

LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

Section Editor: Mark A. Socinski, MD

Optimal Treatment of Unresectable Stage III Non–Small Cell Lung Cancer



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H&O How common is stage III NSCLC?

JB Stage III non–small cell lung cancer (NSCLC) is defined by involved lymph nodes in the mediastinum (Table). Previously, stage III NSCLC represented approximately 40% of lung cancer patients. With the advent of positron emission tomography (PET) scanning, however, that percentage has dropped to approximately 30% because PET can find small distant metastases in some patients that are not identifiable on computed tomography (CT) imaging and that indicate stage IV disease. Stage IV is the most common stage. Among the remaining patients, most have stage I. It is unusual to find stage II NSCLC in the nonoperative setting. The stage II patient subgroup is typically identified at the time of resection.

H&O What is the standard treatment for patients with stage III NSCLC?

JB The standard treatment is concurrent combination chemotherapy and radiation, with or without surgery. Whether a patient will undergo surgery is based on the surgeon's evaluation. Concurrent combination chemotherapy and radiation therapy followed by surgery is usually reserved for patients who are younger and healthier, and who have close to normal lung function and disease that is limited to resectable status, which tends to mean only 1 lymph node station is involved. These patients can tolerate removal of a lobe of the lung or the whole lung without much difficulty in terms of their oxygenation status.

H&O What is the standard treatment for patients with unresectable stage III NSCLC?

JB The standard treatment is concurrent combination chemotherapy and radiation therapy. That approach is used worldwide, although the chemotherapeutic agents will vary. In the United States, the most common chemotherapy regimen is carboplatin and paclitaxel given weekly. The radiation dose is 60 Gy given in roughly 30 fractions. After completion of the radiation, patients usually receive another 2 to 3 cycles of full-dose consolidation chemotherapy.

H&O What types of treatment challenges do these patients present?

JB The combination of concurrent chemotherapy and radiation therapy is difficult for patients to tolerate. The main challenge is how to manage the adverse events, particularly esophagitis and pneumonitis. Patients can also develop fatigue. Chemotherapy can cause anemia and leukopenia (eg, neutropenia), as well as nausea.

The location of the tumor can lead to other challenges. For example, a tumor situated next to the esophagus can cause esophagitis. Radiation pneumonitis is more common when the tumors are located in the lower lobe of the lung than in the upper lobe. A tumor near the brachial plexus increases the risk of brachial plexopathy.

There are also social challenges. Patients may not have access to care. Their diagnosis may be delayed. They may have a difficult time getting to and from their doctors' appointments. Sometimes there are obstacles

Table. Stages of NSCLC

Occult stage	Cancer cells are found in sputum, but no tumor can be found in the lung by imaging tests or bronchoscopy, or the tumor is too small to be checked
Stage 0	Cancer at this stage is also known as carcinoma in situ. The cancer is tiny and has not spread into deeper lung tissues or outside the lungs
Stage I	Cancer may be present in the underlying lung tissues, but the lymph nodes are unaffected
Stage II	The cancer may have spread to the nearby lymph nodes or into the chest wall
Stage III	The cancer is spreading from the lungs to the lymph nodes or to nearby structures and organs, such as the heart, trachea, and esophagus
Stage IV	The cancer has metastasized throughout the body and may now affect the liver, bones, or brain

NSCLC, non–small cell lung cancer.

related to health insurance. For example, an insurance company might not permit the use of intensity-modulated radiation therapy (IMRT).

H&O What are the aims of NRG Oncology?

JB NRG Oncology is a research organization that brings together 3 cooperative groups: the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG). The organization is funded through the National Cancer Institute and runs clinical trials with the aim of improving survival and side effects in all types of cancer. I am the chair of the Lung Cancer Committee.

H&O What are the most notable findings in trials from the NRG Lung Cancer Committee?

JB Trials by the Lung Cancer Committee have made several important discoveries. They found that concurrent chemoradiation for stage III disease is superior to sequential chemotherapy and radiation therapy. Once-daily radiation therapy is just as effective and less toxic than twice-daily radiation therapy when given with concurrent chemotherapy. Using a CT scan and PET scan to restrict radiotherapy to the tumor bed itself, while avoiding uninvolved regions, is just as effective and less

toxic than treating larger volumes. Most recently, we published results from a trial and secondary analyses showing that a radiation dose of 60 Gy, using IMRT, is probably the best option for patients with stage III unresectable lung cancer.

H&O What is known about high-dose vs low-dose radiotherapy?

JB The phase 3, randomized RTOG 0617 trial evaluated low-dose radiotherapy (60 Gy) vs high-dose radiotherapy (74 Gy), with or without cetuximab (Erbix, Lilly), in patients with stage III unresectable NSCLC. The median overall survival was 28.7 months in the low-dose radiotherapy arm vs 20.3 months in the high-dose arm ($P=.004$). The median overall survival in patients who received cetuximab was 25.0 months, vs 24.0 months for those who did not ($P=.29$). Local regional tumor control, a secondary endpoint, was 60% to 70%, depending on the treatment arm. At 2 years, 58% of patients in the study were alive.

The conclusion from the trial is that low-dose radiation is at least as good, if not better, than high-dose radiation for the standard patient when using concurrent chemotherapy. Now, that goes against common thought. Usually, it would appear that a higher amount of radiation would correspond to a greater tumoricidal effect. The RTOG 0617 trial, however, showed that normal tissues, such as the heart, esophagus, and lung, also received that high dose, which was not beneficial. Therefore, the 60-Gy treatment performed better than the 74-Gy treatment, specifically with respect to the heart dose. Multivariate analyses of the primary study and subsequent secondary analyses showed that higher heart doses result in poorer survival, and that this effect is independent of tumor size or location.

H&O Were these results surprising?

JB The standard-dose arm did better than expected, most likely because of the use of PET scans for disease staging. PET provides more sensitive disease staging than conventional staging techniques, and is more likely to assign patients to a higher tumor stage. This phenomenon is known as stage migration, and it may offer the perception that an intervention has improved stage-specific survival when in fact it has not. Previous trials conducted by the RTOG cooperative group in this setting did not include PET scans as a routine staging procedure, and most likely included patients with metastatic disease. Patients enrolled in RTOG 0617 were PET-negative for metastatic disease, and as a result, the survival was higher.

H&O Are there settings in which high-dose radiotherapy might still have a role?

JB There are several settings in which high-dose radiotherapy may be beneficial. High-dose therapy with stereotactic body radiation therapy (SBRT) can be effective. Local control rates for tumors up to 5 cm treated with SBRT exceed 90%. SBRT differs from standard radiotherapy in that it can better exclude normal tissues by focusing the dose on a single cancer nodule.

Several methods are being evaluated in clinical trials to increase the radiation dose. The ongoing RTOG 1106 trial is using a radiation boost. Patients receive 4 weeks of radiation therapy and then undergo a PET/CT scan. An additional 2 weeks of radiation therapy are then directed at the residual disease appearing on the scan. The radiotherapy dose can go as high as 80 Gy, depending on the volume. An alternative idea is that a course of high-dose radiation could be delivered as an SBRT boost to reduce volumes that remain after an earlier course of therapy. This idea is being tested in early-phase clinical trials. Another approach to increase the dose is to use proton beam radiation therapy. Protons avoid normal tissues better than x-rays do. Proton beam therapy reduces normal tissue doses compared with IMRT or conventional radiation therapy. RTOG 1308 is a large, ongoing phase 3 trial testing protons vs IMRT in stage III NSCLC.

H&O What are some other areas of research in unresectable stage III NSCLC?

JB Molecular testing is being used to identify mutations or translocations that drive all types of cancers. Lung cancer has been a leading area of investigation in this area. Targeted therapies are directed toward patients with epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations. We are trying to enroll patients with these mutations into clinical trials evaluating targeted therapies in the stage III setting.

Other ongoing trials are testing immunotherapies. In the past 2 years, immunotherapies have started to have an important impact in lung cancer management.

H&O Do you have any recommendations for the treatment of patients with unresectable stage III NSCLC?

JB The standard of care for these patients is 60 Gy of radiation with concurrent chemotherapy. Based on the RTOG 0617 results, the radiation should be administered via IMRT. The target should be the tumor as seen on the CT scan with contrast and the PET/CT scan. Patients with stage III lung cancer should be tested for known mutations. They should receive concurrent chemotherapy. Options include weekly carboplatin/paclitaxel, carboplatin/pemetrexed (Alimta, Lilly), and cisplatin/pemetrexed. The basic principles are to deliver at least 60 Gy to 95% of the target volume, while minimizing the dose to the lung, heart, esophagus, and spinal cord. In general, these dose limitations consist of keeping the total lung V20 below 35%, the heart V50 below 25%, the mean esophagus dose below 34 Gy, and the spinal cord below 50 Gy to a maximum point.

Disclosure

Dr Bradley has received research funding from ViewRay, Inc, and from Mevion Medical Systems, Inc. He serves on the scientific advisory boards of ViewRay, Inc, and Varian Proton Therapy.

Suggested Readings

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