Evaluation and Definitive Management of Medically Inoperable Early-Stage Non-Small-Cell Lung Cancer: Part 1

By Roy H. Decker, MD, PhD, Lynn T. Tanoue, MD, Joseph M. Colasanto, MD, and Frank C. Detterbeck, MD, FACS

Lung cancer is estimated to be the second most commonly diagnosed cancer in both men and women in 2006, and the leading cause of cancer mortality. Non-small-cell histologies represent the majority of cases. Despite clinical investigation into screening high-risk populations, most patients have locally advanced disease at presentation and are not eligible for curative resection. For the minority of patients who are technically resectable at presentation, lobectomy or pneumonectomy and pathologic mediastinal nodal staging offer the best overall survival. The high rate of comorbid medical illness and poor baseline pulmonary function in this population, however, make many such early-stage patients medically inoperable. For these patients, conventional single-modality radiotherapy has been the primary definitive treatment option, as discussed in part 1 of this two-part article. Numerous retrospective reports demonstrate long-term disease-free and overall survival data that are modestly superior to that expected after observation, but both local and distant failure continue to be significant risks. Investigation of radiotherapy dose escalation is ongoing, in an effort to improve local control while maintaining minimal toxicity. Additionally, emerging evidence suggests that new modalities, such as stereotactic radiosurgery and radiofrequency ablation, may also be potentially curative treatment alternatives. These modalities will be addressed in part 2.

While surgical resection with pathologic nodal staging remains the standard of care in patients with early-stage disease, the high rate of comorbid medical illness in this population often raises concern about perioperative morbidity, postoperative pulmonary function, and long-term quality of life. An evidence-based multidisciplinary evaluation of patient age, cardiovascular health, and baseline pulmonary function can accurately predict which patients may benefit from lobectomy. In the absence of a curative surgical option, many patients and physicians appropriately opt for either a palliative or an observational approach, but there are a substantial number of patients for whom a definitive, nonsurgical approach is appropriate. To date, definitive radiotherapy has been the most commonly employed regimen, based on data suggesting a modest survival benefit. McGarry et al. analyzed the outcomes of 128 patients with stage I/II non-small-cell lung cancer (NSCLC), 47 of whom received no treatment. The median survival time with observation was 14.2 months, and the cause of death was cancer in 53% of the cases. Patients treated with radiotherapy in this series, with either palliative or curative intent, had significantly longer median survival, implying that a nonsurgical option conferred a survival benefit. Chadha et al. similarly reported a relatively poor median survival of 11.9 months (13.7 months for stage I and 8.4 months for stage II) for untreated early-stage NSCLC. Again, the most common cause of death was progressive disease, either local or metastatic. The largest evaluation of the utility of radiation was conducted from a population-based registry by Wisnivesky et al. The authors evaluated 4,357 patients diagnosed with stage I or II NSCLC who did not undergo surgical resection. Median survival was improved in patients treated with radiotherapy, although 5-year survival was not significantly different. Of note, the dataset did not distinguish between definitive and palliative radiation treatment courses.

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primary definitive option. Numerous retrospective reports demonstrate long-term disease-free and overall survival data that are modestly superior to that expected after observation, but both local and distant failure continue to be significant risks. Ongoing trials of dose escalation may improve local control, and the addition of systemic therapy may help to decrease metastatic failure. Additionally, emerging evidence suggests that new modalities, such as stereotactic radiosurgery and radiofrequency ablation (RFA), may offer curative treatment alternatives. These options will be discussed in the concluding part of this article, which will appear in the July issue of ONCOLOGY.

Operability

Defining "operability" in patients with lung cancer often presents a significant clinical challenge. Surgery is the treatment of choice for patients with stage I or II NSCLC. Recent studies support the use of postoperative adjuvant chemotherapy as well for treatment of early-stage NSCLC, but resection remains the primary therapeutic modality and is associated with the best long-term outcomes.[6-10] Many factors may contribute to the determination of whether an individual is suitable for lung resection. The factors that most commonly cause concern regarding morbidity or mortality following a surgical procedure are older age, the presence of significant cardiovascular risk, and the presence of underlying pulmonary disease.

Older Age

Age is increasingly a consideration in lung cancer treatment. Lung cancer generally affects an older population. Data from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program indicate that from 1998 to 2002, the median age at diagnosis of lung cancer was 70 years.[11] The most recent SEER data show that at initial diagnosis of lung cancer, 33.1% of patients were between ages 65 and 74, 27.9% were between ages 75 and 84, and 6.9% were age 85 years and older. As the population ages, an even larger number of patients will predictably fall into older age groups.

That said, an expanding body of evidence shows that age per se should not be a contraindication to surgery. Two recent single-institution retrospective series of pulmonary resections in octogenarians reported by Brock and colleagues (N = 68) and Port and colleagues (N = 61) noted 5-year survival rates in patients with resected stage IA NSCLC of 61% and 82%, and 30-day mortality rates of 8.8% and 1.6%, respectively.[12,13] With proper preoperative evaluation of functional status (such as the ability to perform activities of daily living), comorbidities, and cognitive function, it is clear that appropriately selected elderly patients can safely be offered curative surgical resection.[12-14]

Cardiovascular Risk

Patients with lung cancer are often at higher risk of cardiovascular disease because of shared risk factors, including cigarette smoking and older age. Since surgery for resection of lung cancer is rarely done emergently, preoperative cardiac evaluation should be possible in almost all patients. Perioperative cardiovascular risk assessment for noncardiac surgery, including thoracic surgery, has been studied extensively.

Joint evidence-based practice guidelines from the American College of Cardiology and American Heart Association have been available since 1980, with the most recent update published in 2002.[15] These guidelines make the important point that the purpose of the preoperative evaluation is not to merely grant medical clearance for surgery, but to assess the need for further preoperative testing, to plan for management of the patient's cardiac needs during and after surgery, and to guide treatment decisions.

Intrathoracic surgery falls into the category of intermediate cardiac risk, with the reported overall risk of cardiac complications usually less than 5%. Clinical predictors of increased perioperative risk of myocardial in-farction, heart failure, or death related to cardiac causes have been well described.[15] The presence of unstable coronary syndromes (acute or recent myocardial infarction or unstable angina), decompensated congestive heart failure, high-grade arrhythmias, or severe valvular disease may delay lung cancer surgery until appropriate evaluation and planning for cardiac management can be determined. Patients whose evaluations raise issues about limited life expectancy related to underlying cardiovascular disease or in whom intrathoracic surgery is deemed of unacceptable cardiovascular risk should be evaluated by appropriate specialists before a decision to deny surgery is made.

Pulmonary Disease

As with cardiovascular disease, older age and a high prevalence of cigarette smoking increase the risk for concomitant pulmonary disease. Chronic obstructive pulmonary disease (COPD) related to cigarettes is most commonly associated with lung cancer, but other lung diseases such as pulmonary fibrosis and asbestosis appear to contribute to increased risk of lung cancer as well.

Many patients with lung cancer have abnormal pulmonary function. The challenge of determining
operability for these patients dates to the early days of thoracic surgery. In 1955, Gaensler and colleagues addressed the risk of respiratory failure and death related to chest surgeries in patients with severe pulmonary tuberculosis.[16] Their landmark study was the first to report surgical outcomes in relation to preoperative pulmonary physiologic measurements (vital capacity and maximal breathing capacity) and to define thresholds for operability based on such measurements. In the 50 years that have passed since their observations, physiologic measurements have remained the cornerstone of operative risk assessment in patients undergoing lung resection. Those measurements typically used to determine resectability include absolute and percent predicted values of forced expiratory volume in 1 second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO), as well as exercise capacity. The latter is usually expressed as maximal oxygen consumption (VO2max) measured during formal cardiopulmonary exercise testing. A number of algorithms using these measurements to identify patients who can safely undergo lung resection have been proposed.[17-21] A summary of recommendations relating to assessment of resectability from the evidence-based guidelines for lung cancer proposed by the American College of Chest Physicians is outlined in Figure 1.[22]
Figure 1: Algorithm for the Physiologic Evaluation of Patients Being Considered for Surgical Resection of Lung Cancer—A summary of recommendations relating to assessment of resectability from the evidence-based guidelines for lung cancer proposed by the American College of Chest Physicians. The algorithm is modified from references 12 and 16. DLCO = diffusing capacity of the lung for carbon monoxide; FEV₁ = forced expiratory volume in 1 second; ppo = predicted postoperative; VO₂ max = maximal oxygen consumption.
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• Assessment Considerations—It is widely accepted that patients with absolute FEV1 > 2 L are candidates for pneumonectomy, and those with FEV1 > 1.5 L, candidates for lobectomy without further physiologic testing. These recommendations are based on older series done largely in men, with reported operative mortality < 5%. These studies typically did not report FEV1 as a percentage of predicted normal value, but a normal FEV1 (> 80% predicted) is also accepted as a criterion for resectability. Since cigarette smoking is so common a factor in lung cancer, obstructive airway disease is typically the accompanying pulmonary disease, with measurement of FEV1 providing a reasonable means of assessing severity.

In patients with evidence of interstitial lung disease on radiographic evaluation or in whom dyspnea is a prominent symptom, DLCO is also a useful measurement. Impairments in DLCO correlate with increased surgical morbidity as well as with worse quality of life after resection. Patients who have normal FEV1 and DLCO (ie, both > 80% predicted) should be considered suitable candidates for resection, including pneumonectomy, without further pulmonary evaluation.

The demographics of lung cancer have changed considerably over the past several decades, with women and older persons now comprising a larger percentage of patients. Persons who are female, older, of certain ethnicities (including African or Asian descent), and who are of smaller stature will have smaller lung volumes at their normal baseline. With this consideration, using percent predicted values of FEV1 and other physiologic measurements rather than absolute values are in general more reliable in assessing lung function.

In patients who have either abnormal FEV1 or DLCO, further evaluation is necessary to determine whether resection can be performed with acceptable operative mortality and postoperative morbidity and quality of life. Predictions of postoperative values of FEV1, DLCO, and VO2max require an estimation of how much lung function will be lost with resection. The usual means of measuring "split lung" function is by radionuclide quantitative lung scanning to assess perfusion to different sides and areas of the lung in combination with measurements of FEV1, DLCO, and VO2max.

Predicted postoperative FEV1 (FEV1ppo) is calculated as follows:

FEV1ppo = preoperative FEV1 X (1 - fractional contribution of lung to be resected as estimated by lung perfusion scanning)

Several studies have demonstrated reliable correlation of predicted and measured postoperative lung function using this method. Notably, there is evidence that patients undergoing lobectomy typically have more recovery of pulmonary function (measured as both FEV1 and VO2max) within 3 to 6 months after surgery than would be predicted by split lung function prediction, so that using this method, if anything, errs on the side of patient safety. The lower limit of acceptable FEV1ppo remains controversial. Typically, FEV1ppo of 40% of the predicted normal is felt to be the minimum threshold, although some groups have suggested that 30% may also be acceptable. Similarly, percent predicted postoperative DLCO (DLCOppo) of < 40% appears to correlate with increased perioperative complications and worsened postoperative pulmonary quality of life. Patients with both FEV1ppo and DLCOppo < 40% would generally be felt to have a high risk of surgical morbidity and postoperative severe pulmonary impairment. For some patients in this group, further physiologic assessment with cardiopulmonary exercise testing may be warranted to assess whether resection can still be an option. Alternatively, nonsurgical therapeutic modalities should be considered.

• Cardiopulmonary Exercise Testing—Exercise capacity can be estimated by simple stair climbing, or may be measured with formal cardio-pulmonary exercise testing (CPET). Stair climbing has been used for years as a measure of operability, although the number of stairs required to predict successful surgical outcome has been variably reported. Olsen and colleagues reported that to achieve successful surgical outcome a patient needed to climb at least 76 stairs for lobectomy and at least 100 steps for pneumonectomy. Pollock and colleagues reported that 83 stairs would be acceptable for pneumonectomy, and correlated this amount of effort with a VO2max of 20 mL/kg/min.

Formal cardiopulmonary exercise testing may be less readily available than stair climbing, but offers the ability to measure VO2max in a more standardized fashion. Both the British Thoracic Society and the American College of Chest Physician guidelines for lung cancer evaluation and treatment recommend that CPET be performed to measure VO2max if FEV1ppo and DLCOppo are < 40%. Based on a number of studies correlating VO2max with operative risk, it is generally accepted that patients with preoperative VO2max > 20 mL/kg/min can undergo pneumonectomy
without increased risk of perioperative complications, while VO2max < 15 mL/kg/min is associated
with an increased risk of perioperative complications.[31,34-42] Further, patients with preoperative
VO2max < 10 mL/kg/min are at very high risk of perioperative complications even with lobectomy
only.[18,35,40,43] Patients with VO2max in this range will need careful evaluation before a decision
regarding resectability can be made.

As with measurements of FEV1, concern has been raised about predictions based on absolute values
of VO2max, as women and persons of older age and shorter stature might have normal predicted
values of VO2max < 15-20 mL/kg/min. Several recent studies suggest that percent predicted
VO2max is a better predictor of surgical outcome than absolute preoperative VO2max.[36,37,41,44]
These studies suggest that perioperative complications are substantially increased in patients with
percent predicted VO2max < 50%-60%, but that patients who have exercise capacity above this
threshold can undergo surgery with reasonable safety.

Treatment Alternatives

The issue of resectability in patients whose physiologic evaluation raises concerns about
perioperative risk and postoperative pulmonary compromise clearly can be very challenging. Such
patients should undergo evaluation by a multidisciplinary team at a center with the necessary
expertise in pulmonary medicine and thoracic surgery before a final decision regarding the feasibility
of resection is made.

It should be noted that alternatives to classical lobectomy and pneumonectomy may be a
consideration for individual patients. Lung-sparing surgeries such as segmentectomy and wedge
resection may be reasonable in patients with severely diminished pulmonary function, and may offer
such patients good long-term outcomes.[45-47] Experience in patients with severe emphysema
undergoing lung volume reduction surgery has shown that carefully selected patients with very poor
lung function can safely undergo thoracotomy and may have functional benefit from removal of
severely emphysematous regions of lung.[48,49] In some cases, lung cancers contained within such
areas can also be resected, even though the physiologic parameters outlined in Figure 1 are not
met.[50,51] However, these patients should be very carefully selected, with evaluation performed at
centers with specific expertise in lung cancer and lung volume reduction surgery.

The question of what constitutes acceptable risk for potentially curative surgery remains extremely
difficult to answer. Treatment evaluation in patients who have substantial risk for perioperative
complications and postoperative compromise of quality of life related to limited pulmonary reserve
should include careful consideration of alternatives to surgery. As with other aspects of lung cancer
management, decisions relating to treatment for patients with impaired lung function should involve
multidisciplinary input from an experienced team of specialists in relevant disciplines, including
pulmonary medicine, thoracic surgery, medical oncology, and therapeutic radiology.

Conventional Definitive Radiotherapy

Primary radiotherapy has been used as the sole treatment modality for medically inoperable,
early-stage NSCLC patients for several decades,[5,52-76] and has become the standard of care in
this population. Historically, there have been a wide variety of dose fractionation schemes and
radiotherapy targets used, resulting in a similar variety of outcomes. Despite increased sensitivity of
staging imaging and advances in treatment technology, there have been only modest improvements
in reported local control and survival. Analysis of predominantly retrospective, single-institution
experiences has led to improvements in radiation dose and treatment planning, and has identified
areas where further advances may be made.

Nodal Irradiation

In the earliest series reporting the definitive use of radiotherapy in stage I/II tumors, relatively large
treatment volumes were used, encompassing the primary tumor as well as hilar and mediastinal
nodal regions.[52-54] The elective inclusion of clinically uninvolved nodal regions increases the
volume of normal lung tissue within the radiation portal, increasing the risk of acute and late
pulmonary toxicity.[77] The common use of computed tomography (CT) imaging, as well as the
advent of 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) staging, has theoretically
more accurately identified areas either harboring disease or at risk, and obviated the need for these
large treatment fields in many cases.

Moreover, several authors have specifically examined the utility of such treatment in terms of local,
nodal, and distant failure. Krol et al.[57] reviewed the outcome of 108 patients with inoperable
early-stage disease treated with definitive radiation alone. In the subset of complete responders,
18% failed locally, 4% failed locally and regionally, 6% failed locally and distally, and 6% failed
distally. Only 4% relapsed in the regional lymph nodes only. Hayakawa et al.[55] reviewed the
treatment results of 36 patients with stage I disease. In patients who did not receive elective nodal
irradiation, the investigators found only a 3% isolated regional failure rate. Similarly, Slotman et al.[70] noted a 6% regional nodal failure rate and Lagerwaard et al.[72] reported a 0% rate after treatment with local (ie, limited to the gross tumor) radiotherapy fields. Bradley et al.[73] compared patients who received 45 to 50 Gy of elective regional lymph node irradiation with those treated at the same institution without elective regional lymph node irradiation. These investigators found a 6% regional failure rate in untreated nodal regions, and no significant difference in cause-specific or overall survival between the two groups. Finally, Sibley[63] reviewed 10 published series of definitive radiation in patients with stage I NSCLC. Treatment volumes varied from small, localized fields to comprehensive elective lymph node coverage. Analysis of long-term outcomes demonstrated that 15% of patients were long-term survivors, 25% died of intercurrent disease, 30% died from distant metastasis, and 30% died from local failure only. The researchers observed no benefit to elective lymph node irradiation. Instead, they found a local control and disease-free survival benefit associated with higher radiotherapy doses. Taken together, this analysis of patterns of failure data has led to the conclusion that elective nodal irradiation has little role in the treatment of clinically node-negative early NSCLC.

Dose Escalation

The continued risk of local failure after radiotherapy has generated interest in determining whether increasing tumor dose would result in improved control. The standard radiation dose for definitive treatment of NSCLC, regardless of stage, has long been based on the Radiation Therapy Oncology Group (RTOG) 7301 trial.[78] This randomized dose escalation trial included patients with inoperable stage III or medically inoperable stage I or II disease, randomized to 40 Gy in a split course (20 Gy in 1 week followed by a 2-week rest and then an additional 20 Gy), or 40, 50, or 60 Gy in a continuous course delivered in 2-Gy daily fractions. Radiotherapy fields included the gross tumor volume as well as involved and electively included lymph nodes. The cohorts of patients who received the 50- or 60-Gy continuous-course regimen showed a decreased in-field failure rate (49% at 50 Gy, and 35% at 60 Gy) as well as increased time to failure (12 and 19 months, respectively). Since publication of this study, a minimum dose of at least 60 Gy has been considered by many to represent the standard definitive treatment dose.

Several authors have formally investigated the benefits of further dose escalation. The RTOG 9311 study is one of the largest modern prospective trials to examine doses greater than 60 Gy.[79] The authors stratified patients with stage I-III NSCLC into two groups, according to the volume of normal lung irradiated, and escalated tumor doses to 70.9 Gy, 77.4 Gy, 83.8 Gy, and 90.3 Gy in 2.1-Gy daily fractions. The lower lung-volume group, the majority of which were stage I and II patients, reached dose-limiting toxicity at the 90.3-Gy level. Acute grade 3 pneumonitis was seen in only 9%, and there were no cases of acute grade 3 esophagitis. Late toxicity, however, was significant: 13% late grade 3 or greater pulmonary toxicity including two treatment-related deaths, and 6% late grade 3 or greater esophagitis. The authors concluded that this dose level conferred an unacceptably high risk. Although they found no significant difference in overall survival or local control between the dose levels, the primary end point of the study was toxicity.

Rosenzweig et al.[80] found a similar tolerated dose in their single-institution prospective dose escalation trial. They enrolled 104 patients, 28% of whom had stage I or II disease, at dose levels of 70.2 Gy, 75.6 Gy, 81 Gy, and 84 Gy, and 90 Gy. Among seven patients treated to 90 Gy, two cases of grade 3 and one of grade 5 acute pulmonary toxicity were reported; this was deemed unacceptable. Of 26 patients treated to 84 Gy, only one patient had grade 3 or greater acute pneumonitis, and two had grade 3 late pulmonary toxicity. In contrast to the lack of benefit of higher doses in the RTOG trial, however, an overall survival advantage was seen in patients treated to greater than 80 Gy. Chen et al.[76] also found a survival advantage to higher-dose radiotherapy. The authors examined the stage I and II patients enrolled in the University of Michigan dose escalation trial. Using conformal techniques, patients were treated to doses ranging from 63 to 102.9 Gy in daily fractions. On multivariate analysis, increasing radiation dose was a significant prognostic factor for overall survival, with each 1 Gy in dose escalation associated with a 3% reduction in the risk of death. The median survival for patients treated to the highest dose was 33 months, vs 27 months for those treated in the first dose escalation cohort.

Previously published results of dose escalation in the larger cohort of patients, including advanced-stage patients, had found the highest dose level to carry no significant pulmonary risk.[81] Taken together, these trials provide preliminary evidence that dose escalation over 60 Gy may convey a clinical benefit and that a moderately increased dose confers a low risk of acute and late toxicity. Similar studies have been published establishing the tolerability of dose escalation in patients with more advanced disease and with concurrent chemotherapy.[82]
It is important to note that the studies demonstrating tolerance of these doses all used validated metrics of lung dose and volume, and limited dose escalation in patients deemed at lower risk of pneumonitis. Yet even in these carefully selected patients, using the most modern treatment planning, significant toxicity was noted at the highest dose levels. The optimal dose, balancing local control and treatment-related side effects, remains to be determined and likely will be a function of individual patient pulmonary function and tumor characteristics. Additionally, incremental gains in local control and survival must be balanced against increased time on treatment in this typically elderly population. For this reason, the tolerability and improvements in survival conferred by dose escalation must be borne out in larger cohorts and in appropriate clinical trials.

Continuous- vs Split-Course Radiotherapy

A further area of interest is the value of continuous-course radiotherapy. The most common modern treatment regimen is an uninterrupted course of radiotherapy, typically 60 Gy in 30 fractions over 6 weeks. Several authors have examined split-course radiotherapy using larger fraction size to a total dose of approximately 54 Gy, also over a 6-week period but with a 2-week treatment break at weeks 3 and 4. The addition of such a treatment break has been associated with decreased acute toxicity.[52]

Several studies show no significant difference in outcome between split-course and continuous-course radiotherapy.[57,65,83] This is also supported by a prospective trial involving 273 patients randomized to receive continuous-course vs split-course treatment.[84] This study showed no significant difference in survival (10.9 months for continuous-course vs 11.6 months for split-course radiotherapy), although increased morbidity was noted with the continuous-course regimen.

In contrast, Haffty et al.[52] noted improved survival (45% vs 12% at 5 years) and improved local control with continuous-course radiotherapy. This was also the finding of an RTOG prospective randomized trial that involved 551 patients (with early- and advanced-stage disease).[78] Patients with earlier-stage disease showed improved local control with continuous-course vs split-course radiotherapy (27% vs 38% intrathoracic failure rate).

Despite the apparently inconclusive evidence, continuous radiotherapy has become the most common prescribed course. Given the low reported toxicity of limited-field pulmonary radiation in patients with early-stage disease, treatment breaks are infrequently necessary, and with concern for tumor repopulation during therapy, overall treatment time is typically minimized.

Fractionated Radiotherapy

Both hyper- and hypofractionated, accelerated radiotherapy have been investigated in this setting to determine whether there is any additional benefit or decreased toxicity. The Netherlands Cancer Institute dose escalation trial[85] investigated increasing radiation doses using 2.25-Gy fractions. At doses higher than 67.5 Gy, twice-daily treatment was used to prevent further prolongation of treatment time. Patients were stratified by mean lung dose, and the dose was escalated until limiting toxicity was reached. For the two lowest-volume strata, which included the vast majority of patients with early-stage disease, doses of 87.8 and 81 Gy were reached. The authors concluded that the accelerated fractionation regimen was tolerated without excess toxicity.

Continuous hyperfractionated accelerated radiotherapy (CHART) is a strategy of three-times-daily radiotherapy to 54 Gy in 12 total treatment days. This was tested against standard daily radiotherapy in a randomized trial of 563 NSCLC patients, 169 of whom had early-stage disease.[86] CHART improved overall survival at 2 years—29% vs 20% for standard radiotherapy. Acute esophagitis, however, was also significantly increased. Acute pneumonitis was not increased in the CHART arm (10% vs 19% for standard treatment), but a trend toward increased late pneumonitis was seen.

Hypofractionated radiotherapy has also been investigated, in an effort to deliver a higher dose per fraction in a significantly shorter treatment time to minimize tumor cell repopulation. The use of large fraction sizes produces a theoretical risk of increasing late toxicity. The clinical experience, although limited, seems to demonstrate that such regimens are both well tolerated and effective. Slotman et al.[70] treated 31 stage I patients to 48 Gy in 12 fractions. The overall survival rate at 3 years was 42%, and the researchers found no clinically significant late pneumonitis. Cheung et al.[68] used the same accelerated hypofractionated treatment course in 33 patients with early-stage disease, and reported a 3-year overall survival rate of 43%. Significant pneumonitis, both acute and chronic, was noted in less than 10% of patients. Overall, both trials demonstrate long-term survival comparable to that seen in more conventionally fractionated trials, with acceptable toxicity.
The clinical results of definitive, fractionated radiotherapy are presented in Table 1.[5,52-76] Typically, the patients included in these trials were felt to be medically ineligible for surgery, or refused surgery. The median age ranges from 57 to 74 years. A heterogeneous group of tumor stages are represented, including clinically node-positive patients. In modern series with appropriate staging and tumor doses of 60 Gy or greater, the reported short-term (ie, < 1 year) local control rate ranges from 60% to 90%; at 3 years, the reported range is 40% to 70%. Overall survival in these studies is low—20% to 40% at 3 years—likely reflecting the advanced age and comorbid illness inherent in this population. Cause-specific survival is the most appropriate end point in assessing the efficacy of treatment, given a high risk of intercurrent death, and ranges from 20% to 50% at 3 years. Significant variables affecting local control and survival include radiation dose[63,80] and tumor size.[65]

**Toxicity**—The reported toxicity in these series is low. In contrast to the treatment of locally advanced disease, radiotherapy portals for patients with medically inoperable early-stage NSCLC are typically smaller, encompassing the tumor with a small margin to account for microscopic tumor extension, respiratory motion, and patient set-up error. While esophagitis is the acute dose-limiting toxicity in stage III disease, this would not be expected in patients with stage I or II disease in the absence of elective mediastinal lymph node irradiation. The most clinically concerning intermediate and late toxicity related to treatment of advanced-stage disease is pneumonitis, the risk of which is
known to be a function of the volume of lung irradiated. As expected, given the typically small treatment fields used for early-stage disease, this risk has been demonstrated to be low with conventional treatment to small primary tumors. Clinically significant (RTOG/European Organization for Research and Treatment of Cancer [EORTC] common toxicity scoring criteria grade 3 or above) pneumonitis was reported in less than 10% of patients in the listed series. Authors who specifically did not treat clinically uninvolved nodal regions reported rates of 5% or less. This low expectation of treatment-related side effects is appropriate for this patient population, given that the majority of patients are not at imminent risk of symptoms from their disease and typically have significant comorbid illnesses.

**Conclusions**—Primary radiotherapy has demonstrated efficacy in the definitive treatment of medically inoperable NSCLC. While many medically inoperable patients have significant comorbid illnesses, a significant proportion will die of progressive lung cancer without definitive treatment.[3] Survival following treatment is superior to that seen with observation[3] in multiple series with adequate follow-up, making this the standard treatment for patients not eligible for curative surgery. Even in modern radiotherapy series, however, the risk of both local and distant failure remains significant. In terms of the former, results of recent and current ongoing dose escalation trials hold promise for improving patient outcomes. Given that this patient population is typically elderly, with significant comorbid medical illness (and generally asymptomatic from their disease), advances in definitive treatment must be undertaken with care to maintain the expected low side-effect profile, and with the understanding that prolongation of treatment time may not be appropriate for some patients.

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