Surgery for Locally Advanced and Oligometastatic Non–Small Cell Lung Cancer

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KEYWORDS

• Non–small cell lung carcinoma • Locally advanced non–small cell lung cancer
• Chest wall invasion • Superior sulcus tumors • Salvage surgery • Stage IIIA N2
• Definitive chemoradiation • Oligometastatic lung cancer

KEY POINTS

- Locally advanced non–small cell lung carcinoma is a heterogeneous, complex group of tumors that require a multidisciplinary approach.
- In the absence of N2 disease, complete surgical (R0) resection as part of a multimodal treatment strategy offers the best chance at long-term survival for select patients with locally advanced non-small cell lung carcinoma.
- Salvage lung resection after definitive chemoradiation is safe and may offer a survival advantage to select patients.
- In the absence of N2 disease, oligometastatic non–small cell lung cancer is best treated by aggressive multimodal treatment, including resection of the primary tumor and local therapy for the metastasis.

INTRODUCTION

Lung cancer, of which non–small cell lung cancer (NSCLC) is the most common type, is the leading cause of cancer-related death of men and women in the United States. Unfortunately, a majority of patients with NSCLC are diagnosed at an advanced stage. At the time of diagnosis, 24% of patients have locally advanced NSCLC, defined as tumor invasion into surrounding structures or metastasis to ipsilateral mediastinal lymph nodes.[1] Although the treatment of medically fit patients with early-stage NSCLC is well-established (i.e., surgery), the role of surgery in more advanced tumors is more controversial.[2] This complex, heterogenous group of tumors requires a thorough

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evaluation by an experienced multidisciplinary team of medical oncologists, radiation oncologists, and thoracic surgeons. A select group of these patients derive survival benefit from surgery as part of a multimodal treatment strategy. This review discusses the evaluation, indications, and challenges of surgery for T3 (chest wall invasion) tumors, superior sulcus tumors, stage IIIA N2 disease, resectable T4 tumors, oligometastatic stage IV disease, and salvage lung resections after definitive chemoradiation.

PREOPERATIVE EVALUATION

All NSCLC patients who are potential candidates for resection must undergo a comprehensive preoperative assessment of their cardiopulmonary function to assure that the patient has sufficient cardiopulmonary reserve to undergo the operation with an acceptable risk of perioperative morbidity and mortality. This includes a thorough preoperative history and physical examination with specific attention paid to signs and symptoms of cardiopulmonary compromise. Depending on the presence and severity of clinical predictors of perioperative cardiovascular complications, such as coronary artery disease, heart failure, arrhythmias, valvular disease, diabetes mellitus, and chronic renal insufficiency, additional studies to assess cardiovascular risk may be required. Pulmonary function tests should be obtained, and the percent predicted postoperative forced expiratory volume in the first second of expiration and diffusing capacity of carbon monoxide should be determined, to further risk stratify patients.

To assure NSCLC patients are allocated to the most appropriate treatment strategy, thorough pretreatment staging is essential, including computed tomography (CT), positron emission tomography (PET), and brain magnetic resonance imaging (MRI).[2] Nodal status is one of the most important prognostic indicators[2–4] and drives preoperative decision making[2,3]; therefore, it is imperative to thoroughly assess for mediastinal nodal metastases prior to surgical intervention. Due to the potential for false-negative findings on PET and CT, the mediastinum should be pathologically evaluated with endobronchial ultrasound (EBUS) or mediastinoscopy for all patients with stage IB or higher.[2]

T3 (invasion), N0-1

According to the 8th edition of the American Joint Commission on Cancer (AJCC) Staging System for NSCLC, T3 includes local invasion into the parietal pleura, the chest wall, phrenic nerve, and pericardium.[5] Patients with chest wall invasion may present with severe pain due to pleural and chest wall involvement. Chest CT is useful for assessing the primary tumor and degree of rib involvement whereas chest MRI is useful for assessing soft tissue chest wall involvement.[4] Mediastinal staging is critical for these patients. Patients with T3N0-1M0 tumors are candidates for surgery; patients with T3N2M0 tumors are not. Patients with N2 disease are best treated with concurrent definitive chemoradiation followed by durvalumab.[2]

The location of the tumor and its extension into surrounding structures contributes have technical implications. A standard open posterolateral approach is sufficient in the majority of cases, although the safety and feasibility of a video-assisted thoracoscopic surgery (VATS) approach have been reported.[6] The chest should be entered away from the affected area and the involved chest wall should be resected en bloc with the pulmonary resection (usually a lobectomy). A mediastinal lymph node dissection or sampling should be completed. Although frozen sections of the soft tissue margins are helpful, frozen sections on the bony margin (ideally margins of 1.0 cm) are not.[4] Although some investigators have debated the benefits of skeletal resection

for T3 tumors compared with an extrapleural resection,[4] Doddoli and colleagues[7] found a significant ($P = .03$) 5-year overall survival (OS) advantage with en bloc resection (60.3%) compared with extrapleural resection (39.1%) for patients with T3 tumors involving the chest wall that were resected with negative margins.

Except for defects less than 3 cm and those posterior defects above the fourth rib that otherwise would be covered by the scapula, skeletal reconstruction of the chest wall should be completed to prevent paradoxic chest wall motion. Depending on size and location of the defect and surgeon preference, polytetrafluoroethylene (PTFE), polypropylene, high-density polyethylene (HDPE) mesh, or methyl metacrylate placed between 2 pieces of HDPE mesh secured in place with nonabsorbable suture are traditional methods for reconstruction. Regardless of the chosen material, it should be secured in place with some tension to confer rigidity to the chest wall. For resectable (especially right-sided) tumors that invade the pericardium, the pericardium is reconstructed with a thin (eg, 0.1 mm), loose, fenestrated piece of PTFE mesh to prevent cardiac herniation. Diaphragm plication should be completed after resection of tumors that invade the phrenic nerve.

Given the concern for local recurrence after chest wall resection, Tandberg and colleagues[8] examined the role of adjuvant radiotherapy (RT) in those patients who underwent an R0 resection and found no significant advantage of RT with regards to local control and survival. Adjuvant chemotherapy, however, offers a survival benefit. A large retrospective study found a significant median survival benefit of 71 months versus 39 months ($P<.001$) for those patients receiving adjuvant chemotherapy.[9] Taken together these and other data support the role of adjuvant chemotherapy for T3N0 NSCLC after R0 resections. Adjuvant RT has no role after R0 resection but should be considered for R1 resections.[2]

Superior Sulcus Tumors

Superior sulcus (Pancoast) tumors (T3 invasion, N0-1 and T4 extension, N0-1) are complex due to involvement of the structures that course through the thoracic outlet (ie, branchial plexus and subclavian vessels), spine, and chest wall, which contribute technical challenges at the time of resection.These tumors may be associated with Pancoast-Tobias syndrome, which is characterized by severe and unrelenting shoulder pain with distribution down the arm and into the hand (compression of the C8-T1 nerve roots), Horner syndrome (ptosis, miosis, and anhidrosis from compression of the sympathetic chain and stellate ganglion), and atrophy of the intrinsic muscles of the hand (compression of ulnar nerve).[10,11] The presence of the Pancoast-Tobias syndrome is not a necessary condition to establish the diagnosis of a superior sulcus tumor.[10]

The pretreatment evaluation should include a dedicated chest CT. For patients who may require subclavian resection and reconstruction, CT angiogram is needed. A brachial plexus or cervical/thoracic-spine MRI is helpful for assessing nerve root and vertebral column involvement. A full-body PET and brain MRI (or CT with contrast) is needed to rule out distant metastases. Once a tumor is thought to be technically feasible for resection, invasive mediastinal nodal sampling should be completed, because nodal disease is an extremely poor prognostic indicator in superior sulcus tumors.[2,4,10,11] It is the authors' preference to stage the mediastinum with EBUS prior to neoadjuvant CRT and to restage the mediastinum with a cervical mediastinoscopy after neoadjuvant CRT.

The current recommendation for medically fit patients with resectable superior sulcus tumors is concurrent neoadjuvant chemoradiotherapy (CRT), complete surgical resection, and adjuvant chemotherapy.[2,3] Absolute contraindications for surgical

resection include N2/N3 disease, involvement of the brachial plexus above the T1 nerve root, involvement of more than 50% of the vertebral bodies, and invasion into the esophagus and trachea. Involvement of the subclavian vessels and interforaminal extension of the tumor are no longer contraindications. The ipsilateral supraclavicular and scalene lymph nodes can be resected en bloc and are not a contraindication for resection.[10,11] Superior sulcus tumors often require a collaborative multispecialty surgery team of neurosurgery, vascular surgery, and thoracic surgery to aid in complete resection.

Though a posterolateral (Paulson-Shaw) thoracotomy is suitable for most tumors, an anterior (Dartevelle) thoracotomy is preferable for tumors involving the subclavian artery. Extensive vertebral body resections require posterior stabilization. Similar to early stage NSCLC, lobectomy for Pancoast tumors confers a significantly superior 5-year survival rate (60%) compared with a wedge resection (33%).[12] An in-depth description of Pancoast resection techniques is beyond the scope of this review but has been detailed elsewhere.[10,11,13]

Southwest Oncology Group Trial 9416 (Intergroup Trial 0160) was a multi-institutional prospective trial examining induction CRT prior to surgical resection for superior sulcus tumors. In this landmark trial, patients received 2 cycles of cisplatin and etoposide with concurrent 45-Gy RT and underwent subsequent resection if there was no disease progression; 61% of patients had either a pathologic complete response or minimal residual microscopic tumor with induction CRT. Pathologic complete response was a significant prognostic indicator of improved survival.[14] In a systematic review, trimodal therapy was associated with the best 5-year OS rate (35% to 84%) compared with RT alone (11% to 49%) or surgery alone (20%).[15]

Stage III (N2) NSCLC

NSCLC with N2 metastasis represents a complex group of tumors; their treatment is controversial. Randomized controlled trials have not definitively demonstrated a survival benefit of surgery for patients with N2 disease.[16] However, there may be subgroups of patients that benefit from a trimodal treatment approach. Furthermore, the presentation of N2 disease is diverse and ranges from occult, microscopic disease to bulky, infiltrative multistation nodal involvement. The management requires careful evaluation by a multidisciplinary tumor board and a multimodal treatment approach.

The heterogeneity of stage III-N2 NSCLC adds to the treatment dilemma. If occult N2 disease is discovered at time of surgery, the decision of resectability should be made by the operating surgeon. To minimize the risk of diagnosing occult N2 disease at the time of surgery, all patients with stage IB and greater should undergo pathologic mediastinal staging, independent of PET/CT findings. In the era of thoracotomies, surgeons often proceeded with resection to spare that patient another thoracotomy. In the era of VATS and robotic techniques, however, aborting surgery, giving neoadjuvant therapy, and returning for a minimally invasive resection is a reasonable alternative.[2]

For patients with known N2 disease for preoperative staging, the standard of care is neoadjuvant CRT, based on the results of a hallmark trial for N2 disease, Intergroup (INT) 0139 Trial, which compared concurrent CRT followed by resection and definitive CRT without resection. The group of patients who underwent surgery as part of their multimodal treatment strategy had a significantly better progression-free survival (PFS) (12.8 months), as compared with patients who were treated with definitive CRT (10.5 months)[hazard ratio (HR) 0.77 (95% CI, 0.62–0.96; P= .017]. However, there was no difference in OS between patients treated with CRT and surgery (23.6 months) as compared with patients treated with definitive CRT (22.2 months; HR

0.87 [0.70–1.10; $P = .24$]). The lack of OS benefit in the surgery group was likely driven by the high postoperative mortality (26%) after pneumonectomy, primarily caused by post-pneumonectomy acute respiratory distress syndrome (ARDS). An unplanned subgroup analysis of patients who underwent lobectomy demonstrated an improvement in 5-year OS (36% vs 18%, respectively). Though unplanned analyses should be interpreted with caution, it provides some evidence that subgroups of patients with N2 disease may benefit from surgery as part of a multimodal treatment strategy. As a result of these findings, investigators of the INT-0139 Trial recommended neoadjuvant CRT followed by lobectomy for stage IIIA-N2 disease but definitive CRT if pneumonectomy was necessary.[16]

Other retrospective studies sought to identify which subgroup of patients benefit from an aggressive trimodal therapeutic approach. Bueno and colleagues[17] determined that after induction CRT (with 40–54 Gy of RT) pathologic downstaging of mediastinal lymph nodes had a significant effect on median survival and 5-year OS (35.8% vs 9%, respectively; $P = .023$). In addition to nodal downstaging after neoadjuvant CRT, Stefani and colleagues[18] found 3 additional factors on multivariable analysis that had an effect on OS: clinical response to neoadjuvant chemotherapy, number of chemotherapy cycles, and histopathologic response. Furthermore, the degree of nodal burden (macroscopic vs microscopic) has also been shown to have a significant effect on OS Indeed, macroscopic disease has been shown to be associated with a 2.8-fold increased risk of death (CI 95%, 1.1%–7.3%).[19]

The benefit of nodal downstaging prior to surgery led investigators to try higher doses (50–66 Gy) of neoadjuvant RT, which were previously avoided in the neoadjuvant setting due to concerns regarding ARDS, impairments to wound healing, and development of bronchopleural fistulas, and increased mortality. Cerfolio and colleagues[20] demonstrated an 83% nodal clearance in the high-dose RT cohort, leading to a borderline significance in DFS with high dose and a trend toward significance in OS. Despite the higher dose of RT, the investigators noted that pulmonary resection could still be safely performed. Radiation Therapy Oncology Group (RTOG) 02-29 was a phase II trial, which examined the use of 50.4 Gy to the mediastinum. Primary end-points included nodal clearance and survival. Mediastinal nodal clearance was 63% after neoadjuvant CRT with significant 2-year OS advantage for those who achieved clearance of their nodal disease and underwent resection (75% for node-negative vs 52% for residual nodal involvement vs 23% for no resection; $P = .0002$).[21] In a meta-analysis examining neoadjuvant chemotherapy versus CRT, no increase in perioperative mortality was observed between the 2 groups. Although there was no survival benefit demonstrated with the use of RT, neoadjuvant CRT was associated with a greater tumor response, improved rate of complete surgical resection, and mediastinal downstaging.[22,23]

There is no consensus of which subset of patients with N2 disease derive benefit from resection after neoadjuvant CRT. Nonetheless, while there are no randomized clinical trials that demonstrate an unequivocal survival advantage of surgery, a CTSNet survey of thoracic surgeons found that 84% would offer neoadjuvant therapy followed by surgery for single-station microscopic N2 disease but that dropped to 62% when N2 disease became more bulky.[24] Physiologically fit patients with limited single-station disease, and who had a favorable response to neoadjuvant treatment are likely the best candidates for consideration of trimodal therapy.

Outside of clinical trials, however, there are a significant number of patients who have surgery as part of their pre-treatment plan but do not undergo resection. In a retrospective, single-institution study, Cerfolio and colleagues[24] found that only 37% of patients who completed neoadjuvant CRT underwent an operation. Patients

who did not complete trimodal therapy were significantly older, lacked a response to therapy, and experienced a morbidity during neoadjuvant therapy that precluded resection.[24] Definitive CRT is the treatment of choice for patients with unresectable locally advanced NSCLC, high-risk comorbid conditions that would preclude surgical resection or patients that refuse surgery.[2]

T4 extension (mediastinum), N0-1

Similar to other locally advanced tumors, nodal disease is the most significant prognostic indicator of survival for patients with T4 tumors with mediastinal extension. As such, T4N2-3 NSCLC is unresectable.[2] For potentially resectable tumors, careful surgical planning is essential.

When considering an extended mediastinal resection and reconstruction, additional preoperative work-up may be necessary. When there is concern for left atrial involvement, ruling out coronary artery disease and valvular dysfunction is essential, and obtaining a cardiac MRI may aid in operative planning. The surgeon also may want to coordinate with anesthesia to have transesophageal echocardiography available during the operation.[25] Although only small case series are available, the data demonstrate acceptable benefit if an R0 resection can be accomplished. In 1 small case series, the 5-year OS after resection of T4 tumors with aortic invasion was 37%, atrial invasion was 25%, carinal involvement was 22%, and SVC invasion was 26%.[26]

In patients with great vessel involvement, resection can be accomplished with cardiopulmonary bypass (CPB) support. A systemic review of the literature identified 72 patients that required CPB with pulmonary resection for T4 tumors. Pneumonectomy was the most common pulmonary resection (74%) and the aorta was the most commonly resected organ (43%). The 5-year OS was 37%. The use of unplanned or emergency CPB was associated with worse survival outcomes, but perioperative 30-day and 90-day mortality rates were low, 0% and 1%, respectively.[27] CPB, when utilized in thoughtful surgical planning, is a safe option in these locally advanced tumors.

SALVAGE LUNG RESECTION

Local tumor recurrence occurs in up to 35% of patients with locally advanced NSCLC after definitive CRT and remains the dominant cause of death in these patients.[28,29] For patients with persistent or recurrent disease after definitive chemoradiation, salvage lung resection is a feasible treatment option for select patients.[28–33] Salvage resections are associated with an increased surgical risk due to post-treatment fibrosis and decreased microvascularity, which may impede healing. Nonetheless, salvage resections are indicated for progressing or persistent primary tumors, recurrent tumors, or complications after RT (eg, lung abscess, hemoptysis, empyema, and bronchial stenosis).[28–30,32]

Multiple small retrospective series have reported the feasibility of salvage resections. Kaba and colleagues[30] reported an R0 resection of 93% in a cohort of patients who primarily underwent salvage resection for progression after definitive CRT. A systematic review of 152 patients undergoing salvage lung resection noted an R0 resection rate of 85% to 100% of patients.[31] Although such resections are technically feasible, they are challenging and are associated with significant complications. Casiraghi and colleagues[32] reported a major complication rate of 25.7%, which included 2 bronchopleural fistulas and 2 bronchovascular fistulas, which led to death from massive hemoptysis (5.7% mortality). In the Swedish Cancer Institute experience, 13% of patients experienced intraoperative vascular injuries, 1 which required a conversion from a lobectomy to pneumonectomy.[33] Pneumonectomies were a large

percentage of procedures performed for salvage lung resection within series under a systematic review and were associated with a 90-day mortality rate of 0% to 11.4%.[31] Salvage resections are complex but can be performed with acceptable morbidity and mortality rates and are associated with a survival benefit.

A systematic review demonstrated a mean OS rate of 9 months to 46 months and a 5-year survival rate of 20% to 75%. Distant metastases were the most common site of disease progression.[31] The indication for surgery may be important. Bauman and colleagues[28] found that persistent disease after definitive CRT (evidenced by persistently positive PET scans) was associated with superior median survival rates (43 months) compared with those patients who had recurrent disease (12 months). The extent of resection is also predictive of survival. The Swedish Cancer Institute reported their experience with salvage lung resection. Median OS was 24 months. However, they noted a significant ($P = .02$) difference in survival for patients who required nonextended resection (108.4 months) compared with an extended resection (8.9 months; $P = .02$).[33]

Salvage lung resection should be considered for persistent or recurrent disease after definitive CRT or for complications of RT requiring emergency intervention. As with all oncologic resections, R0 resections have improved survival, and patients require only a pulmonary resection (especially lobectomy) rather than an extended en bloc resection are likely to have the best outcome. Salvage lung resection may require pneumonectomy, highlighting the importance of a preoperative assessment of cardiopulmonary fitness.

STAGE IV OLIGOMETASTATIC DISEASE

Most NSCLC patients present at an advanced stage of diagnosis.[1] The heterogeneity of metastatic disease burden in NSCLC led the 8th edition of the AJCC TMN staging system to divide M1 into 3 separate subcategories: M1a is a separate tumor nodule(s) in a contralateral lobe, pleural or pericardial nodules, or malignant pleural or pericardial effusion; M1b is a single extrathoracic metastasis in a single organ; and M1c is multiple extrathoracic distant metastases in single or multiple organs.[5] This breakdown is due to the differing survival and treatment options for patients of a low burden of metastatic disease.

Oligometastatic state was first reported by Hellman and Weichselbaum[34] in 1995 to describe a state of low systemic burden of distant disease that may be amenable to aggressive local therapy. The oligometastatic state is less biologically aggressive, is limited to a single organ or a to a low-volume tumor load and often is stable over time. As a result, it is amenable to aggressive locally therapy.[35] In contrast to palliative treatment of metastatic NSCLC, which offers a limited survival benefit, long-term survival can be achieved with aggressive intervention with oligometastatic disease. It is important to recognize the nuances of this disease process to identify which patients may benefit from more aggressive treatment.

Brain

The brain is the most common site of distant metastasis in NSCLC. There are several randomized trials supporting aggressive treatment of oligometastatic brain metastases. Patchell and colleagues[36] demonstrated that patients with a single brain metastasis who underwent surgery and RT (versus RT alone) had improved survival (OS, 40 weeks vs 15 weeks, respectively), improved functional status, and decrease recurrence in the brain. Additional series reviews have demonstrated a survival benefit from aggressive management of intracranial metastases, Billing and colleagues[37] reviewed

28 patients with synchronous oligometastatic NSCLC who underwent craniectomy prior to pulmonary resection. The median time between the surgeries was 14 days. The total OS rates at 1 year, 2 years, and 5-years were 64.3%, 54.0%, and 21.5%, respectively. The degree of nodal disease had a significant negative impact on OS. No patient with positive nodal disease survived longer than 3 years.[37] Consequently, in patients with good performance status and no evidence of N2 disease, surgical resection of single brain metastases in combination with RT is recommended for these solitary intracranial metastases.[36,38,39] In particular, because of the risk of neurocognitive decline with whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS) is the preferred approach for patients whose brain metastasis is treated with RT. For patients whose brain lesion is causing mass effect, craniotomy and resection may be required.

patients with unresectable single brain metastases should be treated with definitive RT. RTOG 9508 examined patients with 1 to 3 newly diagnosed brain metastases treated with either whole-brain RT (WBRT) or WBRT with stereotactic radiosurgery (SRS), and demonstrated that WBRT with SRS had improved functional status, and in univariate analysis improved OS with a single brain metastasis.[38] The addition of WBRT with SRS was associated, however, with significant neurocognitive decline[40]; thus, SRS typically is utilized alone for single, surgically unresectable brain metastases or less than 3 brain metastases.[2]

In the absence of nodal disease, select patients with solitary brain metastasis are also candidates for aggressive local treatment of the primary tumor (resection or RT), which offers a survival advantage over chemotherapy alone.[41,42]

The data suggest that aggressive treatment of intracranial oligometastatic disease is associated with improved survival. Patients with intracranial oligometastatic disease that have good performance status, no evidence of N2 disease, limited disease in the chest, limited brain metastases may have a survival benefit from resection of the primary tumor and aggressive local therapy (surgery, or SRS) to the brain along with systemic therapy in the neoadjuvant or adjuvant setting.[36–38,40–42]

Adrenal

Isolated adrenal metastases are rare. The treatment paradigm mirrors that of isolated brain metastases—for patients with small volume disease burden in the chest, no evidence of N2 disease and a solitary oligometastatic site, aggressive local therapy to both the primary tumor and metastasis provide a survival benefit. Raz and colleagues[43] examined the surgical outcomes for patients who underwent adrenalectomy for metastatic NSCLC. The median survival was 19 months after adrenalectomy (5-year OS, 34%), compared with 6 months (5-year OS, 0%) in patients who were treated nonoperatively. In patients undergoing adrenalectomy, the median disease-free interval was 14 months. As compared with contralateral metastases, patients with ipsilateral adrenal metastases had significantly improved 5-year survival, and there was a trend of improved survival with lower lobe tumors, but it did not reach significance. No difference was found between synchronous versus metachronous adrenal metastases in this series.[43] A pooled analysis further examined the outcomes of surgical intervention on 98 patients with isolated adrenal metastases. Half of the patients had metachronous (49%) whereas half had synchronous (51%) adrenal metastases; metachronous metastases were associated with better prognosis.[39]

Summary of Oligometastatic Disease

For select patients with small volume node-negative disease in the chest and limited oligometastatic burden, numerous retrospective, single-institution studies and meta-analyses have demonstrated a survival benefit with aggressive local therapy to both

the primary tumor and metastatic site in combination with systemic therapy.[35,37–44] As with all complex malignancies, a thoughtful evaluation and discussion should be undertaken by a multidisciplinary team of thoracic surgeons, medical oncologists, and radiation oncologists.

LUNG RESECTION AND IMMUNOTHERAPY

The landmark PACIFIC Trial demonstrated that durvalumab, a PD-L1 (programmed death-ligand 1) inhibitor, administered after definitive CRT for unresectable stage III NSCLC improved OS and PFS compared with placebo.[45] Based on these findings, the FDA approved durvalumab in 2017 for consolidation therapy for patients with no progression of disease after definitive CRT. Although durvalumab is approved for unresectable disease, there are trials examining immunotherapies on potentially resectable lung cancers that potentially will have an impact on how advanced, potentially resectable NSCLCs are managed in the future.

Evaluating neoadjuvant administration of nivolumab, a PD-1 (programmed cell death protein 1) inhibitor, in early stage (I–IIIA) NSCLC, investigators demonstrated that immunotherapy did not delay surgery and was associated with a 95% R0 resection; 45% had a major pathologic response (defined as no more than 10% viable tumor cells within the specimen), independent of PD-L1 status.[46] Bott and colleagues[47] reported their experience of pulmonary resection after administration of neoadjuvant nivolumab; 75% of the patients underwent lobectomy, and 54% of patients undergoing a minimally invasive approach (VATS or robotic) were converted to thoracotomy. Most of these patients required conversion to an open approach due to dense adhesions and fibrosis from immunotherapy. Importantly, neoadjuvant immunotherapy was associated with an acceptable morbidity and mortality rate. There were no reported mortalities, and the most common postoperative morbidity was atrial arrhythmia.[47] As experience with immunotherapy evolves through ongoing clinical trials, management of locally advanced and metastatic NSCLC may change.

SUMMARY

Locally advanced NSCLC is a complex, heterogeneous disease process that requires a thoughtful, multidisciplinary approach. In highly select patients with an excellent performance status and the absence of N2 disease, surgical resection of locally advanced and limited oligometastatic NSCLC offers a survival benefit when combined with a multimodal treatment strategy. With advancements in and the increasing application of immunotherapy, the multidisciplinary perspective of locally advanced NSCLC will continue to evolve.

DISCLOSURE

Dr S.S. Groth is a proctor and speaker for Intuitive Surgical Inc. (Sunnyvale, California).

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