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Initial Experience With Lung Cancer Resection Following Treatment With T Cell Checkpoint Inhibitor Therapy

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Abstract

T cell checkpoint inhibitors targeting the programmed death receptor-1 (PD-1) and its ligand (PDL-1) have recently been approved for the treatment of metastatic non-small cell lung cancer (NSCLC), but their safety and efficacy as neoadjuvant therapy are still undefined. Autoimmune toxicities, notably pneumonitis, are a particular concern in the perioperative setting. This series of 5 cases describes for the first time the safety and technical issues relating to pulmonary resection after checkpoint inhibitor therapy.

T cell checkpoint inhibitors, including agents targeting the programmed death receptor-1 (PD-1), its ligand (PD-L1), and CTLA-4 are being widely investigated in the treatment of metastatic cancers. For patients with advanced non-small cell lung cancer (NSCLC), nivolumab, pembrolizumab, and atezolizumab are now FDA-approved for use following progression on platinum-based chemotherapy,[1,2] and pembrolizumab was recently approved as first-line therapy for patients with non-small cell lung cancers that express PD-L1 strongly.[3] Responses to these agents can be dramatic and durable, while toxicity has generally been modest. However, treatment-related toxicity, including nearly any autoimmune condition ranging from asymptomatic to life-threatening, can occur. In patients with lung cancer, pneumonitis is of particular concern,[4] especially when considering surgical intervention. Though more common with anti CTLA-4 than PD-1/L-1 therapies, the etiology of pneumonitis remains unclear, and it is unknown whether general anesthesia and surgery may initiate, worsen, or be complicated by pneumonitis or other immunologic effects of anti-PD-1 therapy.

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To our knowledge, there are no published series reporting resection in lung cancer patients after T cell checkpoint inhibitor therapy. Here, we report 5 patients with advanced NSCLC treated initially with anti-PD-1/L-1 therapies with or without anti-CTLA-4 inhibitors who thereafter were deemed appropriate for lung cancer resection.

Case Reports

Case 1

A 56 year old man, former 60 pack year smoker, was diagnosed with stage IV NSCLC. After 3rd line anti-PD-1 therapy he had marked radiographic response which was maintained for 1 year. Treatment was complicated by hypothyroidism but no pulmonary toxicity and was discontinued due to local disease progression. Positron emission tomography (PET) imaging showed residual disease limited to a 4.2×2.2 cm lingular mass (SUVmax 17) and subcentimeter mediastinal lymph nodes (SUV max 4), so he was referred for resection. He underwent an intrapericardial left upper lobectomy with resection of the phrenic nerve and lymph node dissection. Pathology demonstrated a ypT3N2 (single level 7 node) squamous cell carcinoma. He had an uncomplicated postoperative course and was subsequently given adjuvant mediastinal radiotherapy.

Case 2

A 67 year old woman, former 20 pack year smoker, presented with hypertrophic osteoarthropathy and was found to have stage IIIA lung adenocarcinoma with bulky mediastinal adenopathy. Adenopathy resolved with chemotherapy but the primary tumor eventually enlarged. She was treated with 2nd line anti-PD-L1 therapy for 5 months with stable disease as best response and no pulmonary toxicity. Biopsies from endobronchial ultrasound revealed no viable metastatic disease in multiple lymph node stations. PET scan showed an enlarging right lower lobe mass, with a SUV of 45. Given disease confined to the primary tumor site, she underwent surgical exploration, with right lower lobectomy and mediastinal lymph node dissection for a ypT2bN0 tumor. She had an uncomplicated postoperative course.

Case 3

A 53 year old man, former 35 pack year smoker, was diagnosed with metastatic large cell neuroendocrine carcinoma involving the lung, mediastinal lymph nodes and omentum. He was treated with first line anti-PD-1 plus CTLA-4 therapy, achieving a partial response. Immunotherapy was discontinued because of grade 2 pneumonitis which was managed with a prolonged steroid taper. Imaging showed only disease remaining in the lung and mediastinum, so resection of the residual disease was considered. Because of his history of pneumonitis, he was empirically given a short course of steroids perioperatively. Robotically assisted VATS revealed dense hilar fibrosis requiring conversion to thoracotomy. Hilar dissection was very technically challenging but right upper lobectomy and lymph node dissection were successfully completed. Final pathology revealed fibrosis with no evidence of residual cancer. Patient had an uncomplicated hospital course.

Case 4

A 62 year old man, former 70 pack year smoker, was initially diagnosed with oligometastatic NSCLC to the brain treated with stereotactic radiation followed by an anti-PD-L1 antibody with initial response, then local tumor progression. He has no pulmonary toxicity. PET scan showed a growing right lower lobe mass with a SUV of 22. Right lower lobectomy and mediastinal lymph node dissection showed a sarcomatoid carcinoma with a component of adenocarcinoma, ypT1bN0. The patient had a prolonged chest tube air leak but was discharged on post-operative day 11.

Case 5

A 52 year old woman, former 90 pack year smoker, presented with metastatic poorly differentiated NSCLC involving the right upper lobe and left adrenal gland. She received combined anti-PD-1 plus CTLA-4 therapy with marked radiographic response. She developed auto-immune pancreatic dysfunction, but no pulmonary toxicity. After 16 months treatment was discontinued for maximum clinical benefit. She had a laparoscopic left adrenalectomy, then a robotically-assisted VATS with right upper lobe wedge resection and mediastinal lymph node dissection. She was discharged on postoperative day 2. Final pathology showed no residual viable cancer, ypT0N0M0.

For Cases 1–2 and 4–5, the intervals between cessation of immunotherapy and surgery were only 4, 8, 4 and 5 weeks respectively. For Case 3, the interval was 21 weeks because the patient needed to complete a steroid taper for pneumonitis before surgery could be considered. All patients had a complete (R0) resection. Four patients remain alive, disease free and off treatment postoperatively at intervals of 23, 22, 10 and 7 months respectively. Case 4, who had a sarcomatoid carcinoma, developed mediastinal nodal and distant metastases after being off treatment for 15 months and is alive with disease on platinum-based chemotherapy 25 months postoperatively.

Comment

The increasing use of T-cell checkpoint inhibitors in the treatment of NSCLC makes it important for surgeons to understand the potential indications for resection, and the ways the toxicities of these agents can affect perioperative care. While the role of surgery for residual locoregional disease after initial treatment of metastatic NSCLC requires further investigation, multimodality therapy including checkpoint inhibitors and surgery is particularly relevant because a large multicenter trial testing the use of induction atezolizumab in locally advanced NSCLC has just opened to accrual. It is possible that checkpoint inhibitors will, in the future, become part of standard therapy for this NSCLC subset. These immunotherapies present a learning experience for surgeons and oncologists implementing them into multimodality treatment, just as neoadjuvant chemotherapy did during the 1980’s and 90’s. Our initial experience suggests that pulmonary resection after checkpoint inhibitors is feasible, even in patients who develop pneumonitis or other immune-related toxicities during their treatment. Whether perioperative pulse steroid coverage is indicated in patients who experienced preoperative therapy-related pneumonitis remains to be determined.

Our experience also suggests that a discrepancy between radiologic and pathologic response can occur, and that a persistent lung mass or adenopathy cannot be assumed to represent residual active cancer, even if hypermetabolic on PET. Indeed, standard response criteria used to evaluate the effect of cytotoxic chemotherapy, are known to be inaccurate in assessing the results of checkpoint inhibitors[5] and the role of nuclear imaging remains under studied. Clinical trials will need to define the best criteria for proceeding with resection in patients receiving induction immunotherapy. Conceivably, simple lack of disease progression may prove to be the sole criterion for surgical resection.

Finally, our experience suggests that dense fibrosis may develop in some patients as result of excellent response to immunotherapy. Mediastinal and hilar dissection can be technically challenging under such circumstances. The frequency of this treatment outcome also needs to be defined in clinical trials but is a complicating factor of which thoracic surgeons should be aware.

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