MULTIMODALITY THERAPY FOR STAGE III NSCLC: CONTROVERSIES, ADVANCES, AND EVOLVING APPROACHES

Oliver Gautschi, MD,* Zelanna Goldberg, MD,† Royce Calhoun, MD,‡ and David R. Gandara, MD§

ABSTRACT

Stage III non-small cell lung cancer (NSCLC) comprises a very heterogeneous group of patients with regard to tumor extent, prognosis, and treatment options. Although combined-modality therapy (chemotherapy ± radiotherapy ± surgery) is appropriate in most patient subsets, specific recommendations vary considerably. For example, concurrent chemoradiotherapy paradigms have recently emerged as a standard-of-care for selected patients with unresectable stage III disease (ie, those patients with good performance status, adequate pulmonary function, and low comorbidities). It is important to realize that selection criteria such as these are appropriate in many of the clinical situations described in this article to maximize benefit and reduce the risk of unacceptable toxicities. Of note, this approach does not apply to those patients with stage IIIB disease defined by malignant pleural effusion because this T4 designation characterizes a group of patients incurable with combined-modality therapy. There is no consensus on the treatment of patients with resectable stage III disease. Although surgery is commonly performed in many patient subsets, its role is currently being redefined because of the positive results of adjuvant postoperative chemotherapy and improved efficacy with chemoradiotherapy alone. Novel molecular targeted agents have now shown activity in advanced stage disease, and it is anticipated that ongoing studies will define a role for these agents in the combined-modality therapy of earlier stages. Although the evolution of multimodality therapy in recent years has improved the outlook for patients with locally advanced NSCLC, at present only a minority achieve long-term survival. Further advances will depend on carefully planned and conducted clinical research studies, incorporating the skills and expertise of a wide range of lung cancer specialists, including clinical investigators and basic science collaborators.


Epidemiology, Diagnosis, and Staging

Lung cancer is the most common cause of cancer mortality in men and women in the United States, and is responsible for an estimated 1 million deaths per year worldwide. Approximately 80% of lung cancers are of the non-small cell (NSCLC) type, which accounts for more than 130 000 deaths per year in the United States alone. Although patterns of smoking prevalence in the United States have indicated that lung cancer rates will decrease over the next 2 decades and will then level off, a recent trend toward increasing rates of adenocarcinoma and bronchioloalveolar cancer in never-smokers is alarming, especially since a sizeable proportion are younger never-smoking women.
More than 33% of patients with NSCLC present with locally advanced (stage III) disease at diagnosis. Stage III is subdivided into IIIA and IIIB, and includes T3N1M0, T4N0-3M0, and T1-4N2-3M0 (Table 1). This represents a diverse group with regard to anatomical extent of the tumor and nodal metastases, prognosis, and treatment options. As anatomic and functional imaging techniques have improved, the ability to detect and define the extent of NSCLC has been dramatically altered. This, together with refined treatment options for different stage III patient subsets, has revealed limitations in the current international staging system, only some of which are outlined here. Inclusion of T4 (malignant pleural effusion) as a stage III subset is problematic because these patients have a prognosis much more closely resembling stage IV, and are treated similarly with systemic therapy alone. Additionally, patients with T3 tumors invading the chest wall are reported to have a better prognosis than T3 patients with central localization. The distinction between nodal N1 and N2 stations can also be difficult, as demonstrated in Figure 1. As a result, the current International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM-based staging classification for stage III NSCLC is undergoing revision in a multiorganizational project developed through the International Association for the Study of Lung Cancer (IASLC).

As the management of patients with stage III NSCLC subsets becomes increasingly complex, selecting the best sequence of diagnostic studies to avoid delays or unnecessary invasive procedures is ever more critical. A multidisciplinary approach to staging and management incorporating input from experts in radiology, pulmonology, thoracic surgery, medical oncology, radiation oncology, and pathology is essential. In support of this view are data showing that patients with NSCLC have a better prognosis when managed by a multidisciplinary team. Thus, referral to an experienced thoracic oncology team has been advocated for any patient with suspected or known lung cancer.

In addition to the staging issues discussed above, the clinical presentation of locally advanced NSCLC is heterogeneous. Associated symptoms and clinical findings of stage III disease may include cough, hoarseness, hemoptysis, dyspnea, chest pain, finger clubbing, and fatigue, among others. Careful physical examination may disclose supraclavicular lymphadenopathy consistent with N3 disease, or even findings suggestive of metastasis (M1). Clinical features portending a poor

<table>
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<th>Table 1. Clinically Distinct Subgroups of Stage III NSCLC</th>
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<tr>
<td>Stage IIIA</td>
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<tr>
<td>T3N1</td>
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<td>T1–3N2</td>
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<tr>
<td>Stage IIIB</td>
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<td>T4N0–2</td>
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<td>T1–4N3</td>
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Subgroups and clinical characteristics according to the revised International Union Against Cancer/American Joint Committee on Cancer classification are shown. NSCLC = non-small cell lung cancer. Reprinted with permission from Goldberg et al. Lung Cancer Updates. 2001;1:1-11.

Figure 1. Mediastinal Lymph Node Map

The complete mediastinal lymph node system includes 14 nodal stations, some of which are shown in this figure. Stations 1 to 4 are located in the superior mediastinum (1–3 not shown in this figure), 5 to 6 are the aortic nodes (not shown here), and 7 to 8 are located in the inferior mediastinum. Stations 10 (hilar), 11 (interlobar), 12 (lobar), 13 (segmental), and 14 (subsegmental) are the N1 nodes. N1 = metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region or both; N2 = metastasis to ipsilateral mediastinal lymph nodes and subcarinal lymph nodes; N3 = metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene, or supraclavicular lymph nodes. Reprinted with permission from Mountain. Chest. 1997;111:1710-1717.
prognosis in stage III NSCLC include Karnofsky performance status less than 70, weight loss more than 10% of body weight, palpable supraclavicular lymph nodes, and superior vena cava syndrome.11

The accuracy of a stage III diagnosis depends on the quality of the staging methods. Guidelines for noninvasive staging of NSCLC include computed tomography (CT) of the thorax and upper abdomen and fluorodeoxyglucose positron emission tomography (PET) of the whole body.12 These methods are complementary and cost effective. In addition, integrated PET/CT is reported to be superior to simple visual correlation of PET and CT, especially for mediastinal staging.13,14 However, it is important to appreciate that PET scan has a significant false-positive rate (5%–30%, depending on the geographic area of investigation) and, in general, positive mediastinal PET results should be confirmed with a tissue diagnosis. Some investigators feel that tissue staging of the mediastinum is not necessary in most patients in the context of a negative PET/CT.15 There is obviously need for clinical judgement and risk assessment. For example, a peripheral T1 lesion with a negative mediastinum by PET/CT poses a different risk than a centrally located T3 with a negative PET/CT; most clinicians would favor tissue acquisition in the latter. As discussed in this article, a variety of techniques are now available for staging the mediastinum. Cervical mediastinoscopy remains the gold standard and should reliably provide tissue of level 7, R4, R2, L4, and sometimes L2 (Figure 1).6 When performed by an experienced thoracic surgeon with expertise in this procedure, the accuracy of the staging and the safety of the patient are ensured. Transbronchial needle aspiration (Wang technique) can provide a tissue diagnosis of the mediastinum in select patients but results are highly operator-dependent. Endobronchial ultrasound-guided needle biopsy of N2 (including levels 5 and 6) and even N1 nodes holds promise and has supplanted traditional mediastinoscopy in some European centers. Transesophageal endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) has recently been shown to improve the accuracy of mediastinal staging when performed together with mediastinoscopy because EUS-FNA reaches complementary lymph node stations (level 8).16 The specific role of each of these staging techniques continues to evolve.

In neurologically asymptomatic patients with NSCLC, some guidelines advise that screening brain CT or magnetic resonance imaging (MRI) are unnecessary.17 However, recent data document that the risk of occult brain metastasis in presumed stage III disease may be high enough to justify these procedures. For example, one study reported that MRI detected occult brain metastasis in 21% (stage IIIA) and 11% (stage IIIB) of patients where surgery was planned, primarily in patients with nonsquamous tumor histology. Because combined-modality therapy is applied with curative intent in stage III disease, it can be argued that screening brain imaging should be recommended to avoid aggressive loco-regional treatment in those with occult brain metastases. Although MRI has greater sensitivity than CT in this setting, it is unclear whether it should replace CT scan in screening neurologically asymptomatic patients.18

**TREATMENT-RELATED CONSIDERATIONS**

As discussed later in this article, treatment strategies for stage III NSCLC have evolved substantially in recent years.19-24 Stage III disease can be considered conceptually as a 2-compartment model (Figure 2): a loco-regional compartment in the chest and a distant compartment harboring potential micrometastases.25 Cancer must be eradicated from both compartments to achieve cure. Treatment with radiation therapy (or surgery) is directed toward the intrathoracic tumor burden, whereas chemotherapy eradicates systemic metastases.

**Figure 2. Compartment Model**

Locally advanced NSCLC can be viewed as a therapeutic target involving different anatomical compartments. The thorax represents the loco-regional compartment, addressed mainly by surgery and/or radiotherapy. The distant compartment can harbor micrometastases, which is addressed by chemotherapy. The brain is a distant sanctuary, not currently addressed by combined-modality therapy.

NSCLC = non–small cell lung cancer.

Adapted with permission from Gandara et al. Clin Cancer Res. 2005;11:5057s-5062s.25
microscopic metastatic deposits below current levels of detection by CT or PET scanning. In addition, chemotherapy may contribute a radiosensitizing effect locally and achieve cytoreduction of high-volume loco-regional disease. Recently, a third compartment, the brain sanctuary, has emerged as increasingly important. Isolated brain recurrence has been observed in approximately 20% of cases following combined-modality therapy of stage III NSCLC, supporting a potential role for prophylactic cranial irradiation.

TREATMENT OF POTENTIALLY RESECTABLE DISEASE

The goal of surgery is to extirpate all known cancer (R0 resection), to pathologically stage all relevant nodal stations, and to assure the patient of a postoperative quality of life that is no worse (and sometimes better if symptoms of airway obstruction or invasion were present preoperatively) than their preoperative baseline. An important concept here is that technical feasibility to surgically remove a lung cancer does not necessarily equate with improved outcome due to surgical resection. Defining the adequacy of pulmonary function in relation to the proposed extent of resection (lobectomy or pneumonectomy) is essential. Obviously, consideration of performance status and recognition of comorbidities, such as cardiac disease, are equally important in determining the appropriateness of including surgery in a combined-modality approach in individual patients with stage III disease.

Combined-modality approaches to stage III NSCLC involving surgery include chemotherapy or local radiation after surgical resection (adjuvant or postoperative therapy) or preoperative chemotherapy with or without thoracic radiation (neoadjuvant or induction therapy). Although early studies suggested minimal benefits were achieved with adjuvant chemotherapy, more recent phase III trials (eg, larger studies with more homogeneously staged patients, and uniformly employing platinum-based chemotherapy) have documented substantial improvements in survival, comparable or surpassing those achieved in other tumor types, such as breast cancer. A 1995 meta-analysis of 52 randomized clinical trials, totalling 9387 patients, showed a 13% reduction in the risk of death, equivalent to an absolute benefit of 5% at 5 years, in patients who received postoperative chemotherapy. However, these results were of marginal statistical significance. Many of these earlier trials consisted of relatively small patient numbers, and staging procedures would be considered antiquated by current standards. By comparison, several recently completed and well-designed phase III trials (International Adjuvant Lung Cancer Trial [IALT], Adjuvant Navelbine International Trialist Association [ANITA], BR10, and Cancer and Leukemia Group B [CALGB]) comparing surgery alone to surgery followed by platinum-based chemotherapy in subsets of stages IB to III NSCLC have demonstrated positive results.28-31 IALT, the largest of these studies, included 1867 patients with completely resected stage I to III NSCLC who underwent randomization to adjuvant cisplatin-based combination chemotherapy versus observation. There was a significantly improved 5-year survival rate in the adjuvant chemotherapy group (44.5%) versus observation (40.4%).32 Thirty-nine percent of the patients in the IALT study had operable stage III disease, and subgroup analysis suggested that those patients benefited the most from adjuvant chemotherapy. The subsequent ANITA trial (400 patients per treatment arm) demonstrated a median survival time of 65.8 months in the adjuvant therapy arm versus 48.7 months in the observation arm,29 providing further convincing evidence that cisplatin-based adjuvant therapy for surgically resected stage III NSCLC should be considered as standard-of-care.

The role of surgery following preoperative chemotherapy or chemoradiation (neoadjuvant or induction therapy) in stage III NSCLC continues to evolve. The dual goals of neoadjuvant therapy are to facilitate complete resection by tumor cytoreduction and to eliminate micrometastasis at the earliest time point.32 The 4 published phase III trials using this approach have yielded conflicting results.33-36 The largest of the trials, which was by Depierre et al, included stages IB to III and did not reveal an overall survival advantage, although disease-free survival was improved.36 In addition, the least benefit was observed in the patient subset with stage III disease. Two small phase III studies by Roth et al and Rosell et al focusing on patients with stage III disease each reported a substantial increase in survival with neoadjuvant chemotherapy.33,34 However, these results must be viewed with caution due to the small patient sample sizes, lack of uniform staging, and premature closure due to criteria for early termination. Several recent phase II trials have integrated third-generation drugs, such as the taxanes and gemcitabine, into platinum combinations in well-defined, pathologically staged
patients. The response rates with these drugs, ranging from 39% to 74%, were encouraging. Similar to earlier studies, pathological complete response in the mediastinal lymph nodes and complete surgical resection were important prognostic parameters; it was suggested that patients with stage IIIA pN2 disease found to have residual mediastinal tumor after induction chemotherapy may not benefit from subsequent surgical resection.

Preoperative chemoradiation is also controversial. The North American Intergroup trial 0139 in T1-3pN2 disease is one of the largest randomized studies to test the trimodality approach, comparing chemoradiation alone with cisplatin-etoposide and concurrent thoracic radiation (61 Gy) versus preoperative chemoradiation with the same chemotherapy, but radiation limited to 45 Gy. The results show improved disease-free survival in the surgical arm, but no difference in overall survival. In a retrospective subset analysis of this trial evaluating matched populations, those patients on the surgical arm who underwent pneumonectomy had worse survival than matched patients receiving chemoradiation, whereas survival was improved in lobectomy patients. The authors report this difference as due to an unacceptable mortality rate in pneumonectomy patients receiving trimodality treatment and suggest that, in those patients with stage IIIA N2 disease anticipated to require pneumonectomy, chemoradiation is not likely a preferable approach. Because of these findings, a current Intergroup trial (R0412/S0332) is comparing preoperative chemotherapy alone to chemoradiation in selected patients with stage IIIA N2 disease (eligibility criteria defining less bulky mediastinal lymph nodes and unlikely to require pneumonectomy), with the goal of maximizing efficacy and reducing morbidity and mortality.

Superior sulcus NSCLC (Pancoast tumor) is a good example in which the results of clinical trials have dictated a change in treatment approach. Superior sulcus tumors can be divided into different substages (IIB, IIIA, and IIB), and the great majority are considered inappropriate for surgical management alone because of the high incidence of loco-regional and distant recurrence, resulting in poor long-term survival. It was shown more than 4 decades ago that preoperative radiation allowed radical resection of superior sulcus tumors. Based on the more recent data from Intergroup trial S9416 showing that preoperative chemoradiotherapy led to a 5-year survival rate of 41%, trimodality therapy is now considered standard-of-care for patients with superior sulcus tumor with T3-4, N0, or N1 disease.

Approximately 66% of all patients with stage III NSCLC have unresectable disease at the time of diagnosis, with bulky mediastinal or supraclavicular lymphadenopathy (N2 or N3) or central primary tumors invading vital structures (T4). The current standard-of-care for this group of patients is concurrent chemoradiotherapy. This standard has evolved from earlier observations that although radiotherapy alone provided palliative benefit in patients with unresectable stage III disease, it resulted in few long-term survivors, whereas chemotherapy prolonged survival in metastatic disease. Different approaches to combining radiotherapy and chemotherapy are associated with advantages and disadvantages (Table 2).

Consequently, 4 different treatment paradigms have evolved (sequential chemotherapy followed by radiation, concurrent chemoradiation alone, induction chemotherapy followed by concurrent chemoradiation, and trimodality therapy), each with its own advantages and disadvantages. The choice of treatment depends on various factors such as the stage of the disease, the patient’s medical history, and the availability of resources.

### Table 2. Theoretical Considerations Regarding Chemoradiotherapy

- **Spatial cooperation:**
  - Radiation therapy and chemotherapy work in different disease compartments: radiation therapy focuses on the local, intrathoracic tumor mass, whereas chemotherapy eradicates distant micrometastases.
- **Nonoverlapping toxicities:**
  - Radiation toxicities in the thorax are predominantly pneumonitis and esophagitis. Chemotherapy predominantly causes hematologic toxicity. Radiosensitizing chemotherapy does exacerbate radiation toxicity, but this usually only requires minimal dose/volume modifications.
- **Cellular interactions:**
  - Chemotherapy can act as a radiosensitizer, increasing the efficacy of the radiation therapy (changing the shape of the radiation response curve).
  - Altered cell cycle distribution, thereby increasing the percentage of cells in the most radiosensitive phase of the cycle.
  - Differing treatment schedules decreases the protective effects of acute hypoxia.
  - Cytoreduction of the mass decreases chronic hypoxia.
  - Inhibition of tumor repopulation during treatment.

The table summarizes some of the theoretical considerations in combining radiotherapy and chemotherapy, including advantages and disadvantages. Reprinted with permission from Goldberg et al. Lung Cancer Updates. 2001;1:1-11.
tion, and concurrent chemoradiation followed by consolidation chemotherapy), each based upon biological and clinical considerations in treating patients with unresectable stage III disease (Table 3).

Historically, the sequential approach was investigated first. Between 1994 and 2000, 3 large phase III trials (more than 900 total patients) showed that sequential chemoradiotherapy significantly improved overall survival time compared to radiotherapy alone (13–14 months vs 10–11 months). Once it was appreciated that with appropriate patient selection, concurrent chemoradiotherapy was tolerable, these paradigms were tested in 4 large phase III trials. Although one of these trials failed to show a significant survival benefit of concurrent over sequential therapy (although the results favored the concurrent approach), the other 3 were strongly positive in favor of concurrent chemoradiotherapy, with a resulting median survival time of 15 to 17 months. Short-term toxicity was higher in the concurrent arms because of increased hematologic and esophageal toxicity, but long-term toxicity was not increased.

Incorporation of newer chemotherapeutic agents into an induction-first approach was addressed by a CALGB randomized phase II trial (9431) utilizing 3 cisplatin plus new agent induction regimens (cisplatin/gemcitabine, cisplatin/paclitaxel, and cisplatin/vinorelbine), followed by the same drugs administered together with concurrent radiotherapy. Each regimen was given during induction in full dose, then at reduced doses concurrently with radiotherapy (cisplatin was administered at 80 mg/m² for the duration of all study arms). Efficacy was relatively equivalent among the 3 regimens, with median survival times of 14 to 18 months and 3-year survivals of 19% to 28%, but toxicity patterns varied considerably. A subsequent CALGB phase III trial utilizing paclitaxel/carboplatin and randomizing between induction chemotherapy followed by concurrent low-dose chemoradiotherapy or concurrent low-dose chemoradiotherapy alone had disappointingly low median survival times (13 vs 11 months, respectively; not statistically significant) in both study arms. The authors concluded that low-dose chemotherapy during the concurrent chemoradiation phase is suboptimal.

### Table 3. Chemoradiotherapy Paradigms

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<th>Sequence</th>
<th>Theoretical Advantages</th>
<th>Theoretical Disadvantages</th>
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<tr>
<td>Sequential (Chemo→XRT)</td>
<td>Full doses of each modality can be delivered without combined toxicity; cytoreduction from the chemotherapy may allow smaller radiation portals, decreasing radiation toxicity; also, may decrease regions of hypoxia that are relatively radioresistant.</td>
<td>No benefit from potential radiosensitizing action of the chemotherapy; chemoinsensitive disease continues to grow and potentially metastasize before XRT begins.</td>
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<tr>
<td>Concurrent (Chemo + XRT)</td>
<td>Exploits potential synergy between the modalities.</td>
<td>Enhanced toxicity leading to inability to deliver full dose of both modalities; no pre-XRT cytoreduction.</td>
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<tr>
<td>Induction-first (Chemo→Chemo + XRT)</td>
<td>Cytoreduction from induction chemotherapy may allow smaller radiation portals, decreasing radiation toxicity; full-dose chemotherapy may sterilize micrometastatic disease while clonogen number is minimal.</td>
<td>Chemoinsensitive disease continues to grow and potentially metastasize before CMT begins; enhanced toxicity compared to concurrent only; completing CMT after induction chemotherapy may be too difficult for all but the best performance status patients.</td>
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<tr>
<td>Concurrent-first (Chemo + XRT→Chemo)</td>
<td>Delivering maximal antitumor efficacy from CMT up front; exploits potential synergy between the modalities; most intense treatment is given early when the patient is best able to handle it physically and psychologically.</td>
<td>Enhanced toxicity compared to concurrent only; completing consolidation after CMT may be difficult for all but the best performance status patients.</td>
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Simultaneously, other studies have tested the paradigm of consolidation chemotherapy following concurrent chemoradiation. The Southwest Oncology Group (SWOG) has tested this strategy (concurrent-first) in a consecutive series of 3 phase II studies—S9019, S9504, and S0023. Each study employed a core chemoradiotherapy regimen using cisplatin/etoposide (PE) during the concurrent-first phase. Among currently available chemotherapy regimens, PE is relatively unique in being able to be delivered in full dose concurrently with thoracic radiotherapy with an acceptable toxicity profile. Furthermore, the SWOG version of PE delivers one or both drugs during 12 days of the initial thoracic radiation course, thus maximizing the potential for radiosensitization. S9019 was a phase II trial in patients with pathologically staged IIIB disease that evaluated concurrent PE and thoracic radiation of 61 Gy/33 fractions/6.5 weeks followed by consolidation PE for 2 more cycles. Median survival time was 15 months, and 2-, 3-, and 5-year survival rates were 34%, 17%, and 15%, respectively. S9504 substituted docetaxel for the consolidation PE used in S9019 to combine 2 strategies: full-dose concurrent chemotherapy with radiation and non–cross-resistant consolidation therapy. To facilitate using S9019 as a historical control, the studies used identical eligibility and staging requirements, in addition to the same concurrent chemoradiation. S9504 demonstrated a 26-month median survival time and 3-year survival rate of 37%. Five-year survival of 29% was recently reported. Of interest, a study of similar design by the National Cancer Center of Japan, using cisplatin and vinorelbine together with concurrent radiation and followed by consolidation docetaxel for the consolidation PE used in S9019 to combine 2 strategies: full-dose concurrent chemotherapy with radiation and non–cross-resistant consolidation therapy. To facilitate using S9019 as a historical control, the studies used identical eligibility and staging requirements, in addition to the same concurrent chemoradiation. S9504 demonstrated a 26-month median survival time and 3-year survival rate of 37%. Five-year survival of 29% was recently reported. Of interest, a study of similar design by the National Cancer Center of Japan, using cisplatin and vinorelbine together with concurrent radiation and followed by consolidation docetaxel, has produced similarly encouraging results (median survival time 32.8 months and 3-year survival 44%). The Hoosier Oncology Group LUN01-24 is an ongoing phase III trial for stage III NSCLC that directly tests the concept of consolidation docetaxel by randomizing patients to PE plus concurrent thoracic radiation with or without subsequent docetaxel. Study completion is anticipated in 2006.

Although the induction-first and concurrent-first approaches have not been compared in a phase III setting, a randomized phase II trial (locally advanced multimodality protocol) tested 3 of 4 treatment paradigms described earlier in this article: sequential therapy with paclitaxel/carboplatin followed by thoracic radiation, the same chemotherapy administered as induction-first followed by concurrent therapy, and concurrent-first followed by consolidation paclitaxel/carboplatin. Median survival times were 13, 12.7, and 16.3 months, respectively, with 3-year survival rates of 15% to 17%. Within the limitations of this phase II design, the consolidation therapy arm had a longer median survival, but with a greater degree of toxicity, primarily esophagitis.

PROPHYLACTIC CRANIAL IRRADIATION

The brain is a frequent site of tumor recurrence in patients with stage III NSCLC. In a 2005 retrospective review, tumor recurrence in the brain was reported in up to 26% of patients, and almost 50% of the relapses were diagnosed during treatment or in the first 4 months after treatment. Chemotherapy does not appear to sufficiently reduce the risk of relapse in the brain, which has led to the hypothesis that patients with stage III NSCLC may benefit from prophylactic cranial irradiation (PCI), similar to patients with limited disease small cell lung cancer. Four randomized clinical trials were analyzed in a recent Cochrane Review. The pooled results showed that PCI lowered the risk of brain metastasis in operable NSCLC, but there was no evidence of a survival benefit. At present, PCI is not considered standard in stage III NSCLC, and ongoing phase III trials, such as Radiation Therapy Oncology Group (RTOG) 0214 and the European Organization for Research and Treatment of Cancer trial, will hopefully clarify this issue.

EVOLVING APPROACHES OF RADIOTHERAPY

Although most patients still succumb to metastatic disease, the need for improved intrathoracic control remains clear. Cure is impossible without local regional control and uncontrolled loco-regional disease can give rise to substantial symptoms and further clonogenic evolution toward resistant disease. The actual rate of intrathoracic control was difficult to determine historically given the persistence of radiographic abnormality even with disease control; this was best demonstrated by SWOG 880538 in which 46% of patients found to have pathologic complete response at surgical resection after preoperative chemoradiation were labeled as having “stable disease” based upon CT findings. The best estimate at present is that total intrathoracic tumor control may be 50% or less. As such, methods for improving the delivery of radiation therapy are needed.

The most important approach to improving the delivery of radiation therapy is the use of CT-based treat-
ment planning and 3-dimensional conformal radiation dose delivery, aided by improved imaging and the use of PET. Through improved targeting of the tumor, less of the normal tissue is irradiated, enabling combined-modality therapy to have greater tolerability. Intensity-modulated radiation therapy was approved for the study of intrathoracic tumors in 200566,67 and, combined with new strategies for limiting movement of the tumor through the breathing cycle (“motion management”), it is anticipated that safe delivery of much higher doses to smaller tumor volumes will be feasible. This approach has already been shown to be well tolerated, but alternative fractionation schemes must be evaluated because lengthening overall treatment times has been linked to worsening outcome.69 Many groups have attempted multiple fraction per day strategies (ie, hyperfractionated twice-daily radiation through RTOG, hyperfractionated accelerated radiotherapy [HART], continuous HART, and Eastern Cooperative Oncology Group [ECOG] 2597).70 Although small trials have been positive and intriguing, the larger RTOG trials (RTOG 8808 and RTOG 9410) have failed to demonstrate benefit.48,51 Also, patient accrual to various HART strategies is difficult for practical reasons. It seems likely that for the foreseeable future in the United States, once-daily radiation therapy will remain the standard. Therapeutic advances via adoption of newer treatment techniques will allow for greater dose conformity/dose escalation while respecting overall lung doses (ie, the volume of lung that receives 20 Gy [V20]). Even with good conformity, combining new agents with radiation remains potentially quite toxic, as was reported recently from the CALGB (gemcitabine and conformal radiation therapy to 74 Gy).71 Thus, new agent/radiation combinations must always be evaluated in the clinical trial setting. A newer delivery method of radiation therapy, stereotactic body radiation therapy, is being tested for intrathoracic tumors (RTOG 0236) and could change standard-of-care in years to come.

INTEGRATION OF MOLECULAR TARGETED AGENTS INTO COMBINED-MODALITY THERAPY

During the past 2 decades, important insights into the molecular biology of NSCLC have been achieved, leading to the development of several molecular targeted therapeutic agents.74 It is beyond the scope of this paper to comprehensively review this topic, and the implications for stage III NSCLC have been discussed recently.26 Inhibitors of the epidermal growth factor receptor (EGFR) tyrosine kinase and vascular endothelial growth factor (VEGF) have demonstrated improved patient outcomes in metastatic NSCLC. Ongoing clinical studies integrating these drug classes into combined-modality therapy for stage III disease are briefly described later in this article. EGFR and VEGF are well documented to be important molecular targets in NSCLC. Therapeutic agents directed against these targets include the EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib, the anti-EGFR antibody cetuximab, anti-VEGF antibody bevacizumab, and several VEGF receptor TKIs.

In view of activity of the EGFR TKIs in metastatic disease, there has been considerable interest in their use in stage III disease. However, the negative results of 4 large randomized trials comparing chemotherapy alone to chemotherapy plus gefitinib or erlotinib dampened enthusiasm for concurrent use.73 Therefore, a SWOG phase III trial (S0023) tested gefitinib versus placebo as long-term maintenance therapy following chemoradiation and consolidation docetaxel in unresectable stage III NSCLC. Interim analysis demonstrated that gefitinib did not improve survival and, surprisingly, survival was numerically lower in the gefitinib arm (median survival time 19 months in the gefitinib arm vs 29 months for placebo; \(P = .09\)).74 Several other trials are ongoing with the EGFR TKI erlotinib and monoclonal antibodies to EGFR in stage III disease. At present, these approaches remain investigational, given uncertainty about how to best incorporate these agents within the 4 stage III chemoradiotherapy paradigms (Table 3).3

Integration of the anti-VEGF antibody bevacizumab in the therapy of stage III NSCLC is also being assessed. The SWOG trial S0533 will test the safety of adding bevacizumab to chemoradiotherapy in sequential cohorts of patients with unresectable stage III NSCLC by initiating bevacizumab during consolidation chemotherapy in the first cohort and, if proven safe, then moving introduction of the antiangiogenic agent earlier into concurrent therapy in subsequent patient cohorts. In the neoadjuvant setting of stage III NSCLC, a pilot study using bevacizumab with chemotherapy will assess efficacy and toxicity of this approach. Thalidomide, which inhibits angiogenesis, is being evaluated in combination with chemoradiotherapy in an ECOG phase III study in unresectable, locally advanced NSCLC.
Conclusions

Significant advances in the therapy of stage III patients have been achieved with multimodality treatment. Yet, the optimal sequence of treatment modalities, schedules of drugs, and administration of radiotherapy remain elusive for many subgroups. With new insights from modern chemoradiotherapy, the role of surgery is being critically re-evaluated, plus optimal restaging procedures after induction therapy need to be developed to avoid delays in treatment. Intensification of radiotherapy and the use of neuro–cross-resistant chemotherapy are other strategies being pursued to improve the outcome of patients with stage III disease.7,26

Several novel therapeutic agents directed against a wide array of newly described molecular targets have shown activity in stage IIIB and IV disease, and these agents are now being integrated into the therapy of patients with earlier stages.22 Correlative studies of pertinent molecular pathways are expected to help identify those patient subgroups that can benefit most from these agents. Molecular targeted agents are also of particular interest in those patients least tolerant of multimodality therapy, namely the elderly and unfit.27

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