Radiation Therapy for Early Stage Lung Cancer

Bhupesh Parashar, MD[1] Shruthi Arora, MD[1] A. Gabriella Wernicke, MD, MSc[1]

[1] Stich Radiation Center, Weill Cornell Medical Center, New York, New York

Address for correspondence Bhupesh Parashar, MD, Stich Radiation Center, Weill Cornell Medical Center, New York, NY 10021 (e-mail: bup9001@med.cornell.edu).

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Abstract

Radiation therapy for early stage lung cancer is a promising modality. It has been traditionally used in patients not considered candidates for standard surgical resection. However, its role has been changing rapidly since the introduction of new and advanced technology, especially in tumor tracking, image guidance, and radiation delivery. Stereotactic radiation therapy is one such advancement that has shown excellent local control rates and promising survival in early stage lung cancer. In addition, the toxicity profiles are quite favorable. In addition to stereotactic radiation, advances in brachytherapy techniques have enabled high local control rates in operable patients who receive sublobar resections due to compromised pulmonary function. Isotopes that have been used include iodine-125, palladium-103, and cesium-131. In this review article, the role of radiation therapy in treatment of lung cancer, patient selection, outcomes, toxicity and recent technological advancements are discussed. The radiation therapy techniques described in this article are also being used in the management of locally advanced lung cancers.

Keywords
- stereotactic
- HDR
- LDR
- radiation
- lung
- lung cancer

Objectives: Upon completion of this article, the reader will be able to discuss the different forms of radiation therapy used in the treatment of lung cancers, as well as discuss the outcomes and complications of such therapies.

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Lung cancer is the leading cause of cancer death both in men and women worldwide. In the United States in 2011, there were 160,000 deaths related to lung cancer.[1] Despite rapid advances in treatment technology and additional treatment options for this aggressive cancer, survival remains poor, especially in locally advanced and metastatic lung cancer. In a randomized phase 3 trial comparing the addition of chemotherapy to radiation and its sequence in stage III non–small cell lung cancer (NSCLC), median survival times were 14.6, 17.0, and 15.6 months for sequential chemotherapy and radiation, concurrent chemotherapy and radiation, and concurrent chemotherapy and twice daily radiation, respectively.[2] In metastatic NSCLC, median survival is ~8 months.[3] In early stage disease, 5-year overall survival is in the range of 50 to 80%.[4]

In early stage lung cancer, treatment options generally include surgery, chemotherapy, radiation therapy, and radiofrequency ablation. We discuss radiation therapy as a treatment option for early stage NSCLS, although the techniques are equally relevant to locally advanced cancers depending on the clinical situation. For example, stereotactic body radiation therapy is used primarily for early localized disease but has also been used to treat oligometastasis or for palliation of symptoms.[5,6]

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Selection of Cases

Surgical resection has been the standard of care for the management of early stage (stage I and II) NSCLC. Five-year

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survival rates of 50 to 70% have been reported after surgical resection for stage I lung cancer, although occasional reports suggest higher rates of survival.[4] The standard surgical technique for early stage disease is lobectomy, although wedge resection or segmental resection is sometimes considered an inferior alternative.[7] In patients who are considered medically inoperable, radiation therapy is usually the recommended treatment option. Inoperability in early stage lung cancer is determined by the following criteria: (1) baseline forced expiratory volume in the first second of expiration (FEV_1) <40% predicted; (2) predicted postoperative FEV_1 <30% predicted; (3) carbon monoxide diffusing capacity <40% predicted; (4) baseline hypoxemia or hypercapnia; (5) severe pulmonary hypertension; (6) diabetes mellitus with end-organ damage; (7) severe cerebral, cardiovascular, or peripheral vascular disease; (8) or severe chronic heart disease.[8]

Conventional External-Beam Radiation Therapy

Historically, patients with early stage lung cancer considered inoperable were offered conventional external-beam radiation therapy. Conventional radiation usually involves delivering radiation via two-dimensional beams using a linear accelerator (usually from the front and back). In conventional treatment, planning (simulation) is done using a diagnostic X-ray machine and radiation is delivered based on these simulation (X-ray) images. Detailed anatomical view (such as in a three-dimensional computed tomography [CT]) is not available; therefore accurate information about dose distribution to the target and surrounding normal structures is lacking.

Outcomes with conventional radiation treatment in the management of early stage lung cancer are disappointing.[9] Therefore, radiation was considered an inferior alternative to surgical resection for early stage lung cancer. This has dramatically changed with increased utilization and impressive outcomes seen with stereotactic technology.

Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) enables the delivery of high-dose radiation to the tumor while sparing normal tissues. This novel technology takes advantage of image guidance and radiation dose delivery to deliver high ablative doses of radiation to the tumor. Initially developed as an advancement in treating brain tumors (stereotactic radiosurgery), it is being increasingly used for extracranial sites including the thorax. SBRT allows delivery of high-dose radiation per fraction (e.g., 20 Gy) to the tumor versus 1.8 or 2 Gy per fraction in conventional radiation treatments. It is usually delivered to tumors >5 cm in size with no lymph node involvement. Larger tumors have a high probability of toxicity due to a high fractional dose and large volume of normal tissue treated. Indications for the use of stereotactic radiation in lung cancer includes tumors <5 cm in which lymph nodes are negative; tumors should also be located >2 cm from the tracheobronchial tree (central tumors).

Technique

We use extracranial stereotactic targeting techniques in conjunction with a stereotactic body frame by Elekta (Stockholm, SE). Multiple narrow beams converge to the isocenter, maximizing the dose to the lesion and maintaining low dose levels in the surrounding tissues. The shaping of these multiple beams is performed by a computerized multileaf collimator (MLC). With lung nodules in close proximity to critical structures, (e.g., spinal cord), further dose shaping is possible through the use of inverse planning optimization techniques and the dynamic mode of the MLC (intensity-modulated radiation therapy [IMRT]).

Typically, five coplanar beams are used, all converging to the center of the clinical target volume. The MLC allows shaping of the fields $<4 \times 4$ cm. The Pinnacle planning system by Philips (Andover, MA) is used to carry out the planning and dose calculations. The critical structures, organs at risk (OARs) excluded are the lungs, spinal cord, esophagus, heart, and rib cage (especially if the lesion is close to it). The beams are positioned approximately equidistant from each other and through the use of digitally reconstructed radiographs (DRRs), we try to avoid beam angles that enter or exit through an OAR. The prescription is based on a percentage isodose line that encompasses the planning target volume (PTV), with 100% set at the isocenter. Dose volume histograms and dose distributions in axial, sagittal, and coronal planes are used to evaluate the merit of the plan.

Treatment delivery has been improved with advancements in tumor localization and movement tracking technology. Prior to treatment, simulation using four-dimensional tracking (respiratory gating) tracks the tumor during breathing cycles. This allows for a more accurate treatment delivery, thereby making treatment safer.

Dose escalation has been shown to improve local control. There have also been data suggesting increased tumor local control if the biological effective dose (BED) is >100 Gy.[10]

SBRT Use in Operable Tumors

Encouraged by the impressive results of SBRT in early stage lung cancer for inoperable patients, there have been recent reports of successful utilization of SBRT in operable early stage lung cancer (►**Table 1**). In the analysis of a database of lung cancer patients treated with SBRT who were potentially operable,[11] a dose of 60 Gy was delivered using a risk-adapted scheme in 3, 5, or 8 fractions, depending on tumor size and location (T1–2). The median follow-up was 31.5 months, and median overall survival was 61.5 months, with 1- and 3-year survival rates of 94.7% and 84.7%, respectively

In a Japanese multicenter study,[12] 180 patients received SBRT. Of these, 120 were inoperable and 60 were operable. For tumors that measured <1.5 cm, 1.5 to 3.0 cm, and >3.0 cm in greatest dimension, radiation doses of 44 Gy, 48 Gy, and 52 Gy, respectively, were given in four fractions. The 3-year survival rate was 74% for operable patients and 59% for medically inoperable patients ($p = 0.080$). The 3-year local control rate was 86% for tumors ≤3 cm and 73% for tumors

Table 1 Recent studies on the efficacy of stereotactic body radiation therapy in early stage lung cancer

Study	No. of patients	Stage	Dose/fractionation	Toxicity higher than grade 3 (%)	Local control	Overall survival
Shibamoto et al[12]	180	I	44 Gy, 48 Gy, and 52 Gy	Grade ≥2: 13% (pneumonitis)	3 y: 86% (≤3 cm); 73% (>3 cm)	3 y: 69%; 5 y: 52%
Ricardi et al[25]	62	I	45 Gy (3 fractions of 15 Gy)	None	3 y: 87.8%	3 y: 57.1%
Baumann et al[26]	57	T1–2	45 Gy (3 fractions of 15 Gy)	NA	3 y: 92%	3 y: 60%
Timmerman et al[13]	70	T1–2 N0M0	60–66 Gy in 3 fractions	15.7	3 y: 88.1%	3 y: 42.7%
RTOG 0236[27]	55	T1–2 N0M0	60 Gy in 3 fractions	27.2	3 y: 98%	3yr-56%

Abbreviations: NA, not applicable; RTOG, Radiation Therapy Oncology Group.

>3 cm ($p = 0.050$). Grade ≥2 radiation pneumonitis developed in 13% of patients.

SBRT for Central Tumors

In the seminal phase 2 study[13] using SBRT for inoperable early stage lung cancer, a threefold increased risk of grade 3 to 5 toxicity for centrally located tumors (tumors within 2 cm of the tracheobronchial tree) versus peripheral tumors (27% versus 10.4%, respectively; $p = 0{,}088$) was noted. The radiation fractionation used in this study was 18 Gy per fraction, and three fractions were given. This led to exclusion of centrally located tumors receiving SBRT in the Radiation Therapy Oncology Group protocols.

In another study,[14] 32 patients diagnosed as stage I, T1N0 or T2N0, resectable NSCLC were treated with body frame–based fractionated SBRT. The 1- and 2-year actuarial local tumor control rates were both 85.3%. Overall survival was 70.9% at 1 year and 38.5% at 2 years, and survival was not correlated with SBRT dose. Of nine patients with centrally located tumors, three (33%) experienced grades 3 to 5 pulmonary toxicities. Eight patients showed partial or complete bronchial stricture and secondary loss of normal lung volumes; the median time to bronchial stricture was 20.5 months.

In the Dutch study[11] evaluating operable patients, patients with peripheral T1 tumors without broad contact with the chest wall were treated with three fractions of 20 Gy each; patients with T1 tumors that had broad contact with the chest wall and T2 tumors were treated with five fractions of 12 Gy each. Patients with centrally located tumors were treated with eight fractions of 7.5 Gy each. As mentioned,[11] OAS was 61.5 months, and 1- and 3-year OAS was 94.7% and 84.7%, respectively. At 5 years, OAS was 51.3%. Local control at 1 and 3 years was 98% and 93%, respectively. The 30-day mortality rate observed in the SBRT cohort of 177 patients was 0% versus 2.6% after lobectomy. Grade 3 pneumonitis was observed in 2% of patients.

In a recent study,[15] 58 central lesions in 56 patients were treated. Dosages used were 8 Gy × 6 fractions, 9 Gy × 5 fractions, 10 Gy × 5 fractions, and 12 Gy × 5 fractions. At a median follow-up of 23 months, the actuarial 2-year local tumor control rate was 85% for tumors treated with a BED >100 Gy, compared with 60% for tumors treated with a BED ≤100 Gy. No grade 4 or 5 toxicity was observed. Acute grade 1 to 2 esophagitis was observed in 11% of patients. ►**Table 2** summarizes additional literature evaluating outcomes of treating central tumors with SBRT.

Brachytherapy for Lung Cancer

Brachytherapy has been in use for lung cancer for several years. Brachytherapy techniques include high dose rate (HDR) and low dose rate (LDR) brachytherapy. The two types differ in the rate of radiation delivery as well as the techniques of application.

Table 2 Recent outcomes in lung cancer patients with central tumors

Study	Outcome	Total dose	Fractional dose	Toxicity
Haasbeek et al[28] ($n = 63$)	3-y LC: 92.6%; 3-y OAS: 64.3%	60 Gy	7.5 Gy × 8f	Chest wall grade III ($n = 2$), dyspnea ($n = 2$), no grade IV/V
Janssen et al[29] ($n = 65$; 29 central tumors)	Six local recurrences: 1-y LC: 93%; OAS: 79%	40 Gy (3 patients) 48 Gy (26 patients)	8 Gy × 5f 8 Gy × 6f	Grade 1 and 2 pneumonitis 21.5%
Peulen et al[30] reirradiation ($n = 29$; 32 lesions)	LC at 5 mo was 52%; 2-y survival: 43%			Grade 3 and4 toxicity scored 14 times in 8 patients

Abbreviations: LC, local control; OAS, overall survival; f, fraction.

HDR Brachytherapy

HDR brachytherapy involves delivery of radiation at a rate of >12 Gy/hour. This technique is also known as the "after-loading technique" because radiation delivery applicators are placed in the area of interest first (as a separate procedure), which is then followed by introduction of radiation source (e.g., iridium-192) through the applicators. This technique has significant safety advantages for the medical staff compared with LDR because radiation source placement is performed remotely into the patient's tumor/treatment area while the radiation delivery staff is confined to another room at a safe distance from the patient. This remote controlled application is made possible by computerized HDR delivery machines. HDR techniques have commonly been used to deliver radiation for palliation for endobronchial disease, although peripheral tumors have also been successfully treated using this technology.[16] Most of the data about the effectiveness of HDR brachytherapy have been in advanced or palliative settings rather than early stage lung disease. However, the technology has the potential to treat early stage lung cancer effectively.[17]

LDR Brachytherapy

LDR brachytherapy usually involves placement of radioactive sources at the tumor bed during surgical resection of the tumor. These radioactive sources deliver radiation therapy at the rate of ~2 Gy/hour. The most commonly used radioisotope is iodine-125 (I-125), although other radioisotopes have also been used (e.g., cesium-131 [Cs-131] and palladium-103 [Pd-103]).[18]

Patient Selection

Patients are generally selected based on their past medical and surgical history as well as pulmonary function. Patients who are selected for LDR brachytherapy usually have a prior history of lobectomy/pulmonary resection or compromised cardiovascular function that makes them ineligible for lobectomy.[19]

Selection of Isotopes

The most commonly used isotope is I-125, although other isotopes used include Pd-103 and Cs-131. Radiobiologically, Cs-131 and I-125 are similar, although the dose rate of Cs-131 is significantly higher, which theoretically may make it more effective in aggressive tumors such as lung cancers.

Technique

Brachytherapy can be performed using either a mesh or a "double-suture" method at the discretion of the operating surgeon and radiation oncologist. In mesh brachytherapy, a polyglycolic mesh template is constructed so that each seed is placed at 1-cm strand separation intervals along the surface of the mesh implant. The mesh is then introduced into the chest through a thoracoscopic access site or a thoracotomy incision made by the thoracic surgeon, with the radiation oncologist present. The thoracic surgeon configures the proper orientation of the implant over the resection margin, and then secures the implant to the visceral pleura with tacking sutures of 2-0 to 3-0 silk or polyglycolic acid suture. In the double-suture method, radioactive seeds that are embedded in polyglactin suture come in suture strands containing ten seeds at 1 cm center-to-center separation. The seeds are affixed to the lung surface with several sutures of 3-0 silk spaced 1 to 2 cm apart. The process is continued until both sides of each resection margin have a parallel row of seeds on each side. Any excess of seeds is placed in a lead container. The goal of the implant is to provide a dose of 60 to 80 Gy with Cs-131 or 120 Gy with I-125 to a 5-mm depth and with a 1-cm margin on both sides of the staple line. Outcomes of patients with sublobar resection plus brachytherapy are promising (►**Table 3**).

Safety for Medical Staff and Family

All treating physicians and staff are required to wear protective lead gloves and aprons in the operating room. In addition, it is recommended that the treating physicians and staff have thermoluminescent dosimeter rings and optically stimulated luminescence badges to monitor radiation exposure. It is standard procedure to give the patient and family discharge radiation safety instructions.

Radiation Therapy: Recent Technological Advances

CyberKnife

CyberKnife (Accuray Incorporated, Sunnyvale, CA) is an stereotactic radiosurgery system invented in the early 1990s by John Adler, a neurosurgeon at Stanford University. It is a frameless image-guided radiation therapy system mounted on a robotic arm. It was first approved by the U.S. Food and Drug Administration for intracranial application in 1999 and received clearance for full-body applications (lung, prostate, etc.) in 2001. The CyberKnife room is equipped with an orthogonal X-ray guidance system to track the target during treatment. The guidance uses either the patient's bony landmarks or implanted fiducial markers to track target movement.

Table 3 Studies in lung cancer patients treated with resection plus low dose rate brachytherapy

Study	Disease	Dose	*N*	Local control	Survival
Chen et al[31]	Stage I NSCLC	100–120 Gy	23	100%	95% at 11 mo
Fleischman et al[32]	Stage I–stage III	80–200 Gy	14	1 y: 71%	Median survival: 15.1 mo
Pisch et al[33]	Stage I	140–160 Gy	13	85%	7 of 13 patients at 4–36 mo
Hilaris and Martini[34]	T1–T3, N2	I-125: 160 Gy Ir-192: 30 Gy	88	76%	2 y: 51%

Abbreviations: NSCLC, non–small cell carcinoma; I-125, iodine-125; Ir-192, iridium-192.

There have been reports of successful treatment of early stage lung cancers by CyberKnife using hypofractionated treatments (large radiation fractions, usually >2 Gy). The treatment is reported to be effective and safe.[20,21] A recent retrospective observational cohort study of the pulmonary functions test in patients with lung cancer treated with CyberKnife stereotactic radiation showed no change after treatment in 37 patients.[22]

Tomotherapy

The novel tomotherapy system was developed in 1990s as a way to deliver dynamic helical radiotherapy with imaging guidance. The radiation unit is a linear accelerator that combines fan beam delivery in a continuously rotating gantry, with binary multileaf collimators allowing IMRT. There is an integrated CT scanner with the treatment machine that allows volumetric image acquisition prior to radiation delivery.

There have been a few reports showing the potential efficacy of helical tomotherapy for early stage lung cancers. In a planning study performed in centrally located NSCLC, SBRT plans for 10 patients with centrally located lesions or lesions immediately adjacent to a critical structure were generated. A total of 70 Gy in 10 fractions was delivered to the PTV to satisfy a target volume coverage of ≥95% PTV receiving 70 Gy and an established set of dose constraints for the OARs. Helical tomotherapy allows the sparing of critical structures immediately adjacent to the tumor target, thus making SBRT feasible for these centrally located lesions.[23]

Robot-Assisted Brachytherapy

There have been recent reports of using a robotic system for radioactive seed implantation after sublobar resection. In a recent study,[24] 11 patients with stage I lung cancer who underwent sublobar resection with the da Vinci surgical system (Intuitive Surgical Inc., Sunnyvale, CA) were implanted with I-125 seeds at the resection line. Perioperative mortality rate was 0%, and recurrence rate was 9%.

Conclusion

There have been exciting and promising recent advances in radiation therapy for early stage lung cancer. These include newer radiation technology and treatment techniques. Stereotactic radiation has shown promise in early stage disease, and reported outcomes are quite impressive. In addition, development of new machines and software has enabled highly effective and accurate stereotactic radiation delivery. There have also been advances in LDR and HDR brachytherapy that improve results of sublobar and/or suboptimal resection (e.g., positive margins). Although surgery is still considered the primary treatment for early stage lung cancer, phase 3 randomized studies are needed to evaluate how radiation therapy compares with surgery in treatment outcomes. In addition, studies should be performed combining two or more modalities such as combining radiofrequency ablation and SBRT for unfavorable early stage disease (e.g., T2 cancer or a radio-resistant histology).

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