

Review

A Review of Stereotactic Body Radiation Therapy for the Treatment of Stage I Non-Small Cell Lung Cancer

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Abstract

The standard of care for the treatment of early-stage non-small cell lung cancer is surgical resection. However, many patients with this disease have other medical comorbidities, which may preclude them from undergoing a surgical procedure. In these patients, conventional fractionated radiation therapy over 6-8 weeks has historically resulted in poor outcomes. The development of stereotactic body radiation therapy, a new form of very precise radiation therapy that delivers high doses of radiation in as few as 1 to 5 treatments to the tumor, provides these patients with a promising new alternative. Several phase II studies have demonstrated high local control rates of greater than 80-90% with this approach, and a low risk of severe toxicity (<10%) when patients are appropriately selected. Further study is required to examine the optimal candidates for this treatment and to further refine the technique, but stereotactic body radiation therapy is emerging as a promising, non-invasive treatment for stage I non-small cell lung cancer.

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Key Words: *Non-small cell lung cancer, stereotactic body radiation therapy, medically inoperable*

Introduction

The standard of care for the treatment of early-stage non-small cell lung cancer is surgical resection. However, many patients with this disease have other medical comorbidities including coronary artery disease and emphysema, which may preclude them from undergoing a surgical procedure under general anesthesia. Recent advancements in imaging technology and techniques of delivering radiation therapy have led to the development of stereotactic body radiation therapy, which is emerging as a new treatment approach in this challenging subset of patients. In this article, we will review this technology, and the outcomes that have been achieved in treating stage I non-small cell lung cancer.

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Stage I Non-Small Cell Lung Cancer

Lung cancer remains the second most common cancer in both men and women in the United States, with 220,520 new cases in 2010. However, lung cancer is the leading cause of cancer related deaths in both men and women, with 157,300 deaths expected in the United States in 2010.¹

Non-small cell lung cancer is the most common type of lung cancer, and includes a variety of histologic subtypes including squamous cell carcinoma and adenocarcinoma of the lung. Non-small cell lung cancer is staged by the American Joint Committee on Cancer's TNM staging system. Early-stage non-small cell lung cancer includes tumors that are stage I. Stage I tumors include T1N0M0 and T2N0M0 tumors, which includes patients without evidence of lymph node or distant metastatic disease, and primary lung tumors that are more than 2 cm from the carina and measure up to 3 cm or 3-7 cm in size, respectively. Early-stage disease constitutes approximately 30% of all non-small cell lung cancer, and the overall survival at five years in historical series ranges from 50 to 80%.^{2,3}

Surgical Management of Stage I Non-Small Cell Lung Cancer

The surgical management of stage I non-small cell lung cancer optimally involves a lobectomy or pneumonectomy and sampling or dissection of the mediastinal lymph nodes. Local recurrence rates with these surgical approaches are low, with local control rates of 85 to 95% at five years, and overall survival rates of 50 to 80%.⁴⁻⁶

However, an anatomical resection with wide margins such as a lobectomy, sacrifices a significant amount of normal lung tissue, which may not be tolerated in patients with borderline lung function due to emphysema, pulmonary fibrosis, or other pulmonary disease and these are often co-morbid conditions in patients with lung cancer due to smoking history. In these patients, a less aggressive surgical resection such as a segmentectomy or wedge resection may be the only surgical option, but a randomized trial has shown that wedge resection results in inferior local control rates with a nearly 3-fold increase in local recurrence with wedge resection compared to lobectomy.⁷ Furthermore, some patients may have severely compromised lung function or other medical comorbidities such as cardiac disease that may make them ineligible for any amount of lung resection and/or general anesthesia.

Radiation Therapy in Medically Inoperable Stage I Non-Small Cell Lung Cancer

Historically, patients with medically inoperable (i.e. are not surgical candidates due to medical co-morbidities) stage I non-small cell lung cancer have been treated with conventional fractionated radiation therapy, which entails treatment with ~30 to 35 small doses of daily radiation therapy (e.g. 2 to 2.5 Gray (Gy) per fraction daily) over approximately 6 to 8 weeks. The outcomes with this approach have been poor with local control rates of less than 50% and overall survival of less than 10 to 15%.⁸⁻¹⁰ The likelihood of achieving local control has been associated with smaller tumor size and delivery of higher radiation doses.^{10,11} The limitations of this conventional radiation therapy approach are likely related to the inability to deliver a sufficient dose of radiation without causing injury to the surrounding normal lung tissue, and the protracted treatment course is often prohibitively inconvenient for this population of patients that are typically quite ill.

Stereotactic Body Radiation Therapy for Medically Inoperable Stage I Non-Small Cell Lung Cancer

Stereotactic body radiation therapy describes a highly precise technique of delivering high doses of radiation to a single target using multiple small beams of external radiation over 1 to 5 treatments. The very precise targeting of stereotactic body radiation therapy is accomplished by a number of different techniques including: rigid immobilization of the patient in a frame, referencing the patient to an exact coordinate system in the frame, and imaging immediately before and/or during the radiation treatment to align the patient into the correct position. Additionally, advances in imaging technology allow accurate capture of tumor motion through the respiratory cycle, which further improves the precision of radiation treatment targeting. The high level of precision allows for the safe delivery of much higher doses of radiation than can be accomplished with conventional fractionated radiation therapy. Whereas conventional fractionated radiation therapy regimens treat lung tumors to a total dose of 60-80 Gy in 2 to 2.5 Gy fractions over ~30-35 treatments, the higher doses per fraction and high precision of stereotactic body radiation therapy allow delivery of high doses of radiation to lung tumors over 1 to 5 treatments with this technique to biologically equivalent doses (BED) of > 100 Gy₁₀, which is effectively an ablative dose. Furthermore, since the treatment can be given in as few as 1 to 5 treatments, with each treatment usually given one to two days apart, these patients can complete their stereotactic body radiation therapy course in just 1 to 2 weeks, which is much more convenient than the 6-8 week course of treatment with conventional fractionated radiation therapy.

Outcomes with Stereotactic Body Radiation Therapy

There have been a number of single institution studies in the past 10 to 15 years, and one of the largest single institution series in North America was from Indiana University. In this Indiana series of 70 patients with medically inoperable stage I non-small cell lung cancer and primary tumors less than or equal to 7 cm in size, patients were treated with stereotactic body radiation therapy to the dose of 20 Gy times three fractions (total dose 60 Gy, BED = 180 Gy₁₀) or 3 fractions of 22 Gy (total dose 66 Gy, BED = 211 Gy₁₀) for T1 and T2 tumors, respectively (12, 13). Of note, patients had to have poor pulmonary function or other serious co-morbidities that precluded surgical resection to be eligible for this study. In fact, the median age of the patients on this study was 70 (range, 51-86), and the majority (n=40) had a forced expiratory volume in one second (FEV1) of less than 40% of predicted on pulmonary function testing, which is consistent with severe chronic obstructive pulmonary disease.

With a median follow-up of 50 months, the three year local control rate was 88%; only four patients (6%) had a local recurrence with regional recurrence in 8.6% and distant recurrence in 12.9%. The median survival was 32.4 months, and three-year overall survival was 42.7%. For the majority of patients, stereotactic body radiation therapy was well tolerated, and only 16% of patients had moderate to severe toxicity, which included decreased pulmonary function, pneumonia, pleural effusions, and skin irritation. However, in the subset of patients with centrally located tumors (< 2 cm from the tracheobronchial tree), there was a higher risk of severe toxicity and treatment related mortality compared to patients with peripheral tumors (46% versus 17%), and thus stereotactic body radiation therapy for central lung tumors using this regimen is not recommended.¹³ Nevertheless, this treatment regimen appeared to be safe and resulted in excellent local control rates for peripheral lung tumors, and was further studied in a multi-institutional Phase II trial led by the Radiation Therapy Oncology Group (RTOG).

In the RTOG 0236 trial, 55 patients with medically inoperable stage I non-small cell lung cancer were treated with stereotactic body radiation therapy using 20 Gy in 3 fractions as per the Indiana protocol.¹⁴ Based on the Indiana experience, patients with tumors less than 2 cm from the tracheobronchial tree were excluded. Again, the patients were only enrolled on this study if they had serious pulmonary disease (FEV1 < 40%) or other co-morbidities that ruled out surgery.

With a median follow-up of 34 months, the three year local control rate was 90% and the three-year locoregional control rate was 87%. The distant recurrence rate was 22%, and T2 (>3 cm) tumors were associated with a higher risk of distant recurrence. The three-year disease-free survival was 40% and overall survival was 56%. Of the 26 patients that died, only 10 died of lung cancer (18% of all patients), and the primary cause of death were other co-morbidities in the remaining patients.

Treatment was well tolerated, with moderate (grade 3) and severe (grade 4) toxicity seen in 24% and 4% of patients, respectively. This important study demonstrated that stereotactic radiation therapy can be delivered safely in a multi-institutional setting, and results in excellent control rates and overall survival, which are far superior to historical outcomes with fractionated radiation therapy.

Several other phase II studies and retrospective series of stereotactic body radiation therapy for medically inoperable stage I non-small cell lung cancer have also shown similarly excellent 3-year local control rates of 80 to greater than 90%, cause-specific survival of ~80%, and overall survival rates of 50 to 60%.¹⁵⁻¹⁹ Distant metastases remains a significant issue in patients with larger tumors, but in this population of medically inoperable patients with significant co-morbidities, adjuvant chemotherapy is often not an option. In fact, these series demonstrate that the majority of the patients currently treated with stereotactic body radiation therapy ultimately pass away from their co-morbidities, and not of non-small cell lung cancer, which is likely a reflection of the high local control rates.

Overall, while the results seen with this new treatment approach appear promising, stereotactic body radiation therapy remains a relatively novel treatment modality for stage I non-small cell lung cancer, and the follow-up in the majority of these studies is less than 5-years. Therefore, longer follow-up is needed to further assess whether the excellent local control rates seen thus far result in long-term cures.

Conclusion

Stereotactic body radiation therapy is emerging as a safe and efficacious treatment option for patients with medically inoperable stage I non-small cell lung cancer and small, peripherally located tumors. In several phase II studies, this technique results in local control rates of greater than 80 to 90%, and severe toxicity rates of less than 10%. Treatment of centrally located tumors and larger tumors remains under study and should be treated with stereotactic body radiation therapy only under protocol. The planning and delivery of this treatment technique is complex and requires significant technical expertise and support. Thus, patients should be referred to centers with high volume and significant institutional experience.

Future Directions

Currently, ongoing RTOG trials are studying whether central tumors can be treated safely with stereotactic body radiation therapy using more extended fractionation regimens (RTOG 0813 trial). For peripheral lesions, areas of research include identifying the optimal fractionation regimen (RTOG 0915 trial).

Furthermore, there is significant interest in determining whether stereotactic body radiation therapy can achieve

outcomes including local control and cure rates comparable to surgery in patients with stage I non-small cell lung cancer who are healthy enough to tolerate surgery. A phase II RTOG study (0618) is studying the use of stereotactic body radiation therapy in patients with stage I non-small cell lung cancer who are surgical candidates. And a joint RTOG and American College of Surgeons Oncology Group (ACOSOG Z4099/RTOG 1021) phase III study will be opening to compare sublobar resections to stereotactic body radiation therapy. The results of these studies may lead to further growth in the utilization of stereotactic body radiation therapy in the treatment of patients with stage I non-small cell lung cancer, and may set the stage for a new era of less-invasive treatment that preserves lung function.

Disclosure of Interests

Authors have no conflicts of interest to report.

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