjuvant immunotherapy are emerging, with promising results. In a study of 21 patients who received 2 doses of preoperative nivolumab, a 45% major pathologic response (MPR) rate (defined as $\leq 10\%$ viable tumor cells) was documented.² The LCMC3 trial (ClinicalTrials.gov identifier NCT02927301) similarly revealed a 19% MPR rate in a series of 90 patients who received 2 doses of neoadjuvant atezolizumab.³ NeoSTAR (ClinicalTrials.gov identifier NCT04230109) was a randomized phase 2 study in which patients with stage I through IIIA nonsmall cell lung cancer (NSCLC) received either nivolumab 3 mg/kg on days 1, 15, and 29 or nivolumab on the same schedule plus a single dose of ipilimumab 1 mg/kg on day 1. An MPR rate of 17% was observed in the 23 patients who received nivolumab, and the rate was 33% in the 21 patients who received nivolumab and ipilimumab.⁴ Another study using a combination of chemotherapy and avelumab failed to achieve the response rates needed, and the study was terminated.⁵ Most recently, the CheckMate 816 trial (ClinicalTrials.gov identifier NCT02998528) was reported at the 2021 annual meeting of the American Society of Clinical Oncology, in which 358 patients with stage IBO through IIIA NSCLC were randomized to receive either 3 cycles of neoadjuvant chemotherapy or 3 cycles of chemotherapy with nivolumab. Patients who were randomized to neoadjuvant chemotherapy and nivolumab had an MPR rate of 37%, including a 24% complete pathologic response rate.⁶ Although the standard of care for neoadjuvant therapy in NSCLC remains chemotherapy,

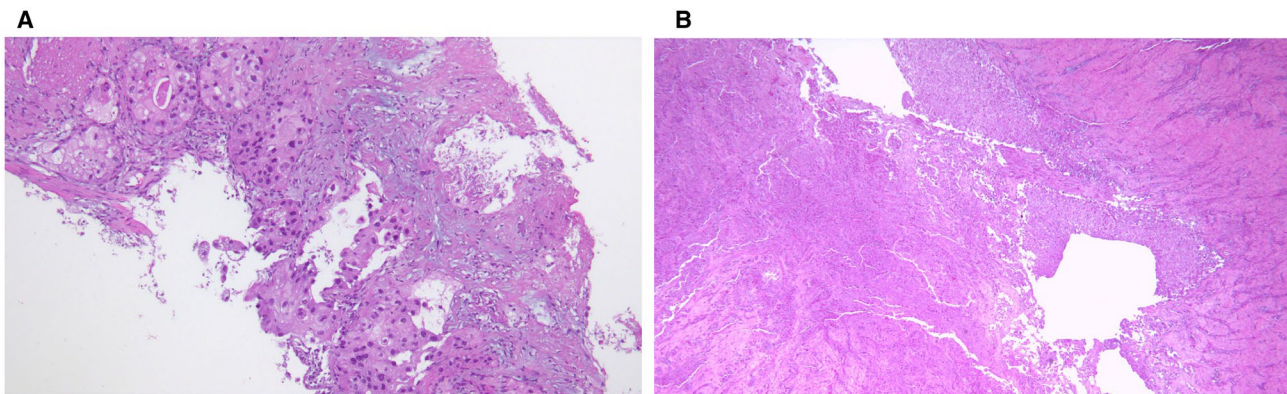


FIGURE 3. Histology of Tumor (A) at Baseline and (B) After Neoadjuvant Therapy Showing Extensive Necrosis.

emerging data on the combination of chemotherapy and immunotherapy are very promising. Our patient received 3 cycles of carboplatin/gemcitabine and pembrolizumab and had a near-pathologic complete response (98% necrosis).

The third point of decision is whether to continue systemic therapy after tumor resection. Neoadjuvant chemotherapy trials routinely delivered all chemotherapy protocols in the preoperative setting, and no additional systemic therapy was administered postoperatively. Conversely, all ongoing phase 3 trials testing the efficacy of neoadjuvant chemotherapy and immunotherapy, including CheckMate 816, give postoperative immunotherapy for 1 to 2 years. Because our patient's tumor had a remarkable response to neoadjuvant therapy and had PD-L1 expression on 50% of tumor cells, we believe it is reasonable to continue with maintenance systemic pembrolizumab, although this approach remains investigational.

Surgical Oncology Perspective: Timing of Surgery and Systemic Therapy

This patient presented with a biopsy-proven, 4.4-cm squamous cell carcinoma invading the vertebral bodies of T8 and T9 with symptoms consisting of back pain. According to the eighth edition of the tumor, node, metastasis (TNM) staging system, she was classified as with cT4N0M0, stage IIIA disease.

The National Comprehensive Cancer Network (NCCN) guidelines designate upfront surgery as a *preferred* initial treatment strategy for resectable T4N0/N1 tumors. They also emphasize that en-bloc resection of the involved structure with negative margins is required for T4 tumors that have local extension. According to the same guidelines, neoadjuvant therapy is an established second option used most to potentially improve the chance of an R0 resection.

T4 lesions include a tumor size >7 cm and invasion of mediastinal structures, like the heart, great vessels, trachea, carina, esophagus, and vertebral bodies. Gross heart invasion and esophageal invasion are generally unresectable, although partial left atrial resections have been performed with or without cardiopulmonary bypass by some groups in very specialized centers. However, carinal or vertebral body resections are more common and have been associated with better long-term outcomes, especially if R0 resection is achieved in the absence of nodal involvement.⁷

Neoadjuvant concurrent chemoradiation followed by surgery has been shown to benefit T3 and T4 superior sulcus tumors (Pancoast tumors) involving ribs and spine, with a 56% 5-year overall survival rate after a complete resection.⁸ Extrapolating the benefits of neoadjuvant treatment to other T4 lesions is not possible because most of the data available consist of small, retrospective, single-center reviews from ultra-specialized centers, the results of which are often difficult to reproduce. A prospective, randomized phase 3 trial to assess induction versus no induction will probably not be possible because the relative low incidence of these tumors leads to very slow accrual.

A best-evidence review by Chambers et al identified 15 publications among 151 articles reviewed that helped define the role and timing of surgery in T4N0/N1 lung cancer. Unanimous good survival rates were obtained by upfront resection of T4 tumors (excluding Pancoast tumors) in patients with N0 nodal status and complete resection.⁷ A recent review by Collaud et al included 135 pooled patients from 4 different studies reporting no significant survival difference comparing neoadjuvant treatment with surgery or adjuvant therapy alone. In that report, 37% of patients received neoadjuvant chemoradiation, and 22% received chemotherapy alone. Among the neoadjuvant group of patients, impressive 5-year survival rates of 80% among complete

responders and 35% among partial responders were reported, establishing a trend favoring neoadjuvant treatment in those patients.⁹

Two published series had all patients receiving neoadjuvant chemoradiation. Yokomise et al reported a 5-year survival rate of 67.7%.¹⁰ Anraku et al reported an overall 3-year survival rate of 58%, which rose to 92% in those patients who achieved a complete or near-complete response (viable tumor cells in <1%).¹¹ The latest report along the same trend was a very recent query of the National Cancer Database identifying 1101 patients with cT4N0/N1M0 disease who met inclusion criteria over a 10-year period. In that trial, 595 patients (54%) received primary surgery, and 506 (46%) received neoadjuvant treatment. The latter group was associated with fewer positive surgical margins (46 of 506 patients [9.3%] vs 186 of 595 patients [33.1%]; $P < .001$) and longer overall survival (65.9 vs 27.5 months; $P < .001$). The benefit of neoadjuvant therapy extended to 331 propensity-matched pairs for both margins and survival.¹²

The 2 most important factors necessary to achieve a good survival in resectable T4 tumors are R0 resection and the absence of N2 nodal involvement. Both of these factors can be directly affected by neoadjuvant therapy, especially in responders, giving this strategy increasing appeal among surgical oncologists. As evidenced by the many published reports, induction therapy is likely to favorably influence the prognosis by optimizing patient selection, increasing the rate of R0 resections, and guiding postoperative multimodal management on the basis of real-time assessment of the pathologic response.

However, the potential drawbacks of adopting this approach universally on all T4 lesions should be kept in mind. For the patient who presents with a clearly technically resectable tumor, the delay of a potentially curable resection may negatively affect their survival, especially if the patient is a nonresponder and the chemotherapy proves ineffective. Our patient received neoadjuvant treatment with a good near-complete response, leading to a successful R0 resection.

Radiation Oncology Perspective: Radiation Role in Locally Advanced NSCLC

Patients with stage IIIA (T4N0) NSCLC represent a heterogeneous group with several treatment options. The NCCN guidelines recommend definitive concurrent chemoradiation followed by maintenance immunotherapy for patients with unresectable disease. If the disease is resectable, the NCCN preferred option is upfront surgery followed by adjuvant therapy.

As extensively discussed above, neoadjuvant therapy has been shown to increase R0 resection rates and improve oncologic outcomes, especially in patients who achieve a complete or near-complete pathologic response.⁹⁻¹² Because our patient was offered neoadjuvant immunotherapy along with chemotherapy, we avoided the use of concurrent RT to decrease the risk of pneumonitis. Hence, RT was offered in the adjuvant setting to improve local control.

We offered RT following the recommendation of the multidisciplinary tumor board and the input of the cardiothoracic surgeon and the pathologist on the closeness of the margin; in general, we tend to offer adjuvant RT for close or uncertain margin status. We delivered a total dose of 50.4 grays in 28 fractions to the tumor bed and involved vertebrae using IMRT. Regional nodal irradiation was not offered. IMRT is preferred over 3-dimensional conformal RT for lung cancer to decrease the risk of toxicities. In a prospective trial of definitive chemotherapy/RT for patients with stage III NSCLC (Radiation Therapy Oncology Group trial 0617; ClinicalTrials.gov identifier NCT00533949), compared with 3-dimensional conformal RT, IMRT was associated with a 55% reduction in the risk of grade 3 radiation pneumonitis (from 7.9% to 3.5%; $P = .039$) as well as reduced cardiac RT doses.¹³

Finally, not all patients with T4N0 NSCLC will benefit from adjuvant RT. Furthermore, adjuvant RT in NSCLC is associated with increased toxicity. The potential toxicity of adjuvant RT was illustrated in a phase 3 trial presented at the European Society of Medical Oncology meeting in 2020, in which adjuvant RT for patients who had stage III NSCLC with N2 disease was associated with increased early and late grade 3 and 4 toxicities versus no adjuvant RT (11.6% and 14.6% vs 7.7% and 8.9%, respectively). The risk of death was also increased in the RT arm compared with no RT (14.6% vs 5.3%).¹⁴ The use of adjuvant RT in NSCLC should be discussed on a case-by-case basis at a multidisciplinary tumor board to weigh the risks versus the benefits.

Conclusion

The management of patients with locally advanced NSCLC is complex and requires close collaboration between all treating specialties. Although most patients with T4 lesions are treated with concurrent chemotherapy and RT, some could be surgical candidates. In this report, we present a patient with a locally advanced lung cancer who was treated successfully with a neoadjuvant approach using a combination of chemotherapy and immunotherapy followed by surgical excision of the tumor and RT.

Conflicts

The authors made no disclosures.

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