Intensity-Modulated Radiotherapy of the Lung

Description

Radiotherapy (RT) is an integral component in the treatment of lung cancers. Intensity-modulated radiotherapy (IMRT) has been proposed as a method of RT that allows adequate RT to the tumor while minimizing the radiation dose to surrounding normal tissues and critical structures.

Background

For certain stages of some cancers, randomized controlled trials have shown that postoperative radiation therapy improves outcomes for many patients. Adding radiation to chemotherapy also improves outcomes for those with inoperable lung tumors that have not metastasized beyond regional lymph nodes.

Radiation techniques

Conventional External-Beam Radiation Therapy: Over the past several decades, methods to plan and deliver radiation therapy (RT) have evolved in ways that permit more precise targeting of tumors with complex geometries. Most early trials used 2-dimensional radiation therapy (2D-RT) treatment planning, based on flat images, and radiation beams with cross-sections of uniform intensity that were sequentially aimed at the tumor along 2 or 3 intersecting axes. Collectively, these methods are termed "conventional external-beam radiation therapy" (EBRT).

Three-Dimensional Conformal Radiation: Treatment planning evolved by using 3-dimensional images from computed tomography (CT) scans to delineate the tumor, its boundaries with adjacent normal tissue, and organs at risk for radiation damage. Computer algorithms were developed to estimate cumulative radiation dose delivered to each volume of interest by summing the contribution from each shaped beam. Methods also were developed to position the patient and the radiation portal reproducibly for each fraction and immobilize the patient, thus maintaining consistent beam axes across treatment sessions. Collectively, these methods are termed 3-dimensional conformal radiation therapy (3D-CRT).

Intensity-Modulated Radiotherapy (IMRT): IMRT, which uses computer software, CT images, and magnetic resonance imaging (MRI), offers better conformity than 3D-CRT as it is able to modulate the
Intensity of the overlapping radiation beams projected on the target and to use multiple-shaped treatment fields. It uses a device (a multileaf collimator, MLC) which, coupled to a computer algorithm, allows for “inverse” treatment planning. The radiation oncologist delineates the target on each slice of a CT scan, and specifies the target’s prescribed radiation dose, acceptable limits of dose heterogeneity within the target volume, adjacent normal tissue volumes to avoid, and acceptable dose limits within the normal tissues. Based on these parameters and a digitally reconstructed radiographic image of the tumor and surrounding tissues and organs at risk, computer software optimizes the location and shape of beam ports, and beam and beamlet intensities, to achieve the treatment plan’s goals.

Increased conformity may permit escalated tumor doses without increasing normal tissue toxicity, and may thus improve local tumor control, with decreased exposure to surrounding normal tissues, potentially reducing acute and late radiation toxicities. Better dose homogeneity within the target may also improve local tumor control by avoiding under-dosing within the tumor and may decrease toxicity by avoiding overdosing.

Because most tumors move as patients breathe, dosimetry with stationary targets may not accurately reflect doses delivered within target volumes and adjacent tissues in patients. Furthermore, treatment planning and delivery are more complex, time consuming and labor-intensive for IMRT than for 3D-CRT. Thus, clinical studies must test whether IMRT improves tumor control or reduces acute and late toxicities, when compared with 3D-CRT.

Methodologic Issues with IMRT Studies

Multiple-dose planning studies have generated 3D-CRT and IMRT treatment plans from the same scans, then compared predicted dose distributions within the target and in adjacent organs at risk. Results of such planning studies show that IMRT improves on 3D-CRT with respect to conformity to, and dose homogeneity within, the target. Dosimetry using stationary targets generally confirms these predictions. Thus, radiation oncologists hypothesized that IMRT may improve treatment outcomes compared with those of 3D-CRT. However, these types of studies offer indirect evidence on treatment benefit from IMRT, and it is difficult to relate results of dosing studies to actual effects on health outcomes.

Comparative studies of radiation-induced side effects from IMRT versus alternative radiation delivery are probably the most important type of evidence in establishing the benefit of IMRT. Such studies would answer the question of whether the theoretical benefit of IMRT in sparing normal tissue translates into real health outcomes. Single-arm series of IMRT can give some insights into the potential for benefit, particularly if an adverse effect that is expected to occur at high rates is shown to decrease by a large amount. Studies of treatment benefit are also important to establish that IMRT is at least as good as other types of delivery, but in the absence of such comparative trials, it is likely that benefit from IMRT is at least as good as with other types of delivery.

Regulatory Status

In general, IMRT systems include intensity modulators, which control, block, or filter the intensity of radiation; and, RT planning systems, which plan the radiation dose to be delivered.
A number of intensity modulators have received marketing clearance through the U.S. Food and Drug Administration (FDA) 510(k) process. Intensity modulators include the Innocure Intensity Modulating Radiation Therapy Compensators (Innocure, LLC) decimal tissue compensator (Southeastern Radiation Products) FDA product code: IXI. Intensity modulators may be added to standard linear accelerators to deliver IMRT when used with proper treatment planning systems.

RT treatment planning systems have also received FDA 510(k) marketing clearance. These include the Prowess Panther (Prowess, Inc.), TiGRT (LinaTech, LLC), Ray Dose (Ray Search Laboratories), and the Standard Imaging eIMRAT Calculator (Standard Imaging) FDA product code: MUJ.

Fully integrated IMRT systems also are available. These devices are customizable, and support all stages of IMRT delivery, including planning, treatment delivery, and health record management. One such device to receive FDA 510(k) clearance is the Varian IMRT system (Varian Medical Systems). FDA product code: IYE.

Related Policies

8.01.48 Intensity-Modulated Radiation Therapy (IMRT): Cancer of the Thyroid
8.01.49 Intensity Modulated Radiation Therapy (IMRT) of the Abdomen and Pelvis
8.01.59 Intensity Modulated Radiation Therapy: Central Nervous System Tumors

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Intensity-modulated radiotherapy (IMRT) may be considered medically necessary as a technique to deliver radiation therapy in patients with lung cancer when all of the following conditions are met:

- Radiotherapy is being given with curative intent.
- 3D conformal will expose >35% of normal lung tissue to more than 20 Gy dose-volume (V20).
- IMRT dosimetry demonstrates reduction in the V20 to at least 10% below the V20 that is achieved with the 3D plan (eg, from 40% down to 30% or lower).

IMRT is considered not medically necessary as a technique to deliver radiation therapy in patients receiving palliative treatment for lung cancer.

IMRT is not medically necessary for the treatment of lung cancer for all indications not meeting the criteria above.

Policy Guidelines

Table 1: Radiation Tolerance Doses for Normal Tissues of the Chest and Abdomen

<table>
<thead>
<tr>
<th>Site</th>
<th>Portion of Organ Involved</th>
<th>TD 5/5 (Gy)</th>
<th>TD 50/5 (Gy)</th>
<th>Complication End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/3</td>
<td>2/3</td>
<td>3/3</td>
<td>Portion of Organ Involved</td>
</tr>
</tbody>
</table>
The tolerance doses in the table are a compilation from the following 2 sources:
Kehwar TS, Sharma SC. Use of normal tissue tolerance doses into linear quadratic equation to estimate normal tissue complication probability. Available at: http://www.rooj.com/Radiation%20Tissue%20Tolerance.htm
NP: not provided.
a TD 5/5, the average dose that results in a 5% complication risk within 5 years
b TD 50/5, the average dose that results in a 50% complication risk within 5 years

Rationale

Intensity-modulated radiotherapy (IMRT) methods to plan and deliver radiotherapy (RT) are not uniform.1-3 IMRT may use beams that remain “on” as multileaf collimator (MLC) devices move around the patient (dynamic MLC), or that are off during movement and turn on once the MLC reaches prespecified positions (“step and shoot” technique). A third alternative uses a very narrow single beam that moves spirally around the patient (tomotherapy). Each of these methods uses different computer algorithms to plan treatment and yields somewhat different dose distributions in and outside the target.

Patient position is another variable that can alter target shape and thus affect treatment plans. Some investigators and clinicians deliver 3-dimensional conformal radiation therapy (3D-CRT) and IMRT with the patient prone, (4) while most treat supine patients as in conventional (2D) external beam radiotherapy (EBRT). A recent comparative dosimetric analysis (published only as an abstract) concluded that target coverage is similar with either position, but plans generated for the prone position spared more lung tissue than those generated if the same patient was supine. (5) However, data are unavailable to compare clinical outcomes for patients treated in prone versus supine positions, and consensus is lacking.

Respiratory motion of the breast and internal organs (heart and lung) during radiation treatments is another concern when using 3D-CRT or IMRT to treat breast cancer. (6, 7) Treatment plans are usually based on 1 scan, a static 3D image. They partially compensate for day-to-day (interfraction) variability in patient set-up, and for (intrafraction) motion of the target and organs at risk, by expanding the target volume with uniform margins around the tumor (generally 0.5-1 cm for all positional uncertainty).

Current methods and ongoing investigations seek to reduce positional uncertainty for tumors and adjacent normal tissues by various techniques. Patient immobilization cradles and skin or bony markers are used to minimize day-to-day variability in patient positioning. Investigators are exploring an active breathing control device combined with moderately deep inspiration breath-holding techniques to improve conformity and dose distributions during IMRT for breast cancer. (6,7) Techniques presently being studied with other tumors (eg, lung cancer ) (8) either gate beam delivery to the patient’s respiratory movement or continuously monitor tumor (by in-room imaging) or marker (internal or surface) positions to aim radiation more accurately at the target. The impact of these techniques on outcomes of 3D-CRT or IMRT for breast cancer is unknown. However, it appears likely that respiratory
motion alters the dose distributions actually delivered while treating patients from those predicted by plans based on static computed tomography (CT) scans, or measured by dosimetry using stationary (nonbreathing) targets. In addition, non-small-cell lung cancer (NSCLC) has more irregular, spiculated edges than many other tumors, including breast cancer. This precludes drawing tight margins on CT scan slices when radiation oncologists contour the tumor volume. It is unknown whether omitting some tumor cells or including some normal cells in the resulting target affects outcomes of 3D-CRT or IMRT. Another, more recent concern for highly CRT is the possibility that tumor size may change over the course of treatment as tumors respond or progress. Whether outcomes might be improved by repeating scans and modifying treatment plans accordingly (termed adaptive RT) is unknown.

These considerations emphasize the need to compare clinical outcomes rather than treatment plan predictions to determine whether one RT method is superior to another.

The literature search found no reports directly comparing health outcomes of IMRT with those of 3D-CRT for either breast or lung cancer treatment. There were no prospective comparative trials (randomized or nonrandomized). Because available data are scant, the report summarizes the studies that reported health outcomes.

**Lung Cancer**

**Systematic Reviews**
In 2012, Bezjak et al published a systematic review that examined the evidence for the use of IMRT in the treatment of lung cancer to quantify its potential benefits and make recommendations for RT programs considering adopting this technique within Ontario, Canada. (9) This review consisted of 2 retrospective cohort studies (through March 2010) reporting on cancer outcomes, which was considered insufficient evidence on which to make evidence-based recommendations. These two cohort studies reported on data from the same institution (M.D. Anderson Cancer Center); the study by Liao et al (2010, reported next) (10) acknowledged that patients included in their cohort (n=409) were previously reported on in the earlier cohort by Yom et al (n=290), but it is not clear exactly how many patients were added in the second report. However, due to the known dosimetric properties of IMRT and extrapolating from clinical outcomes from other disease sites, the review authors recommended that IMRT should be considered for lung cancer patients where the tumor is in close proximity to an organ at risk, where the target volume includes a large volume of an organ at risk, or in scenarios where dose escalation would be potentially beneficial while minimizing normal tissue toxicity. (9)

**Randomized and Nonrandomized Studies**
Holloway et al reported on a phase 1 dose escalation study of IMRT for patients with lung cancer that was terminated after the first 5 patients received 84 Gy in 35 fractions (2.4 Gy per fraction).(11) Treatment planning used combined CT and positron emission tomography for volumetric imaging, and treatment beams were gated to patients’ respiration. Acute toxicities included 1 patient with RTOG grade II dysphasia, 1 with grade I odynophagia, and 1 with grade I skin desquamation. In addition, 1 patient died of lung toxicity and was shown on autopsy to have bilateral diffuse pulmonary fibrosis with emphysema and diffuse alveolar damage. Of those who survived, 1 remained disease-free at 34 months, 2 developed metastases, and 1 developed an in-field recurrence.
Noting that the use of IMRT for inoperable NSCLC had not been well-studied, Sura et al reviewed their experience with IMRT for patients with inoperable NSCLC. (12) They reported a retrospective review of 55 patients with stage I-IIIB inoperable NSCLC treated with IMRT between 2001 and 2005. The study end points were toxicity, local control, and OS. With a median follow-up of 26 months, the 2-year local control and OS rates for stage I/II patients were 50% and 55%, respectively. For the stage III patients, 2-year local control and OS rates were 58% and 58%, respectively, with a median survival time of 25 months. Six patients (11%) experienced grade 3 acute pulmonary toxicity; 2 patients (4%) had grade 3 or worse late treatment-related pulmonary toxicity. The authors concluded that these results were promising.

Liao et al report on a nonrandomized comparative study of patients who received one of these forms of RT, along with chemotherapy, for inoperable NSCLC at 1 institution (M.D. Anderson Cancer Center). (10) This study involved a retrospective comparison of 318 patients who received CT/3D-CRT and chemotherapy from 1999–2004 (mean follow-up of 2.1 years) to 91 patients who received 4-dimensional computed tomography (4DCT)/IMRT and chemotherapy from 2004 to 2006 (mean follow-up of 1.3 years). Both groups received a median dose of 63 Gy. Disease endpoints were locoregional progression, distant metastasis, and OS. Disease covariates were gross tumor volume (GTV), nodal status, and histology. The toxicity endpoint was grade III or greater radiation pneumonitis; toxicity covariates were GTV, smoking status, and dosimetric factors. Data were analyzed using Cox proportional hazards models. The hazard ratios for IMRT were less than 1 for all disease endpoints; the difference was significant only for OS. The median survival was 1.40 (standard deviation [SD]: 1.36) years for the IMRT group and 0.85 (SD: 0.53 years) for the 3D-CRT group. The toxicity rate was significantly lower in the IMRT group than in the 3D-CRT group. The V20 (volume of the lung receiving 20 Gy) was higher in the 3D-CRT group and was a factor in determining toxicity. Freedom from distant metastasis was nearly identical in both groups. The authors concluded that treatment with 4DCT/IMRT was at least as good as that with 3D-CRT in terms of the rates of freedom from local/regional progression and metastasis. This retrospective study found a significant reduction in toxicity and improvement in survival. The nonrandomized, retrospective aspects of this study from one center limit the ability to draw definitive conclusions from this report.

In a 2012 follow-up study, Liao et al (Jiang et al) published long-term follow-up data from the M.D. Anderson Cancer Center on the use of definitive IMRT, with or without chemotherapy, for newly diagnosed, pathologically confirmed, inoperable NSCLC from 2005 to 2006. (13) This retrospective review included 165 patients, 89% of whom had Stage III to IV disease. The median radiation dose was 66 Gy given in 33 fractions. Median OS time was 1.8 years; the 2-year and 3-year overall survival rates were 46% and 30%, respectively. Rates of Grade 3 or greater maximum treatment-related pneumonitis were 11% at 6 months and 14% at 12 months. At 18 months, 86% of patients had developed Grade ≥1 maximum pulmonary fibrosis, and 7% Grade 2 or greater fibrosis. The median times to maximum esophagitis were 3 weeks (range, 1-13 weeks) for Grade 2 and 6 weeks (range, 3-13 weeks) for Grade 3. These rates of treatment-related toxicities with IMRT have been reported in other series to be no different than that in patients treated with 3D-CRT. (14, 15)

Harris et al in 2014, compared the effectiveness of IMRT, 3D-CRT, or 2D-RT in treating stage III NSCLC using a cohort of patients treated between 2002 and 2009 from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. (16) OS was better with IMRT and 3D-
CRT than 2D-CRT. In univariate analysis, improvements in OS and cancer-specific survival were associated with IMRT (hazard ratio [HR] 0.90, p=.02 and HR 0.89, p=.02, respectively). However, IMRT was similar to 3D-CRT after controlling for confounders in OS and cancer-specific survival (HR=0.94, p=0.23 and HR=0.94, p=0.28, respectively). On multivariate analysis, toxicity risks with IMRT and 3D-CRT were also similar. Results were similar between the propensity score matched models and the adjusted models.

In 2013, Shirvani et al reported on an M.D. Anderson Cancer Center study on the use of definitive IMRT in limited-stage small cell lung cancer. (17) In this study, 223 patients were treated from 2000 to 2009, 104 received IMRT and 119 received 3D-CRT. Median follow-up times were 22 months (range, 4-83 months) for IMRT and 3D-CRT and 27 months (range, 2-147 months) for IMRT. In either multivariable or propensity score-matched analyses, OS and disease-free survival did not differ between IMRT and 3D-CRT. However, rates of esophagitis-related percutaneous feeding tube placements were lower with IMRT than 3D-CRT (5% vs 17%, respectively, p=0.005).

**Ongoing Clinical Trials**
Some currently unpublished trials that might affect this policy are listed in Table 1.

<table>
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<tr>
<th>NCT No.</th>
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<td>NCT01185132</td>
<td>A Phase III Randomized Study Comparing Intensity Modulated Planning vs 3-</td>
<td>660</td>
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<td></td>
<td>dimensional Planning for Accelerated Partial Breast Radiotherapy</td>
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<td>NCT01322854</td>
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<td>Integrated Boost to Conventional Radiotherapy With Consecutive Boost in</td>
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<td>Patients With Breast Cancer After Breast Conserving Surgery</td>
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<td>NCT01349322</td>
<td>A Phase III Trial of Accelerated Whole Breast Irradiation With Hypofractionation Plus Concurrent Boost Versus Standard Whole Breast Irradiation Plus Sequential Boost for Early-Stage Breast Cancer</td>
<td>2312</td>
<td>Aug 2020</td>
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<tr>
<td>NCT01803139</td>
<td>Long Term Outcomes of a Multicentre Controlled Clinical Trial of Breast</td>
<td>358</td>
<td>Jun 2014</td>
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</table>
Irradiation Using Intensity-Modulated Radiation Therapy

NCT00103181 A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) vs Partial Breast Irradiation (PBI) for Women With Stage 0, I, or III Breast Cancer 4216 Jun 2016

NCT00632853 Phase III Comparison of Thoracic Radiotherapy Regimens in Patients With Limited Small Cell Lung Cancer Also Receiving Cisplatin and Etoposide 729 Jun 2023

NCT00520702 A Randomized Trial to Compare Time To Common Toxicity Criteria for Adverse Effect (CTC AEC) 3.0 Grade Treatment Related Pneumonitis (TRP) in Patients With Locally Advanced Non-Small Cell Carcinoma (NSCLC) Receiving Concurrent Chemoradiation Radiation Treated With 3-Dimensional Conformal Radiation Therapy (3D CRT, ARM 1) vs Intensity Modulated Radiatoin (IMRT, ARM2) Using 4 Dimensional CT Planning and Image Guided Adaptive Radiation Therapy (IGART)

NCT: national clinical trial

Practice Guidelines and Position Statements
Current National Comprehensive Cancer Network (NCCN) guidelines for NSCLC indicate that “more advanced technologies are appropriate when needed to deliver curative radiation therapy safely. These technologies include (but are not limited to) IMRT...Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.” (18)

The current NCCN guidelines for small cell lung cancer indicate “use of more advanced technologies is appropriate when needed to deliver adequate tumor dose while respecting normal tissue dose constraints.” IMRT is included in the technologies listed. (19)

The American Society for Radiation Oncology published consensus guidance on radiation to the lung in 2010. The guidance recommends limiting the 20-Gy dose-volume (V20) of radiation to the lung to less than or equal to between 30% to 35% or less and mean lung dose to 20 to 23 or less Gy (with conventional fractionation) to reduce the risk of radiation pneumonitis to 20% or less. (20)

Summary
For the treatment of lung cancer, based on nonrandomized comparative studies, IMRT appears to produce clinical outcomes comparable to that of 3D-conformal radiation therapy. Dosimetry studies report that IMRT can reduce radiation exposure to critical surrounding structures, especially in large
lungs. There is strong support for IMRT when alternative radiotherapy dosimetry exceeds a threshold of 20 Gy dose-volume (V20) to at least 35% of normal lung tissue. As a result of available evidence, in conjunction with a strong indirect chain of evidence and potential to reduce harms, IMRT of the lung may be considered medically necessary for lung cancer when: 1) RT is given with curative intent, 2) alternate RT dosimetry demonstrates radiation dose exceeding 20 Gy dose-volume (V20) for at least 35% of normal lung tissue, and 3) IMRT reduces the 20-Gy dose-volume (V20) of radiation to the lung at least 10% below the V20 of 3-D-CRT (eg, 40% reduced to 30%). IMRT for the palliative treatment of lung cancer is considered not medically necessary because conventional radiation techniques are adequate for palliation.

Medicare Status
There is no national coverage determination.

References


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<th>Date</th>
<th>Action</th>
<th>Notes</th>
</tr>
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<tr>
<td>June 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature search. References 16-17 added; reference 19 updated. Policy statement added stating other indications not meeting the criteria for medical necessity are considered not medically necessary.</td>
</tr>
<tr>
<td>June 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review. Reference 27 added. Title changed from “radiation therapy”. No change to policy statements.</td>
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**Keywords**

IMRT  
Intensity modulated radiation therapy  
IMRT - Lung  
Intensity modulated radiation therapy, Lung

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*This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 19, 2015 and is effective July 15, 2015.*

*Signature on File*

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