Despite recent therapeutic advances, lung cancer continues to be one of the leading causes of cancer-related mortality. Of the various histologic subtypes, non–small-cell lung cancer (NSCLC) is the most common—accounting for approximately 85% of all lung cancers—and will be the focus of this article. In general, the treatment of lung cancer may include surgery, radiation therapy, systemic therapy (eg, chemotherapy with or without targeted therapy), or a combination of the above. Surgery continues to offer the best chance of long-term cure. The initial treatment of stage I and II NSCLC usually entails surgical resection, whereas stage IV disease is primarily treated with systemic agents, in light of the lack of curative potential with surgery and/or radiation therapy alone. It is locally advanced NSCLC, including stage IIIA and IIIB disease, that continues to pose a therapeutic dilemma, given its heterogeneous nature.

TABLE 1

| TNM Descriptions Based on 1997 Staging System for Lung Cancer |

Despite recent therapeutic advances, lung cancer continues to be one of the leading causes of cancer-related mortality. Of the various histologic subtypes, non–small-cell lung cancer (NSCLC) is the most common—accounting for approximately 85% of all lung cancers—and will be the focus of this article. In general, the treatment of lung cancer may include surgery, radiation therapy, systemic therapy (eg, chemotherapy with or without targeted therapy), or a combination of the above. Surgery continues to offer the best chance of long-term cure. The initial treatment of stage I and II NSCLC usually entails surgical resection, whereas stage IV disease is primarily treated with systemic agents, in light of the lack of curative potential with surgery and/or radiation therapy alone. It is locally advanced NSCLC, including stage IIIA and IIIB disease, that continues to pose a therapeutic dilemma, given its heterogeneous nature.

The tumor-node-metastasis (TNM) staging guidelines for NSCLC established in 1997 (see Table 1)[1] staged IIIA disease as encompassing tumors ranging from T3, N1 to T3, N2, whereas stage IIIB encompassed tumors that were more locally advanced, ranging from T4, N0 to T4, N2/N3 (Table 2). The distinction between the two subsets of stage III disease is important, as surgical resection can be used for stage IIIA disease, whereas stage IIIB disease is usually initially addressed.
As of the fall of 2009, a new lung cancer staging system has been in place (Table 3).[2] While the N description has not changed, some modifications have been made in the T and M categories. The data presented in this paper are based on the old lung cancer staging system; however, the recent changes do not affect the information and recommendations provided herein. Underlying the decision regarding any treatment planning is consideration of the patient’s performance status, comorbid medical conditions, age, cardiopulmonary status, and preferences.

The various therapeutic options available for the initial treatment of locally advanced NSCLC include surgery, neoadjuvant chemotherapy or concurrent chemoradiation followed by surgery, and definitive concurrent chemoradiation. Each option will be discussed separately.

Treatment Options

Surgery

As noted above, surgery is an important consideration for any patient diagnosed with stage I/II NSCLC. It is also an important consideration for stage III NSCLC. However, the extent of local disease as well as the extent and location of nodal involvement might preclude surgery as an initial treatment option. The bulkiness of nodal involvement is an important distinction for operable disease. Patients with bulky stage IIIA/IIIB disease are usually considered inoperable, whereas those with nonbulky disease might be surgical candidates. Bulky disease is defined in various ways, but most often is described as lymph nodes > 2 cm in the short-axis diameter on chest computed tomography, disease in a group of lymph nodes, or involvement of more than two lymph node stations. In general, surgery may be indicated as initial treatment for T3-4, N0-1 disease, including cases where satellite nodules are present within the same lobe or ipsilateral lung.
Locally advanced stage IIIA/IIIB non–small-cell lung cancer comprises a heterogeneous group of diseases with multiple treatment options. Treatment is variable for each patient. The role of surgery in patients with locally advanced disease, especially N2 disease, needs to be better defined.

T3, N0-1 tumors usually invade the chest wall or are within 2 cm of the carina, and are not associated with mediastinal lymph node involvement. Resection with negative margins is possible for these tumors despite surgeries that are usually complex. There is no clear evidence of a role for neoadjuvant chemotherapy in this setting.

The Neoadjuvant/Adjuvant Taxol (paclitaxel) Carboplatin Hope (NATCH) trial showed feasibility and tolerability of neoadjuvant chemotherapy for early-stage NSCLC including T3, N1 disease. In this phase III trial, 624 patients with stage I, II, or T3, N1 disease were enrolled into three arms: (1) 212 received surgery only, (2) 201 received three cycles of preoperative carboplatin and paclitaxel followed by surgery, and (3) 211 underwent surgery with three cycles of adjuvant carboplatin and paclitaxel planned. The initial results showed a possible improvement in overall survival in patients with T3, N1 disease who received neoadjuvant chemotherapy, compared to those who received adjuvant therapy vs surgery alone. However, a more recent presentation at the 2009 annual meeting of the American Society of Clinical Oncology showed no difference in disease-free survival among the three arms. In addition, there was no difference in overall survival at 5 years. Most current practices recommend resection as first-line treatment in T3, N1 disease. Adjuvant chemotherapy is also recommended.

Surgery also has a role in the initial treatment of T3-4, N0-1 disease due to satellite lesions within the same lobe of the primary tumor or ipsilateral lung. A retrospective analysis by Port et al indicated that patients with satellite lesions within the same lobe of the primary tumor have a 5-year survival rate resembling that of patients with stage IB or II disease after resection. The 5-year survival for all patients with a resected intralobar satellite lesion was 47.6%. Thus, surgery should be considered appropriate initial treatment followed by adjuvant chemotherapy for patients with such disease.

Chemotherapy

- Induction chemotherapy followed by surgery
- Concurrent chemoradiation followed by surgery
- Definitive concurrent chemoradiation
- Definitive radiation

Neoadjuvant chemotherapy is an important consideration for any patient presenting with locally advanced NSCLC. Survival is poor in patients with N2 disease who undergo surgery alone, as they have a high chance of recurrence and distant relapse following resection. The benefits of neoadjuvant chemotherapy include better patient tolerability of therapy, the potential for treating micrometastatic disease, and decreased tumor size to improve potential surgical resection. Neoadjuvant chemotherapy was first studied as a therapeutic option beginning in the late 1980s, when the data regarding its efficacy were mixed. Trials in the early 1990s, including those of Rosell et al,[6,7] Pass et al,[8] and Roth et al,[9] showed an improvement in overall survival in patients with stage III disease receiving neoadjuvant chemotherapy compared to surgery alone. Depierre et al[10] conducted a larger trial than the earlier studies and found no survival advantage from neoadjuvant chemotherapy. The chemotherapy used in most of these trials were older regimens, which have since been replaced. More recent trials[11,12] have used gemcitabine (Gemzar)- and platinum-based therapy in the preoperative setting and have found not only a good tolerability of the therapy, but also a benefit to neoadjuvant therapy.

The Bimodality Lung Oncology Team (BLOT) trial[13] assessed the feasibility of perioperative paclitaxel and carboplatin in patients with early-stage IB–IIIA NSCLC. In this phase II trial, 94 patients were enrolled with an intention to receive two cycles of neoadjuvant chemotherapy with paclitaxel and carboplatin, followed by surgery and three additional adjuvant cycles of chemotherapy. After induction therapy, 53 of 94 patients had a significant response and 81 patients underwent complete surgical resection. A total of 90 patients successfully received the two cycles of neoadjuvant therapy;
however, only 45% received adjuvant therapy.

Based on the results of the BLOT study, the Southwest Oncology Group (SWOG) S9900[14] was a phase III trial designed to compare neoadjuvant chemotherapy with surgery alone. A total of 354 patients were enrolled in the study. The neoadjuvant group received three cycles of carboplatin and paclitaxel, whereas the other arm underwent surgery alone. The trial was closed early since adjuvant therapy became the standard of care. However, of the 133 patients treated with neoadjuvant therapy, 95% were able to achieve complete resection of their tumor, compared with only 88% of patients in the surgery-alone group. Overall survival was 47 months with neoadjuvant therapy, compared to 40 months for surgery alone. Progression-free survival was 31 months for neoadjuvant therapy, compared to 20 months for surgery alone. This trial showed the feasibility and tolerability of neoadjuvant chemotherapy, with improvement in overall survival.

Neoadjuvant chemotherapy is advisable in patients with disease minimally involving the mediastinal lymph nodes or a mass that is locally invasive where a possible decrease in size will make it amenable to resection.

Concurrent Chemoradiation Therapy Followed by Surgery

Case Report: A Woman With a Pulmonary Mass and Lymphadenopathy

Ms. W. is a 48-year-old previous smoker who began complaining of cough and shortness of breath, for which she was initially treated with antibiotics. Given the persistence of her symptoms, she eventually underwent a chest computed tomography (CT), which was notable for a 5.2 × 5.7 cm mass involving the superior segment of the right lower lobe. There was also evidence of mediastinal lymphadenopathy, with the largest lymph node measuring 1.8 cm. A positron-emission tomography (PET) scan indicated uptake at the right lower lobe mass and the mediastinal lymph nodes. Biopsies of both the mass and a mediastinal lymph node were consistent with adenocarcinoma of the lung.

The woman underwent two cycles of neoadjuvant chemotherapy with cisplatin and pemetrexed, with the hope of undergoing a surgical resection. Repeat chest CT showed decrease in size of the mass to 4.6 × 3.7 × 5 cm; however, the mediastinal lymph nodes were still slightly enlarged.

What are the patient’s options at this point?

(1) Proceed with surgery.
(2) Continue with chemotherapy in hopes of shrinking the mass further.
(3) Begin definitive chemoradiation, given the extent of the mass.
(4) Concurrent chemoradiation to 45 Gy followed by surgery.

After presenting her case to a multidisciplinary thoracic tumor conference, the patient went on to receive concurrent chemoradiation with a re-evaluation after 45 Gy radiation therapy. She was noted to have a significant response on chest CT with resolution of the mediastinal lymphadenopathy. She was able to undergo a successful lobectomy. Pathology showed no evidence of metastatic disease to the mediastinal lymph nodes and only microscopic disease at her primary site.

Ms. W. went on to receive two cycles of adjuvant chemotherapy with carboplatin and pemetrexed. She has been in complete remission for the past 2 years.

This case illustrates an aggressive approach to the treatment of a stage IIIA (T2, N2) non–small-cell lung cancer in a young patient who had no medical comorbidities, a good performance status, and an otherwise good pulmonary function. Various modalities were used in a multidisciplinary setting in order to obtain the best possible outcome.

Preoperative concurrent chemoradiation therapy is another important consideration for locally advanced NSCLC, especially in cases of bulky primary disease and with superior sulcus tumors. The intent of this preoperative therapy in cases of bulky disease is to decrease the disease burden and eradicate mediastinal lymph node involvement to enable a surgical resection. It is also an important consideration in patients with superior sulcus tumors, where decreasing the disease burden enables a more successful surgical resection.

The SWOG 8805 trial[15] was a phase II study looking at the concurrent use of chemotherapy and radiation followed by surgery in locally advanced NSCLC. Of the 126 eligible patients, 75 had stage IIIA disease with N2 involvement and 51 had stage IIIB disease. Patients underwent induction
chemotherapy consisting of two cycles of cisplatin and etoposide with concurrent radiation to 45 Gy. Patients with improved or stable disease after induction went on to surgical resection, whereas those with persistent unresectable disease continued to receive further chemotherapy with radiation. The overall 3-year survival rate was 26% with the trimodality approach. Of those who underwent surgery, the 3-year survival rate was 44% in patients whose mediastinal lymph node disease was eradicated by induction chemoradiotherapy, compared to 18% who had persistent mediastinal disease.

The design of SWOG 8805 was based on a study by Friess et al,[16] where patients with locally advanced NSCLC underwent four 1-month cycles of cisplatin and etoposide along with concurrent radiotherapy to 60 Gy, achieving a median survival of 16 months with a 30% 2-year survival rate. As seen in the SWOG 8805 study, the addition of surgery to induction chemoradiotherapy does provide a survival benefit, with improved overall 2- and 3-year survival rates. However, the benefit is derived mostly in patients who do not have mediastinal lymph node disease following induction therapy.

In the Intergroup 0139 study,[17] 396 eligible patients with stage IIIA (pN2) NSCLC were randomized to two arms, one receiving induction cisplatin/etoposide with concurrent radiation to 45 Gy followed by surgery, then two more cycles of cisplatin/etoposide; and the other receiving cisplatin/etoposide with radiotherapy to 61 Gy, followed by two more cycles of chemotherapy. Progression-free survival was superior with the trimodality approach (12.8 vs 10.5 months, \( P = .017 \)) compared to chemoradiotherapy alone. However, there was only a marginal benefit in the 5-year survival rate with the trimodality approach (27.2% vs 20.3%). Similar to the SWOG 8805 study, the pN0 at the time of surgery predicted long-term survival. The 5-year survival rate was 41% in patients with pN0 disease at the time of surgery, compared to 24% in those with residual mediastinal disease.

One of the most notable findings of the Intergroup 0139 study was the increase in mortality associated with pneumonectomy following induction chemoradiotherapy. Approximately 7.9% of patients in the trimodality arm had treatment-related deaths, compared to 2.1% in the chemoradiotherapy-only arm. Approximately 5% of the deaths in the trimodality arm were within the 30-day postoperative period, and 9 of the 10 deaths were related to pneumonectomy. These findings indicated an increased risk and mortality with pneumonectomy following induction chemoradiotherapy. When evaluating patients who underwent pneumonectomy vs lobectomy in the study, those in whom a lobectomy was performed did better. At 5 years, 36% of patients who had undergone lobectomy were alive, compared to 22% of those who underwent pneumonectomy. Other trials[18,19] have also noted increased mortality with pneumonectomy when followed by chemoradiotherapy.

On the other hand, Gaissert et al[20] reported that pneumonectomy is a feasible option following induction chemoradiotherapy in carefully selected patients. In a retrospective study, they reviewed 183 patients who had undergone pneumonectomy, 46 of whom had received concurrent neoadjuvant chemoradiation and 137 who had only undergone a resection. The 46 patients had disease ranging from stage IIB to IV. However, they were also younger and had better pulmonary and cardiac function. Hospital mortality was 4.3% after preoperative therapy and 6.6% after resection only. They concluded that induction therapy with chemoradiation did not increase operative mortality after pneumonectomy in carefully selected patients.

Patients with superior sulcus tumors may also benefit from concurrent chemoradiation. These tumors usually arise in the apex of the lung and may invade the brachial plexus, second or third rib, the subclavian vessels, the stellate ganglion, and the adjacent vertebral bodies. Traditionally, these tumors were treated with radiation followed by surgery,[21,22] which produced a 5-year survival rate of around 30%. The phase II SWOG 9416 trial[23] studied the use of concurrent chemoradiation followed by surgery. A total of 110 patients with a T3-4, N0-1 superior sulcus tumor received two cycles of cisplatin and etoposide concurrently with radiation to 45Gy. Patients with stable or responding disease then underwent resection followed by two more cycles of chemotherapy. The 5-year survival rate was 44% for all patients and 54% after complete resection. This trial showed that a combined-modality approach was feasible, with improvement in overall survival, in patients with superior sulcus tumors.

Induction chemoradiotherapy may be a good option for selected patients with bulky nodal disease, particularly N2 disease. Patients who have a dramatic response to combined-modality therapy and are able to tolerate a surgical resection may benefit from surgery. The risk of pneumonectomy after concurrent chemoradiotherapy needs to be considered prior to surgical planning. Concurrent chemoradiation is also indicated in patients with superior sulcus tumors, where a combined-modality approach is feasible and allows for a better surgical outcome.
Definitive Concurrent Chemoradiation Therapy

As compared to induction concurrent chemoradiation therapy, definitive concurrent chemoradiation is given with the intention of being the sole combined-modality treatment, without a surgical option. The dose of radiation therapy in this setting is usually > 60 Gy. These patients are usually either unable to withstand surgery due to poor lung function or too many comorbid conditions, or have disease that is too advanced to enable a resection. Radiation alone was the sole treatment modality used in the 1980s. Earlier studies initially used sequential chemotherapies followed by radiation compared to radiation alone, showing a survival advantage with the combination. Subsequent studies demonstrated a survival benefit for concurrent rather than sequential use of chemotherapy and radiation.

REFERENCE GUIDE

Therapeutic Agents

- Carboplatin
- Cisplatin
- Etoposide
- Gemcitabine (Gemzar)
- Mitomycin
- Paclitaxel
- Vinblastine
- Vindesine

Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.

The Cancer and Leukemia Group B (CALGB) 8433 trial[24] was one of the first studies to show a survival advantage for chemotherapy and radiation compared to radiation alone. The trial randomized 155 patients with stage III NSCLC to two groups: 78 patients were randomized to receive cisplatin and vinblastine followed by radiation at 60 Gy, and 77 patients were randomized to receive 60-Gy radiation only. The median survival was 13.7 months with chemotherapy and radiation used sequentially, compared to 9.6 months for radiation alone ($P = .012$).

An Intergroup trial[25] also studied the addition of chemotherapy to radiation and confirmed the results of the CALGB trial. Sause et al randomized 458 patients with stage II, IIIA, or IIIB disease to receive 2 months of cisplatin/vinblastine followed by 60 Gy of radiation, or hyperfractionated radiation delivered twice daily for a total of 69.6 Gy, or once-daily radiation with 60 Gy. Overall survival was statistically superior for the patients who received chemotherapy followed by radiation. The median survival was 13.2 months for chemotherapy plus radiation vs 12 months for...
hyperfractionated radiation vs 11.4 months for standard radiation. This trial also proved the benefit of adding chemotherapy to radiation.

Subsequent trials studied the efficacy of using concurrent chemotherapy and radiation as compared to using the sequential method. In a Japanese phase III study,[26] 320 patients with unresectable stage III disease were randomized to receive either two cycles of cisplatin, vindesine, and mitomycin concurrently with split-course thoracic radiation to 56 Gy, or two cycles of cisplatin, vindesine, and mitomycin followed by a single course of radiation to 56 Gy. The use of concurrent chemotherapy and radiation produced a longer median survival compared to the sequential arm (16.5 vs 13.3 months, \( P = 0.03998 \)). The 2-, 3-, 4-, and 5-year survival rates were better in the concurrent group than in the sequential group (34.6%, 22.3%, 16.9%, and 15.8% vs 27.4%, 14.7%, 10.1%, and 8.9%, respectively). This study also demonstrated an increased response rate with concurrent use of chemotherapy and radiation compared to sequential use in patients with unresectable stage III NSCLC.

Induction chemotherapy followed by chemoradiotherapy was compared to chemoradiotherapy alone in the phase III CALGB 39801 trial.[27] A total of 366 patients were randomly assigned to receive either immediate concurrent chemoradiotherapy with weekly carboplatin and paclitaxel during 66 Gy of chest radiation, or two cycles of carboplatin and paclitaxel every 21 days followed by the identical chemoradiotherapy regimen. Survival differences were not statistically significant, with a median survival of 12 months for those who received immediate chemoradiation vs 14 months for those who received induction chemotherapy followed by chemoradiation. This trial demonstrated that the addition of induction chemotherapy prior to concurrent chemoradiation did not provide a survival benefit over concurrent therapy alone. In addition, it showed that induction chemotherapy followed by chemoradiation increased the chance of neutropenia and overall chemotherapy-related toxicity. The Radiation Therapy Oncology Group (RTOG) 9410 trial[28] was a three-armed study that randomized 610 patients with unresectable stage II and III disease to receive (1) sequential chemotherapy with cisplatin and vinblastine followed by 60 Gy of radiotherapy, (2) concurrent cisplatin and vinblastine with radiation to 60 Gy, or (3) concurrent cisplatin and oral etoposide with hyperfractionated radiation delivered twice daily to a total dose of 69.6 Gy. The acute grade 3/4 nonhematologic toxicity rates were higher for the concurrent therapy arms than for the sequential therapy arm, but late toxicity rates were similar. The median survival was 17 months for concurrent therapy with daily radiotherapy, 15.2 months for concurrent therapy with hyperfractionated radiotherapy, and 14.6 months for sequential therapy, indicating a benefit in median survival for the use of concurrent chemoradiotherapy with daily radiation. The 4-year overall survival data showed similar results: 21% for concurrent therapy with daily radiotherapy, 17% for concurrent therapy with hyperfractionated radiotherapy, and 12% for sequential therapy.

Concurrent chemoradiotherapy is a good option for patients who have unresectable NSCLC without a possibility of resection even after concurrent therapy. The risks involved with the concurrent therapy are increased side effects including esophagitis and pneumonitis. It is important to note that even though concurrent chemoradiotherapy is a sensible option for patients with locally advanced unresectable NSCLC, long-term survival continues to be poor.

**Definitive Radiation**

| Treatment of patients with locally advanced NSCLC requires a combined-modality approach involving medical, radiation, and thoracic surgical oncologists as well as radiologists, pulmonologists, and pathologists. |
| Surgery is an initial option for patients with T3, N1 disease or for those with T3-4, N0-1 disease due to satellite lesions in the same lobe as the primary tumor or ipsilateral lung. |
| Neoadjuvant chemotherapy should be considered in patients with minimal mediastinal nodal involvement or with a mass, where reduction will lead to a surgical resection. |
| For bulky nodal disease, neoadjuvant concurrent chemoradiation should be considered, and patients should be restaged for surgical resection once they complete radiotherapy of 45 Gy. |
Definitive radiation is the final treatment option that is available for patients with locally advanced NSCLC. As mentioned previously, this single modality was the treatment of choice prior to trials that proved the benefit of using both chemotherapy and radiation. Definitive radiation should be offered to patients with locally advanced or unresectable stage III disease and a poor performance status who are unable to tolerate chemotherapy or surgery. The benefit of using radiation under these circumstances would be for palliation and local tumor control. Long-term survival with definitive radiation treatment continues to be poor, with a 5-year survival rate of about 5%[29-31] and patterns of local as well as distant relapse.

The current standard dose of radiation is 60 Gy in 30 daily fractions, after a phase III trial published in 1986[31] evaluated the use of various doses and their associated outcomes. Radiation doses of 40, 50, or 60 Gy were used in 2-Gy daily fractions. A radiation dose of 60 Gy was found to produce the best local control; however, survival was similar in all groups.

Hyperfractionated, accelerated radiation has also been studied, with evidence supporting a marginal benefit for this strategy compared to standard radiation. However, this practice has not been widely adopted, and daily radiation continues to be the standard.[32-35]

Definitive radiation frequently offers palliative support for patients with symptoms related to their tumor and provides some degree of local control. However, it should be offered as an initial treatment option only to patients who are unable to tolerate chemotherapy or surgery, given a median survival of only about 10 months.

Summary

Locally advanced stage III NSCLC is a complex and heterogeneous group of diseases that require a combined-modality approach for optimal treatment.[36-38] The patient’s preferences, age, comorbid conditions, and functional status all need to be taken into consideration before any type of therapy is offered.

Recent studies have indicated histologic variability with regard to chemotherapeutic response in lung cancer patients.[39] Also, novel targeted agents have opened up new possibilities in terms of therapeutic options. Ongoing studies based on these developments and using state-of-the-art methods of radiation and surgery might lead to new treatment strategies, which, in turn, could produce an improved overall survival in patients with this complex disease.

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