Evaluation and Definitive Management of Medically Inoperable Early-Stage Non-Small-Cell Lung Cancer: Part 2

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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 lung cancer represents the majority of such cases. Most of these 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 article, which appeared in last month's issue. 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 are addressed in part 2.

Stereotactic Body Radiotherapy
Stereotactic radiosurgery is well established as an appropriate definitive treatment modality for both primary and metastatic intracranial neoplasms. Highly conformal dose distributions delivering high single-fraction doses that spare nearby critical structures are possible because organ motion within the confines of the skull is limited, and the cranium therefore serves as an ideal medium to which a fiducial reference system may be attached. Extracranial stereotactic radiosurgery, or stereotactic body radiotherapy (SBRT), is emerging as a new treatment option for primary or metastatic targets in the liver, lung, retroperitoneum, and pelvis.[1] This strategy has become possible because of technical advances in treatment planning, immobilization, patient imaging, and tumor targeting. The safe use of SBRT to treat early, medically inoperable primary NSCLC with curative intent has been documented in numerous single-institution experiences[2-10] and is currently the subject of an ongoing multicenter phase II investigation (Radiation Therapy Oncology Group [RTOG] 0236). Radiosurgery seeks to take advantage of basic radiobiologic principles of dose, fraction size, and treatment duration. By delivering a high dose in an abbreviated treatment course, the biologically effective dose is far larger than that achievable with a conventional dose escalation scheme. Because overall treatment time is not extended, this should result in an increased tumoricidal effect without increased tumor cell repopulation. Additionally, such a treatment may prove far more convenient for many patients. Typical treatment regimens incorporate doses of 20 to 60 Gy in three to six fractions; the ongoing RTOG 0236 specifies 60 Gy in three fractions over 8 to 14 days. The high biologically effective dose of SBRT also exerts increased normal tissue effects, and thus,
there is a theoretical risk of markedly increased acute and late toxicity. This is especially of concern in this population of patients who frequently have borderline pretreatment pulmonary function. For this reason, greater care is taken to limit both the volume of such tissue included and the dose that it receives. Multiple converging beams, often noncoplanar, are often used. Normal tissue margins, included in conventional radiotherapy regimens to account for setup variation, organ motion, and dose buildup, are significantly reduced. This follows the paradigm of intracranial stereotactic radiosurgery, in which meticulous pretreatment imaging evaluation, effective immobilization, and highly conformal treatment planning results in rapid dose falloff between a well-defined target and surrounding normal tissue.

Minimizing Setup Variability and Tumor Motion
The high dose per fraction, small number of fractions, and minimal normal tissue margin treated during SBRT necessitates specialized methods to account for reproducible patient setup. When SBRT is delivered by linear accelerators, patient immobilization frames—either custom-designed or commercially produced—minimize intertreatment setup variability by decreasing patient translational and rotational motion. They may also provide the fiducial markers in reference to which the treatment is delivered. Stereotactic treatment implies that treatment beams are delivered in reference to such markers, placed either on the patient, in the tumor, or on the immobilization frame.

In the case of primary lung tumors, minimizing treatment margins also requires accounting for tumor motion associated with breathing. Diaphragmatic movement with breathing can alter the craniocaudal position of lung targets by up to 2-5 cm,[11-13] an effect that is most prominent in cases of peripheral, lower lobe lesions. With linear accelerator-based treatment, reducing such movement can be accomplished in two distinct ways: either by reducing diaphragmatic excursion or by gating treatment to the respiratory cycle.[11,14] The former is implemented with immobilization devices that limit abdominal wall motion,[15] or via patient breathing control.[13,16] In the latter case, beam-on time can be controlled by chest wall excursion, or by real-time fluoroscopic imaging on the treatment table. Alternatively, emerging technology allows treatment beams to move and conform to targets that vary with the respiratory cycle.

Several authors have used linear accelerators linked with a diagnostic computed tomography (CT) scanner to obtain patient and target imaging immediately prior to treatment.[17,18] The patient remains on the treatment couch, appropriately immobilized, throughout the separate scan and treatment. In this way, normal tissue margins included to account for systematic variations in patient daily setup may be eliminated. New linear accelerators from multiple manufacturers now include onboard three-dimensional kilovoltage imaging acquisition that can reconstruct detailed axial images with soft-tissue discrimination. Such data may be used to make incremental daily adjustments in patient setup and can significantly increase the confidence of treatment design, allowing little variation in patient and tumor position.

Efficacy
The efficacy of SBRT in the definitive treatment of NSCLC has been demonstrated in multiple single-institution series, often included among data concerning treatment of metastatic lung tumors, as well as primary and metastatic targets in other organs. Table 1 lists the reported end points of selected modern series of SBRT,[2-10] in which the subjects were predominantly patients with primary NSCLC. All authors limited treatment to node-negative patients. Tumors included T1-T3 lesions, as indicated. Local control was typically assessed with CT imaging, and radiographic regression or stable disease scored as successful local control. In some studies, 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) was used to assess tumor viability if there was a partial response.[6] Local tumor control at 6 to 12 months ranged from 80% to 100%. At 2 to 3 years, local control was 70% to 94% where such follow-up was available. Although these series are small, this implies that the initial radiographic response was reasonably durable. In some reports,[3,4] investigators noted a trend toward decreased local control as a function of tumor size, with superior results for tumors less than 3 cm. In reports where the dose varied, local control appeared to be better with a higher total dose.[10,19] Authors who included such data reported cause-specific survival rates at 2 to 3 years of 64% to 95%, which compares favorably to previously reported outcomes of conventional radiotherapy. Rates of failure at nodal and distant sites ranged from 4% to 15%, and 10% to 50%, respectively.

Toxicity
The overall reported toxicity in these series is low. Commonly reported peritreatment side effects include fatigue, low-grade fever, and mild discomfort. Patients with peripheral tumors experienced...
mild pneumonitis was reported in 40% to 100% of patients at short-interval follow-up. By RT0G/European Organization for Research and Treatment of Cancer (EORTC) common toxicity scoring criteria, grade 3 pneumonitis was seen in less than 10% of patients.

In terms of long-term morbidity in this at-risk population, two studies systematically examined pulmonary function tests before and after treatment and reported no significant postradiation differences,[5,20] although a temporary decrease of up to 10% in forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), or diffusing capacity of the lung for carbon monoxide (DLCO) has been reported.[19] This limited toxicity is likely a result of the highly conformal nature of the treatment, which largely avoids the high-dose treatment of a significant volume of normal lung tissue that is inherent in conventional radiotherapy for advanced-stage disease.

Of concern, however, are case reports of symptomatic bronchial stenosis after treatment of peribronchial lesions.[10,21] This appears to be a similar effect to that reported in a conventionally fractionated radiation dose escalation trial,[22] and may be a cause of concern when planning treatment to a central lesion. For this reason, patients with tumors within 2 cm of the proximal bronchial tree are excluded from the ongoing RTOG 0236. Rib fracture has also been noted in a minority of patients treated for pleural-based lesions.[2,6]

Summary

Overall, radiosurgery is a promising new method of delivering definitive radiation treatment to early-stage primary NSCLC. Local control as reported in single-institution series is superior to that seen for conventionally fractionated radiation. Clinically significant pulmonary toxicity is uncommon, although care must clearly be taken when considering treatment of tumors adjacent to major bronchi. Optimal candidates would include patients with tumors less than or equal to 5 cm in size, not adjacent to a primary or secondary bronchus. Patients would, depending on the radiosurgery system used, have to be able to tolerate immobilization and perhaps submit to control of breathing during prolonged treatment times. We would strongly recommend that eligible patients be considered for enrollment in RTOG 0236, or similar institutional trials, so that long-term outcomes and toxicity may be more clearly defined.

Radiofrequency Ablation

An alternative, definitive treatment option for node-negative tumors is radiofrequency ablation (RFA). This technique involves the placement of an electrode directly into the tumor, most commonly via a CT-guided percutaneous approach, although ultrasound guidance or direct palpation during minithoracotomy are alternatives. The exposed conductive tip of the electrode may have deployable tines, and multiple placements can be made during a single treatment session. These two factors technically limit the size of the target to 3 cm or smaller. An alternating current is applied between the centrally placed electrode and a reference electrode placed on the skin. Frictional heating raises tissue temperature above 60°C, hot enough to cause coagulation necrosis throughout the target volume.

The current is maintained until one of several end points: Ground-glass opacification is seen on CT, target tumor temperature is reached, impedance increases, or the manufacturer's recommended treatment time elapses. The natural impedance of air-filled lung limits the effect to the target mass, except in some cases where the lesion is immediately adjacent to a mediastinal structure or larger blood vessel. The procedure can be performed under conscious sedation, which is advantageous in patients who are, by definition, of marginal pulmonary status.

Clinical Data

The clinical results of RFA are reported primarily in single-institution experiences.[23-28] Most such series are heterogeneous, including not only primary early-stage NSCLC, but also nonbronchogenic metastases, as well as local and distant pulmonary recurrences of previously treated NSCLC.

Selected series with significant numbers of patients treated for primary NSCLC are summarized in Table 2.[28-28] Primary lung cancer patients included those who were inoperable due to pulmonary function, medical comorbidity, or patient refusal. Often, prior treatments included surgery, chemotherapy, or radiation. While some authors included patients with primary tumor sizes up to 5 cm,[23,25] others included more extensive lesions, up to 10 cm or greater.[24,26]

Because results are reported for the entire population treated, and the absolute patient numbers are small, survival end points cannot be meaningfully abstracted from these data. Local control has been assessed variably by follow-up CT scan[23,24,26,27] or by FDG-PET imaging.[25] The latter has clearly been shown to be both sensitive and specific[29] in assessing tumor viability, and Akeboshi et al[25] report somewhat lower complete response rates as a result. More commonly, complete necrosis of targets is assessed by follow-up CT imaging.
The expected changes after RFA are well described,[30] including early ground-glass opacification followed by bubble lucencies, cavitation, and late linear opacification. After treatment of peripheral lesions there may be pleural changes. Treatment response can be difficult to assess in this context, as variable changes in lesion size after RFA can mimic progression of disease. Lee et al.[26] however, used contrast-enhanced CT densitometry and found that 1- or 3-month radiographic assessment reliably predicted overall survival. Belfiore et al.[31] described a subset of patients in whom pathologic response rates were documented; of note, the complete response determined by microscopic examination was similar to the complete radiographic response reported for the entire cohort, suggesting a valid correlation. The relative value of radiographic partial necrosis or stable disease is not entirely clear, and longer follow-up of treated patients will presumably better define the predictive value of these end points in terms of both survival and symptomatic progression.

The overall local control rates reported in the literature for metastatic and primary lesions range from 40% to 90%; in series where primary NSCLC results are reported separately, they are similar. Several authors report significantly better local control in smaller lesions (ie, less than 3 or 4 cm) compared to larger.[25,26,32] In one report, lesions treated definitively, rather than palliatively, had a significantly better response.[26]

Side Effects

Side effects of RFA include periprocedural discomfort (generally well controlled) and, in some patients, low-grade fever. Among possible acute complications, pneumothorax is of the most concern, occurring in up to 40% of patients, but most of these may be followed without intervention; chest tube placement is required in only 5% to 15% of patients treated with CT-guided techniques. Pleural effusions may occur in 10% to 20% of patients, perhaps more frequently in patients treated for pleural-based lesions, but again, intervention is normally not required. One case report noted a pulmonary hemorrhage[32] after treatment of a central lesion, and the authors recommended against RFA as the first-line therapy in such patients. The development of lung abscess after treatment of larger lesions has also been noted.[25]

Patient Selection

The optimal candidate for RFA would have an isolated, peripheral lesion less than 3 cm in size.[32] The patient's pulmonary function must be such that the risk of pneumothorax inherent in the percutaneous approach would be acceptable. The advantages of such an approach would include the convenience of a single treatment, the low side-effect profile, and the ability to treat lesions in previously irradiated tissue. Additionally, RFA would be expected to be effective in necrotic, hypoxic lesions and therefore may be superior to definitive radiation for these tumors.

Centrally located lesions are more difficult to treat with RFA because of rapid heat dispersion by the rich vascular supply. Use of the technique for these tumors may also carry a higher risk of side effects. An additional theoretical disadvantage of RFA is that the natural impedance of air-filled lung that limits the effect to the tumor also precludes any treatment of microscopic disease extension. Whether this concern has any clinical significance is a question that will only be answered with longer follow-up and more intense study. Clearly, though, in patients with nodal disease, the multifocal nature of tumor and the high expectation of intervening microscopic disease would make RFA unsuitable. We would strongly recommend that appropriately selected, medically inoperable patients be enrolled in prospective trials to evaluate long-term local control, disease-specific survival, and quality of life. The upcoming American College of Surgeons Oncology Group (ACOSOG) Z4033 trial will examine these end points, and will evaluate the use of postprocedural FDG-PET in predicting long-term local control.

Looking Ahead

Further advances in outcomes after RFA may be improved with combined-modality treatment paradigms. Local control may be improved and marginal lesions may become suitable for treatment with the addition of further definitive local therapy. Combination treatment with RFA and radiotherapy is already the subject of phase II trials.[33]

Endoscopic Intervention

The use of endoscopic techniques in the palliation of pulmonary obstruction or hemorrhage due to intraluminal tumor is well established, but emerging evidence suggests that such methods can be used in a curative setting for carefully selected patients.[34] Commonly available modalities include photodynamic therapy, laser, electrocautery, cryotherapy, and brachytherapy. Eligible patients typically have radiographically occult lesions. Lesions that are strictly intraluminal, superficial, accessible endoscopically, and visible to their distal extent are candidates for treatment.[35] Case reports exist for the use of photodynamic therapy with curative intent in such patients.[36]
Deygas et al[37] used cryotherapy in 35 patients with endobronchial lesions. At 1 year, the complete response rate was 91%; at 4 years, the researchers noted a 28% local recurrence rate. Freitag et al[38] used sequential photodynamic therapy and brachytherapy in 32 patients and, with a mean follow-up of 24 months, found 26 to be free of disease. It should be noted, however, that substantial toxicity has been reported with the use of photodynamic therapy in tissue previously exposed to radiation.[39] Although these data are limited and largely preliminary, endoscopic therapy of selected, meticulously staged patients with entirely intraluminal disease may offer a curative approach with minimal risk to patients who are not eligible for surgery.

Adjuvant Systemic Therapy

The use of adjuvant systemic therapy in selected early-stage NSCLC patients after curative surgery has now more firmly demonstrated to confer a survival benefit. Three recent randomized trials[40-42] and a meta-analysis[43] of patients in the modern era have demonstrated an overall survival benefit, although the evidence is strongest for stage IB and II patients. This benefit is not unexpected, given that the distant relapse rate in such patients without adjuvant treatment can be as high as 40%.[44]

In medically inoperable patients, as improvements in therapy increase local control, nodal and metastatic sites will become more important as sites of first failure. Although this population includes patients who are not candidates for aggressive intravenous chemotherapy—either due to poor performance status or comorbid medical illness—such therapy should be considered in patients who are able to tolerate such treatment and would be expected to benefit. With the advent of active single-agent and multiagent targeted therapy, and ongoing interest in evaluating these agents in the adjuvant setting, a greater proportion of the medically inoperable population may become eligible for such systemic therapy.

Conclusions

The majority of patients with non-small-cell lung cancer present with advanced, unresectable, disease. For those who present with limited disease, a surgical approach—lobectomy or pneumonectomy and surgical nodal staging—offers superior long-term overall survival and is the standard of care. Careful evaluation by an experienced multidisciplinary team and, if appropriate, assessment of cardiovascular risk as well as preoperative and predicted postoperative pulmonary function will identify patients who would benefit from such intervention. Many such patients, however, are not candidates for potentially curative surgery due to advanced age, comorbid medical illness, or poor pulmonary function.

For patients who are medically inoperable or who refuse surgery, both palliative and definitive treatment options are available. Conventionally fractionated radiotherapy is the most well-established definitive option, with several decades of published results. Retrospective review of long-term survival after standard radiotherapy demonstrates a modest benefit compared to observation, but improvements in staging evaluation, imaging, and treatment planning may make such treatment both more tolerable and more effective. Dose escalation holds promise as an area that may help to improve local control and survival, and is the subject of ongoing clinical trials. Given the established benefit and low toxicity, conventional radiotherapy remains the standard treatment approach for the majority of early-stage NSCLC patients who are ineligible for surgery.

Emerging treatment modalities such as stereotactic radiosurgery and radiofrequency ablation are being actively investigated as alternative, definitive treatment options. Short-term results are promising, and toxicity appears to be tolerable. Both modalities offer the advantage of improved local control, compared to historical controls treated with conventional radiation, and an abbreviated treatment schedule. Patients who have relatively small (i.e., < 3-5 cm) tumors and are technically able to undergo the necessary procedures are good candidates for such treatment. Appropriately selected patients should be enrolled in prospective trials to establish the long-term efficacy and toxicity of these modalities. Such trials will help to better define the role of these potentially curative, nonsurgical treatment options.

Disclosures:
The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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