The challenge for oncologists treating patients with stage III non-small-cell lung cancer (NSCLC) is to optimize a treatment strategy using nonsurgical therapies. The recognition that chemotherapy response rates for patients

The term "locally advanced non-small-cell lung cancer" (NSCLC) is used to describe disease that is too extensive for primary surgical resection, is limited to the thorax, and, technically, allows inclusion of the entire tumor within a reasonable radiation field. This definition typically includes patients with stage IIIB and bulky stage IIIA lesions and usually excludes patients with a malignant pleural effusion. In the most recent revision of the American Joint Committee on Cancer staging system for lung cancer,[1] T3N0 tumors were reassigned from stage IIIA to stage IIB, due to their distinctively more favorable prognosis, when compared with lymph-node-positive subgroups of stage IIIA disease. Controversy exists regarding the use of surgery as a component of the initial management of patients with clinical stage IIIA disease. This discussion, however, addresses issues related only to the nonsurgical management of patients.

Effect of Thoracic Radiation Therapy on Local Control

Patients with NSCLC were expected to comprise 25% to 40% of the 178,100 new lung cancer patients diagnosed in 1997 in the United States.[2] Historically, the standard treatment administered to those patients has been a 6-week course of fractionated external-beam thoracic radiation therapy to 60 Gy. The dose of photon irradiation necessary to provide durable intrathoracic control has been investigated in trials conducted by the Radiation Therapy Oncology Group (RTOG). For example, RTOG 73-01,[3] randomized 551 patients to treatment with four arms of thoracic radiotherapy: 40 Gy delivered in a continuous fashion (2 Gy daily, 5 days a week, for 4 weeks), 40 Gy in a split course, 50 Gy as a continuous dose, or 60 Gy as a continuous dose. Patients assigned to the 60-Gy arm achieved the highest response rate (55%), the lowest rates of local tumor failure at 3 years (36% vs 63% in the other arms), and the best 3-year survival rate (20% vs 10% for the other arms). Unfortunately, these tumor-control and survival advantages were lost by 5-year follow-up, with estimated local failures and survival rates (70% and 7%, respectively) identical in the 60- and 40-Gy arms. In response to the therapeutic advantage seen at 3 years in this study, 60 Gy/6 weeks was adopted as the standard dose for definitive radiotherapy of patients with NSCLC. It became evident, however, that higher radiation doses are necessary to control tumors and further improve the survival results.

In a randomized Southeastern Cancer Study Group trial[4] involving 319 patients whose NSCLC was treated either with thoracic radiotherapy, single-agent vindesine, or a combination of the two, the main conclusion drawn was that standard thoracic radiotherapy did not provide a survival benefit. The overall response rate was superior in both radiotherapy arms (30% vs 10%; $P = .001$), but median survival time was 8.4 months for patients receiving radiotherapy alone, 9.4 months for those receiving radiotherapy/vindesine, and 10.1 months for those receiving vindesine alone ($P = .58$). The study was criticized because a large proportion of patients on the vindesine arm (37%) received delayed radiotherapy, thus resulting in a study of immediate vs delayed thoracic radiotherapy. Reports on the capability of any nonsurgical therapy to control NSCLC vary markedly, depending on the nature of the assessment and the time interval since therapy. When posterior-anterior and lateral chest radiographs were used in RTOG 73-01[5] and a cross-section of the tumor or the pulmonary shadow was recorded, a complete response was reported for 24% of patients treated with 60 Gy, a partial response was noted in 32%, 35% had stable disease, and only 9% were shown to have progressive disease. One has to note, however, that two-dimensional measurements may not reflect true volumetric responses.

If a complete response is defined rigorously as absence of tumor by clinical, radiographic, and
bronchoscopic examination, with a negative endoscopic biopsy,[6] and evaluation of response is repeated every 6 months, only 16% to 20% of patients could be said to have had a complete response. Further, when evaluated in accordance with these assessments, only 15% had a partial response, 16% to 20% had stable disease, and 45% to 53% had progressive disease 3 months after the completion of radiotherapy. At 3 years, local control rates are only 7% to 8%.

More recently, an impressive bronchoscopically verified local control rate of 71% at 2 years was reported by King et al,[7] who used a novel hyperfractionated accelerated radiotherapy regimen to a total dose of 73.6 Gy directed to the primary tumor and adjacent enlarged lymph nodes. As argued elegantly by Emami,[8] tumor control probability for bronchogenic carcinoma can be estimated at 10% for tumors > 4 cm at a dose of 80 Gy, and the probability of controlling an average-sized lung cancer with even 100 Gy is estimated at 50% to 80%. This is consistent with the original observations of Fletcher.[9] Therefore, if local tumor control is a prerequisite for improved survival, one may expect to start seeing the influence of improved local control rates on survival rates only when eradication of the tumor is possible in over 50% of treated patients.

In addition to external-beam radiotherapy, there may be a role for endobronchial brachytherapy as a means of delivering radiotherapy dose escalation to a bulky parabronchial tumor. In one prospective randomized study,[10] local control was improved with the addition of two sessions of high-dose endobronchial brachytherapy to a standard thoracic radiotherapy regimen (\( P = .05 \)).

### Radiotherapy for Medically Inoperable Stage I NSCLC

Radiotherapy can effectively control small lung tumors. There are several reports of durable intrathoracic control achieved in patients with clinical stage I (T1 or T2) tumors who could not be treated with surgery because of coexisting medical conditions or refusal.[11-17] Such patients provide an opportunity to better assess the effectiveness of radiotherapy, since their longer survival time is due to the lower stage of disease and local control can therefore be evaluated with less of a competing risk of distant failure.

Precise data on the relationship between tumor size (or volume) and degree of local control are lacking in the radiotherapy literature, but it appears that the rate of local failure with standard thoracic radiotherapy increases sharply when the largest tumor diameter exceeds 3 or 4 cm. For example, the intrathoracic failure rate at 3 years was only 4% (1 of 24) in medically inoperable patients whose stage I tumors measured no more than 4 cm, but the rate increased to 47.8% (11 of 23) in patients with larger tumors treated with a hyperfractionated course of radiotherapy to a dose of 48 or 56 Gy.[8]

Similarly, Kupelian et al.[17] quoted a 3-year local failure rate of 11% for patients with T1 lesions and 39% for those with T2 tumors. Significant favorable prognostic factors for local control included tumor size of 4 cm or smaller, no chest wall invasion, a radiation dose of at least 60 Gy, and a complete response at 6 months after radiotherapy. It appears, however, that with longer follow-up, local failure rates increase significantly, even for those with small tumors.[13] Nevertheless, definitive radiotherapy can provide 3-year cause-specific survivals of 30% to 49%[13,15,17] for patients with small tumors and no radiographic evidence of lymph-node involvement, serving as a noninvasive equivalent of wedge resection.

A clear-cut dependence of local control and disease-free survival of T1 tumors on radiotherapy dose is evident in several reports,[12,13,17] with a 90% disease-free survival at 3 years when doses of 65 Gy or higher are used, compared with 29% if delivered doses are between 60 and 65 Gy (\( P = .0611 \)).[12] Overall, it appears that the dose-response relationship in NSCLC is evident only for tumors 3 cm or smaller, at least within the range of 60- to 65-Gy doses. In those patients with larger tumors, doses much higher than 65 Gy would have to be considered to expect local control. This is difficult to achieve with larger tumors because of the constraints of toxicity to the surrounding normal tissues, most notably lung, spinal cord, and heart.

Results achieved with definitive radiotherapy cannot be directly compared with those of surgical resection, since the pathologic status of regional lymph nodes is not routinely investigated prior to initiation of radiotherapy, and patients frequently do not undergo the rigorous systemic staging before radiotherapy that is standard before surgery.[15]

### Altered Fractionation RT for Locally Advanced Non-Small-Cell Lung Cancer

The realization that local control of lung cancer with conventional radiotherapy (2 Gy daily, 5 days per week) remains unsatisfactory has led to various efforts of optimizing radiotherapy, including altering the radiotherapy fractionation schedule. One such alteration, called hyperfractionation,
refers to delivery of a larger number of smaller radiation fractions and may allow delivery of a higher total dose to the tumor, resulting in improved local control with the same probability of late effects to surrounding normal tissues.

Hyperfractionation was investigated by the RTOG in a dose-seeking phase II trial (83-11) designed to identify the maximum tolerable dose of hyperfractionated irradiation and to evaluate tumor control at each dose level.[18] Patients with favorable performance and minimal weight loss were randomized to receive 60, 64.8, 69.6, 74.4, or 79.2 Gy, in two daily fractions of 1.2 Gy. Although the median survival time (13 months) and 2-year survival rates (29%) in the 69.6-Gy arm appeared superior to the benchmark standard fractionation results, there was no apparent improvement in 5-year survival results, which ranged between 6% and 8% at all dose levels.[19] Again, as in the RTOG 73-01 trial, a survival benefit was seen for short-term but not for long-term survival, suggesting the need for more aggressive therapies.

In a phase III study coordinated by the RTOG—RTOG 88-08/Eastern Cooperative Oncology Group (ECOG) 4588—the 69.6-Gy hyperfractionated dose was tested against both standard once-daily radiotherapy and induction chemotherapy/standard radiotherapy.[20] In that study, the hyperfractionated radiotherapy produced an early survival result that was intermediate between that of the combined-modality arm and the standard radiotherapy, with 1-year survival rates of 59%, 51%, and 46%, respectively. This study is discussed in greater detail later in this section.

It has long been recognized that cells in rapidly proliferating normal tissues and in tumors are not only able to divide during a course of radiotherapy but even divide more rapidly than normal, in a process of accelerated repopulation.[21] This is beneficial in the case of normal tissues, allowing for the healing of acute reactions, but it may be detrimental in the tumor, where such proliferation impairs eradication of disease tissue.[21] A fractionation scheme in the form of accelerated hyperfractionated radiotherapy, ie, delivery of more than one standard-sized (1.6-2.0 Gy) fraction daily, may minimize tumor cell repopulation by shortening the overall treatment time, thereby increasing the probability of tumor control for a given dose level.

CHART (Continuous Hyperfractionated Accelerated Radiation Therapy) is a continuous-treatment regimen that tests the hypothesis that tumor-cell repopulation is an important cause of failure in conventional radiotherapy. To counteract repopulation, CHART was designed to deliver 1.5 Gy three times per day for 12 consecutive days, to a total dose of 54 Gy. An interval of at least 6 hours is maintained between radiotherapy fractions to avoid late toxicity in slowly repairing tissue, such as spinal cord.

Preliminary results have been published of a randomized trial,[22] comparing CHART with standard radiotherapy with 66.0 Gy in 563 patients with locally advanced NSCLC and a good performance status. With a minimum potential follow-up of 2 years, this study showed significant improvement in survival rates for the CHART-treated patients over conventionally treated patients (30% vs 20%; \( P = .006 \)). Although the incidence of significant acute esophagitis was higher in the CHART arm (40% vs 19%), it subsided quickly in both arms and without apparent chronic sequelae. These results are exciting, but longer observation will be necessary before final conclusions can be drawn.

In the United States, thrice-daily radiotherapy (1.1 Gy tid, 5 days a week, to 79.2 Gy) was tested in the RTOG 92-05 trial. Results of this study are pending. An ECOG pilot study also was completed[23] in which 30 patients were treated with 1.5 Gy delivered three times daily, to a total dose of 57.6 Gy. The 1-year survival rate of 63% provided the basis for a larger trial to assess the true efficacy of such a regimen.

**Role of Radiotherapy in Symptomatic Control**

For patients with known extrathoracic metastases, poor performance status, or intrathoracic disease not amenable to aggressive, full-dose irradiation, thoracic radiotherapy may provide rapid and durable relief from several life-threatening or distressing symptoms. Intrathoracic symptoms palliated by thoracic radiotherapy in more than 80% of patients include hemoptysis, tumor-related pain, and superior vena cava obstruction. Cough and dyspnea are palliated in about two thirds of patients, and atelectasis and vocal cord paralysis are improved in a smaller proportion, 23% and 6%, respectively.[24-26] Total symptomatic relief may be accomplished in 61% of patients.[20] It is important to note that comparative information regarding palliation of these symptoms by multiagent chemotherapy is limited.[27]

The optimal radiotherapy dose/fractionation schedule for palliation of intrathoracic symptoms is uncertain. While most practicing radiation oncologists would agree that a 6-week course of treatment is unnecessarily protracted for patients with known distant metastases, there is also
concern that an accelerated course may produce more severe treatment-related esophagitis. A randomized trial conducted by the Medical Research Council compared two radiotherapy fractionation schemes for 509 patients with metastatic disease. Subjects received either 39 Gy in 13 daily fractions or 17 Gy as two weekly 8.5-Gy fractions.[28] The symptoms were more rapidly palliated by the shorter regimen, and esophagitis was shorter-lasting in the two-fraction regimen than in the 13-fraction schedule (6.5 days vs 14 days).

**Patient Selection**

One of the observations derived from the RTOG 73-01[3] was a better treatment outcome at 2 to 3 years for patients with a favorable performance status (Karnofsky index of more than 70). Since then, evidence has accumulated, attesting to the need for identifying different prognostic groups within the broad category of NSCLC. A large group of patients (1,052) with locally advanced or metastatic NSCLC treated with platinum-based chemotherapy by the European Lung Cancer Working Party was analyzed with regard to prognostic factors for survival, using univariate and multivariate methods.[29]

Among 16 pretreatment variables, limited disease, good Karnofsky performance status, normal leukocyte and neutrophil counts, normal serum calcium, absence of skin metastases, age less than 60 years, and female gender were all associated with a significantly improved survival. After application of recursive partitioning algorithm and amalgamation algorithm, four subgroups of patients were identified, heterogeneous for survival. The most favorable group included females with limited disease and a Karnofsky index of at least 80; these women had a median survival time of 14.1 months. The group with the least favorable prognosis for survival included those patients with disseminated disease, abnormal leukocyte count, and poor Karnofsky index; in this group, the median survival time was 3.3 months. A thorough knowledge of factors affecting outcome is essential for the appropriate design of therapeutic trials, since an effective treatment applied to a group of patients with unfavorable survival characteristics may result in an erroneous conclusion regarding the likelihood of treatment benefit.

**Combined-Modality Studies**

**Chemotherapy and Standard Fractionated Radiotherapy**

Since most patients with NSCLC have metastatic disease at the time of their death,[3] it is logical to evaluate the impact of systemic therapy in the management of these patients. Several prospective randomized trials have been conducted to examine the role of chemotherapy, in addition to thoracic radiotherapy, in NSCLC. Conclusions have varied. Dillman et al from the Cancer and Leukemia Group B (CALGB 8433)[30] reported a median survival time of 13.7 months for patients receiving induction chemotherapy with vinblastine (Velban)/cisplatin (Platinol) for 2 cycles followed by 60 Gy standard-fractionated radiotherapy, compared with 9.6 months for those receiving radiotherapy alone ($P = .012$). This study was terminated early due to an observed survival benefit in the combined-modality arm, so only 180 patients were enrolled.

Of note, a 7-year follow-up report[31] confirmed a long-term improvement in survival rate for chemotherapy/radiotherapy-treated patients (13%) over radiotherapy-treated patients (6%). It is crucial to emphasize, however, that only patients with a favorable prognosis (ie, those with a maximum 5% weight loss and a Karnofsky score of at least 70) were eligible for the CALGB study. Two landmark European studies [6,32] examined a similar question. In a report on the European Organization for the Research and Treatment of Cancer (EORTC) study 08844, Schaake-Koning et al[32] noted that concurrent chemoradiation comprising a schedule of low-dose daily cisplatin or weekly carboplatin (Paraplatin) during radiation therapy provides a statistically significant survival benefit over radiotherapy alone ($P = .009$). The survival benefit seen with the daily combined treatment appeared to be attributable to improved control of local disease ($P = .003$).

Reporting on the French Multicenter Trial CEBI 138, Le Chevalier et al[6] noted similar results with cisplatin-based therapy (vinodesine/cyclophosphamide (Cytoxan)/cisplatin/lomustine (CCNU). In 353 patients, the median survival time for chemoradiotherapy-treated patients was 12 months, vs 10 months for those treated with radiation therapy alone. Although a survival benefit over thoracic radiation therapy alone was observed among patients in the low-dose daily cisplatin arm, with a 3-year survival rate of 16% vs 2% ($P = .009$), the weekly schedule did not provide a statistically significant benefit. The survival benefit seen with the daily combined treatment appeared to be attributable to improved control of local disease ($P = .003$).

The metastasis rate was significantly lower in the
combined-modality arm (P < .001). A subsequent update did report a statistically significant survival advantage at 3 years (P = .02). Despite a radiotherapy dose of 65 Gy in both treatment arms, local tumor control rates evaluated at 3 months were disappointingly low (15% to 17%). Complete remission was indicated in this study by the complete disappearance of all objective tumor on chest x-ray, with no evidence of new disease evident by visual and histologic examination during fiberoptic bronchoscopy.

As noted, RTOG 88-08/ECOG 4588 was a phase III randomized three-arm study aimed at directly comparing standard treatment (standard fractionated radiotherapy to 60 Gy) with two promising experimental regimens, induction chemotherapy with vinblastine/cisplatin followed by standard-fractionated radiotherapy to 60 Gy (CALGB regimen), or hyperfractionated radio-therapy to 69.6 Gy (RTOG 83-11 regimen)[20] in 452 patients with a favorable prognosis. The chemoradiotherapy group had a survival benefit, with a median survival time of 13.8 months compared with 11.4 months for the standard radiotherapy arm (P = .008) and 12.3 months for the group treated with hyperfractionated radiotherapy (P = .03). Results of this trial confirm the short-term survival results of the CALGB report by Dillman et al[31] and, in this larger number of patients, provide further evidence that nonoperative management using platinum-based chemotherapy is able to improve survival rates in selected good-prognosis patients with NSCLC. Further support to the superiority of a combined-modality treatment over standard radiotherapy alone was given by the North Central Cancer Treatment Group’s trial, comparing standard radiotherapy vs twice-daily hyperfractionated radiotherapy vs twice-daily hyperfractionated radiotherapy with concurrent etoposide (VePesid).[33] Subsequent to presentation of the results from RTOG 88-08, this study was closed prematurely as it was then felt to be inappropriate to offer radiotherapy without chemotherapy.

In RTOG 88-04,[34] 30 patients received induction vinblastine and cisplatin as well as concomitant cisplatin during a standard radiotherapy course. Although nearly 30% of enrolled patients did not meet good performance status and minimal weight loss criteria, the survival results were encouraging, with a median survival time of 16.1 months and a 2-year survival rate of 34%. Several published studies did not support the conclusion that chemotherapy in addition to radiotherapy provides superior survival[35-37] and the issue was therefore further investigated using a statistical method of pooling data from several trials. Two such meta-analyses used data extracted from all published randomized trials comparing radiotherapy alone to radiotherapy and cisplatin-based chemotherapy in locally advanced NSCLC.[38,39] Although these reports differ with regard to the methodology used[40] (analysis based on published data vs updated individual patient data), they both reported a small improvement in survival for the combination regimen (absolute benefit of 4% at 2 years and 2% at 5 years, or a prolongation of life by 4 months, or a 13% reduction in the risk of death). In summary, although the observed benefits of chemotherapy given in addition to thoracic radiotherapy are modest, they offer hope of progress and demonstrate that the role of chemotherapy should be further investigated.

Chemotherapy and Altered-Fractionation Radiotherapy

The RTOG has completed three phase II trials evaluating concomitant delivery of high-dose cisplatin-based chemotherapy and hyperfractionated thoracic radiotherapy for NSCLC. RTOG 90-15 enrolled 42 patients who received immediate hyperfractionated radiotherapy (69.6 Gy) plus cisplatin/vinblastine.[19] Toxic reactions were primarily hematologic, and the median survival time was 12.1 months in this unfavorable patient population. Among the 10 favorable-prognosis patients in this protocol, the median survival time was 16 months.

In RTOG 91-06[41] 76 patients received immediate hyperfractionated thoracic radiotherapy with concomitant cisplatin plus oral etoposide. As recently analyzed, the estimated 1-year survival rate was 67%, and the median survival time is 19 months. The rate of grade 4 hematologic toxic reactions in RTOG 91-06 was 57%, and was comparable with the 48% rate seen in the induction-chemotherapy arm of RTOG 88-08. However, grade 3 or higher esophagitis was substantially worse, with a rate of 36% vs 4% in RTOG 88-08. A third phase II trial (RTOG 92-04) confirmed the encouraging results of RTOG 91-06 and RTOG 88-04.

Other evidence supporting indications of an improved survival rate with the addition of chemotherapy to hyperfractionated radiotherapy came from a randomized Yugoslavian/Japanese study[42] including 131 patients and reporting a median survival time of 14 months for those treated with hyperfractionated radiotherapy alone (69.6 Gy) vs 22 months for those given hyperfractionated radiotherapy and carboplatin/etoposide, with a 4-year survival rate of 9% vs 23%, respectively. Improved survival was probably due to improved local control and may suggest a radiosensitizing effect of daily chemotherapy dosing in that study.
An ongoing RTOG study (94-10) attempting to define the optimal sequencing of chemotherapy is currently comparing sequential chemotherapy with radiotherapy to both concurrent chemotherapy/radiotherapy and concurrent chemotherapy with hyperfractionated radiotherapy. As of July 1997, this trial has accrued 482 of the 597 patients required. Using the median survival time of 13 to 14 months seen in both the RTOG and CALGB trials with sequential cisplatin-based chemoradiation, this trial is powered to detect a 43% improvement in median survival time, based on the 19-month median survival time seen in the phase II RTOG trial of concurrent oral etoposide, cisplatin, and hyperfractionated radiotherapy.

**Conformal Radiotherapy**

Since the established pathways for spread of the primary lung tumor follow the lymphatic flow from the tumor to the hilum, mediastinum, and supraclavicular lymph nodes, classic radiation volumes include the primary lesion, ipsilateral hilum, bilateral mediastinum, and often the ipsilateral supraclavicular region. Elective nodal irradiation has been established as a standard approach, since results of study RTOG 73-01 demonstrated diminished survival time for patients who did not receive elective nodal radiotherapy compared with those who did.[43] However, there is a recent tendency to limit the size of the radiotherapy fields to include only gross primary and known nodal disease, as defined by thoracic computed tomography scans and sometimes by invasive staging. Since larger radiotherapy field sizes have been related to increased acute and late toxicity, especially pronounced in combined-modality regimens,[44-46] several investigators have delivered thoracic radiotherapy to the gross tumor only, reporting no compromise in locoregional control or survival.[17,47,48] Despite interest in treating smaller radiotherapy volumes in lung cancer, the concept has not yet been universally accepted.

Tumor-volume definition is improved with three-dimensional planning, often allowing reduction of doses to critical structures, especially if multiple noncoplanar beams are used.[49] An ongoing RTOG study is evaluating the feasibility of dose escalation for patients with NSCLC treated with three-dimensional conformal radiotherapy to the gross tumor only, without elective nodal irradiation. Maximum doses as high as 77.4 to 90.3 Gy are being planned, depending on the percentage of the total lung receiving more than 20 Gy. Such dose escalation is based on pilot experience[50] correlating the incidence of grade 3 or higher radiation pneumonitis with the percentage volume of normal lung to doses exceeding 20 Gy. A prospective trial is currently under way at the University of Michigan in which total radiotherapy doses are also partitioned according to the percentage of the entire lung volume receiving 20 Gy. Among patients with the lowest percentage of lung receiving 20 Gy, the currently prescribed dose is 100 Gy.

**Future Directions**

The prognosis for the vast majority of patients with NSCLC remains poor, and more effective therapies need to be investigated, including new approaches such as radiotherapy dose escalation as well as novel chemotherapy agents. Identification of prognostic factors may facilitate the design of clinical trials, allowing investigators to limit the more aggressive and toxic approaches for application to the subgroups of patients who may derive benefit from them.

New and improved staging methods are based not only on radiographic evidence of anatomic organ enlargements (eg, chest x-ray, computed tomography) but also on functional and immunologic or molecular techniques, such as immunohistochemical assessment of individual tumor cells in lymph nodes[51] and functional scans (labeled monoclonal antibodies; thallium 201 or PET scans).[52-54] These developments may allow definition of more uniform patient populations with predictable treatment outcomes. Finally, an international effort is under way to increase participation of adult patients in clinical trials from the current 2% of all patients with cancer, a change that would allow for more effective investigation of new therapeutic modalities and a faster establishment of new standards of care.

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