Intensity Modulated Radiation Therapy (IMRT) of the Breast and Lung

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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for IMRT of the breast and lung when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Intensity-modulated radiation therapy (IMRT) may be considered medically necessary as a technique to deliver whole breast irradiation in patients receiving treatment for left-sided breast cancer after breast-conserving surgery when all the following conditions have been met:
- Significant cardiac radiation exposure cannot be avoided using alternative radiation techniques
- IMRT dosimetry demonstrates significantly reduced cardiac target volume radiation exposure. (See Considerations)

Intensity-modulated radiation therapy (IMRT) may be considered medically necessary in individuals with large breasts when treatment planning with 3D conformal results in hot spots (focal regions with dose variation greater than 10% of target) and the hot spots are able to be avoided with IMRT. (See Considerations)

Intensity-modulated radiation therapy (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:
- Radiation therapy 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 (e.g. from 40% down to 30% or lower)

When Policy Topic is not covered
Intensity modulated radiation therapy (IMRT) of the breast is considered investigational as a technique of partial breast irradiation after breast-conserving surgery.

Intensity modulated radiation therapy (IMRT) of the chest wall is considered investigational as a technique of postmastectomy irradiation.

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

Intensity-modulated radiation therapy (IMRT) is not medically necessary for the treatment of breast or lung cancer for all indications not meeting the criteria above.

Considerations

Radiation Tolerance Doses for Normal Tissues of the Chest and Abdomen

<p>| TD 5/5 (Gy)a | TD 50/5 (Gy)b |</p>
<table>
<thead>
<tr>
<th>Portion of organ involved</th>
<th>Portion of organ involved</th>
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<tbody>
<tr>
<td>Site</td>
<td>1/3</td>
</tr>
<tr>
<td>Heart</td>
<td>60</td>
</tr>
<tr>
<td>Lung</td>
<td>45</td>
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<tr>
<td>Spinal cord</td>
<td>50</td>
</tr>
</tbody>
</table>

The tolerance doses in the table are a compilation from the following 2 sources:
Philadelphia: Lippincott Williams and Wilkins.
Kehwar TS, Sharma SC. Use of normal tissue tolerance doses into linear quadratic equation to estimate normal tissue complication probability.
http://www.rooj.com/Radiation%20Tissue%20Tolerance.htm
NP: not provided.

*TD 5/5*, the average dose that results in a 5% complication risk within 5 years.
*TD 50/5*, the average dose that results in a 50% complication risk within 5 years.

The following are an example of clinical guidelines that may be used with IMRT in left-sided breast lesions:
- The target volume coverage results in cardiac radiation exposure that is expected to be greater than or equal to 25 Gy to 10 cc or more of the heart (V25 greater than or equal to 10 cc) with 3D conformal RT despite the use of a complex positioning device (such as Vac-Lok™), and
- with the use of IMRT, there is a reduction in the absolute heart volume receiving 25 Gy or higher by at least 20% (e.g., volume predicted to receive 25 Gy by 3D RT is 20 cc and the volume predicted by IMRT is 16 cc or less).

The following are examples of criteria to define large breast size when using IMRT to avoid hot spots, as derived from randomized studies:
- Donovan and colleagues (1) enrolled patients with ‘higher than average risk of late radiotherapy-adverse effects’, which included patients having larger breasts. The authors state that while breast size is not particularly good at identifying women with dose inhomogeneity falling outside current International Commission on Radiation Units and Measurements guidelines, they excluded women with small breasts (less than or equal to 500 cc), who generally have fairly good dosimetry with standard 2D compensators.
- In the trial by Pignol and colleagues, (2) which reported that the use of IMRT significantly reduced the proportion of patients experiencing moist desquamation, breast size was categorized as small, medium or large by cup size. Multivariate analysis found that smaller breast size was significantly associated with a decreased risk of moist desquamation (p less than .001).

Description of Procedure or Service
Radiation therapy is an integral component in the treatment of breast and lung cancers. Intensity modulated radiation therapy (IMRT) has been proposed as a method of radiation therapy that allows adequate radiation therapy to the tumor while minimizing the radiation dose to surrounding normal tissues and critical structures.

For certain stages of many cancers, including breast and lung, randomized clinical trials have shown that postoperative radiation therapy improves outcomes for operable 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 have evolved in ways that permit more precise targeting of tumors with
complex geometries. Most early trials used 2-dimensional 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”.

3-dimensional conformal radiation (3D-CRT). Treatment planning evolved by using 3-dimensional images, usually from computed tomography (CT) scans, to delineate the boundaries of the tumor and discriminate tumor tissue from adjacent normal tissue and nearby 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 radiation therapy (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, shape, and intensities of the beams ports, to achieve the treatment plan’s goals.

Increased conformity may permit escalated tumor doses without increasing normal tissue toxicity and thus may 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 underdosing within the tumor and may decrease toxicity by avoiding overdosing.

Since 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.
Rationale
This policy was originally created in 2005 and was regularly updated with searches of the MEDLINE database. The most recent literature search was performed for the period of March 11, 2013 through March 20, 2014. The following is a summary of the key findings to date.

General Information

Intensity-modulated radiation therapy (IMRT) methods to plan and deliver radiation therapy are not uniform. (3-5) IMRT may use beams that remain “on” as multi-leaf 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 3D-conformal radiation therapy (3D-CRT) and IMRT with the patient prone, (6) while most treat supine patients as in conventional (2D) external-beam radiation therapy (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. (7) 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. (8, 9) Treatment plans are usually based on one scan, a static 3-dimensional image. They partially compensate for day-to-day (inter-fraction) variability in patient set-up, and for (intra-fraction) 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 conformality and dose distributions during IMRT for breast cancer. (8, 9) Techniques presently being studied with other tumors (e.g., lung cancer) (10) 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 CT scans, or measured by dosimetry using stationary (non-breathing) targets. In addition, non-small cell lung cancer has more irregular, spiculated edges than many other tumors, including breast cancer. This precludes drawing tight margins on computed tomography (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 conformal radiation therapy 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 radiation therapy) is unknown.

These considerations emphasize the need to compare clinical outcomes rather than treatment plan predictions to determine whether one radiotherapy 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...
Breast Cancer

Systematic reviews

In 2012, Dayes and colleagues published a systematic review that examined the evidence for IMRT for whole-breast irradiation in the treatment of breast cancer to quantify its potential benefits and to make recommendations for radiation treatment programs. (11) Based on a review of 6 published reports through March 2009 (one randomized clinical trial [RCT], 3 retrospective cohort studies, one historically controlled trial, and one prospective cohort) including 2,012 patients, the authors recommended IMRT over tangential radiotherapy after breast-conserving surgery to avoid acute adverse effects associated with radiation. There were insufficient data to recommend IMRT over standard tangential radiotherapy for reasons of oncological outcomes or late toxicity. The RCT included in this review was the Canadian multi-center trial by Pignol and colleagues reported below. In this RCT, IMRT was compared to 2D-RT, and CT scans were used in treatment planning for both arms of the study; the types of tangential radiotherapy regimens were not reported for the other studies. (2)

Two (of 6) cohort studies reviewed by Dayes and colleagues reported on breast cancer-related outcomes. (11) Neither of these studies reported statistically significant differences between treatment groups for contralateral breast cancer rates, clinical recurrence-free survival or disease-specific survival. Despite differences in reported outcomes, all 6 studies reported reductions in at least one measure of acute toxicity as a result of IMRT-based breast radiation. These toxicities typically related to skin reactions during the course of treatment, with reductions being in the order of one-third. The RCT by Pignol and colleagues (reported below), for example, found a reduction in moist desquamation specific to the inframammary fold by 39%. Only 2 retrospective cohort studies reported on late toxicity effects; one cohort study reported a significant difference between IMRT and tangential radiotherapy in favor of IMRT for breast edema (IMRT, 1% vs. 25%, p<0.001), and the other study found a trend toward a reduction in lymphedema rates (p=0.06). No differences were observed across both studies in other late effects including fat necrosis or second malignancies. (11)

In 2010, Staffurth and colleagues conducted a review of clinical evidence from studies on IMRT. (12) Included in the portion of the review addressing IMRT for breast cancer were 6 studies comparing the results of IMRT and 2D-radiation therapy (2D-RT) for postoperative radiotherapy, including 2 randomized controlled trials (RCTs) [Donovan and Pignol, noted below (1, 2)] and 4 nonrandomized comparative trials. The authors reported that the studies showed improvements in long-term cosmesis and toxicity when IMRT was used for breast cancer. However, health-related quality of life did not improve with forward-planned IMRT when compared with conventional tangential breast 2D-RT. Despite the lack of long-term health outcomes, the authors concluded reductions in radiation-induced side effects were sufficient to warrant the use of IMRT.

Randomized and nonrandomized studies

Donovan et al. reported the treatment planning and dosimetry results from an ongoing RCT comparing outcomes of radiation therapy for breast cancer using conventional 2D-RT with wedged, tangential beams or IMRT (n=300) in 2002. (13) In an abstract, these investigators reported interim cosmetic outcomes at 2 years after randomization for 233 evaluable patients. Changes in breast appearance were noted in 60 of 116 (52%) randomly assigned to conventional external-beam radiation therapy (EBRT) and in 42 of 117 (36%) randomly assigned to IMRT (p=0.05). Other outcomes were not reported. In 2007, Donovan et al. published a subsequent report on this trial. (1) Enrolled patients had ‘higher than average risk of late radiotherapy-adverse effects’, which included patients having larger breasts. The authors stated that while breast size is not particularly good at identifying women with dose inhomogeneity falling outside current International Commission on Radiation Units and Measurements guidelines, their trial excluded women with small breasts (less than or equal to 500 cc),
who generally have fairly good dosimetry with standard 2D compensators. All patients were treated with 6 or 10 MV photons to a dose of 50 Gy in 25 fractions to 100% in 5 weeks followed by an electron boost to the tumor bed of 11.1 Gy in 5 fractions to 100%. The primary endpoint was change in breast appearance scored from serial photographs taken before radiotherapy and at 1, 2, and 5 years' follow-up. Secondary endpoints included patient self-assessments of breast discomfort, breast hardness, quality of life, and physician assessments of breast induration. Two-hundred forty (79%) patients with 5-year photographs were available for analysis. Change in breast appearance was identified in 71/122 (58%) allocated standard 2D treatment compared to 47/118 (40%) patients allocated 3D IMRT. Significantly fewer patients in the 3D IMRT group developed palpable induration assessed clinically in the center of the breast, pectoral fold, inframammary fold and at the boost site. No significant differences between treatment groups were found in patient-reported breast discomfort, breast hardness, or quality of life. The authors concluded that the analysis suggests that minimization of unwanted radiation dose inhomogeneity in the breast reduces late adverse effects. While the change in breast appearance was statistically different, a beneficial effect on quality of life was not demonstrated. Since whole-breast radiation therapy is now delivered by 3D-conformal techniques, these comparison data are of limited value. As the authors note, quality-of-life changes were not noted. No other clinical outcomes were reported.

In a 2008 study, Donovan and colleagues evaluated methods for breast cancer IMRT planning and compared IMRT methods to conventional wedge planning in 14 patients. (14) The majority of IMRT plans were found to improve dose homogeneity over wedge-only treatment plans. In patients with a breast size of 500 cm³ or greater, the dose distribution improved between 5.6% and 11.1% (p<0.05), regardless of the planning method used. The authors noted in the discussion that IMRT may be inappropriate for patients with a breast volume of less than 1000 cm³.

In another RCT, IMRT was compared to 2D-RT, and computed tomography (CT) scans were used in treatment planning for both arms of the study. Thus, this is close to the ideal comparison of 3D-CRT and IMRT. In 2008, Pignol and colleagues reported on a multicenter, double-blind, randomized clinical trial that was performed to determine if breast IMRT would reduce the rate of acute skin reaction (moist desquamation), decrease pain, and improve quality of life compared with radiotherapy using wedges. (2) Patients were assessed each week during and up to 6 weeks after radiotherapy. A total of 358 patients were randomly assigned between July 2003 and March 2005 in 2 Canadian centers, and 331 were included in the analysis. The authors noted that breast IMRT significantly improved the dose distribution compared with 2D-RT. They also noted a lower proportion of patients with moist desquamation during or up to 6 weeks after their radiation treatment; 31% with IMRT compared with 48% with standard treatment (p=0.002). A multivariate analysis found the use of breast IMRT and smaller breast size were significantly associated with a decreased risk of moist desquamation. The use of IMRT did not correlate with pain and quality of life, but the presence of moist desquamation did significantly correlate with pain and a reduced quality of life. The focus on short-term outcomes (6 weeks) is a limitation when assessing net health outcome.

Barnett and colleagues have published baseline characteristics and dosimetry results of a single-center randomized trial of IMRT for early breast cancer after breast-conserving surgery. (15) In this trial, 1,145 patients with early breast cancer were evaluated for EBRT. Twenty-nine percent had adequate dosimetry with standard radiotherapy. The other 815 patients were randomly assigned to receive either IMRT or conventional 2D-RT. In this study, inhomogeneity occurred most often when the dose-volume was greater than 107% (V107) of the prescribed dose to greater than 2 cm³ breast volume with conventional radiation techniques. When breast separation was greater than or equal to 21 cm, 90% of patients had received greater than V107 greater than 2 cm³ with standard radiation planning. Subsequently, in 2012, Barnett and colleagues reported on the 2-year interim results of the trial. (16) The incidence of acute toxicity was not significantly different between groups. Additionally, photographic assessment scores for breast shrinkage were not significantly different between groups. The authors noted overall cosmesis after RT or IMRT was dependent upon surgical cosmesis, suggesting breast shrinkage and induration were due to surgery rather than RT, thereby masking the potential cosmetic benefits of IMRT.
Several other publications report findings from single institutions from patients who received IMRT compared to patients who received 2D-RT (nonrandomized studies). The grading of acute radiation dermatitis is relevant to these studies. Acute radiation dermatitis is graded on a scale of 0 to 5, with 0 as no change and 5 as death. Grade 2 is moderate erythema and patchy moist desquamation, mostly in skin folds; grade 3 is moist desquamation in other locations and bleeding with minor trauma.

McDonald et al. reported on a single institution retrospective review of patients who received radiation therapy after conservative surgery for Stages 0-III breast cancer from January 1999 to December 2003. (17) Computed tomography simulation was used to design standard tangential breast fields with enhanced dynamic wedges for 2D-RT and both enhanced dynamic wedges and dynamic multileaf collimators for IMRT. In this report, 121 breasts were treated with IMRT and 124 with 2D-RT. Median breast dose was 50 Gy in both groups. Median follow-ups were 6.3 years (range: 3.7–104 months) for patients treated with IMRT and 7.5 years (range: 4.9–112 months) for those treated with 2D-RT. Decreased acute skin toxicity of Radiation Therapy Oncology Group (RTOG) grade II or III was observed with IMRT treatment compared with 2D-RT (39% vs. 52%, respectively; p=0.047). For patients with Stages I-III (n=199), 7-year Kaplan-Meier freedom from ipsilateral breast tumor recurrence (IBTR) rates were 95% for IMRT and 90% for 2D-RT (p=0.36). For patients with stage 0 (ductal carcinoma in situ, n=46), 7-year freedom from IBTR rates were 92% for IMRT and 81% for 2D-RT (p=0.29). There were no statistically significant differences in overall survival (OS), disease-specific survival, or freedom from IBTR, contralateral breast tumor recurrence, distant metastasis, late toxicity, or second malignancies between IMRT and 2D-RT. The authors concluded that patients treated with breast IMRT had decreased acute skin toxicity, and long-term follow-up showed excellent local control. Interpretation of this study is limited by its retrospective design and limited outcome measures (no quality of life measures).

Kestin et al. reported they had treated 32 patients with early-stage breast cancer using multiple static multileaf collimator (MLC) segments to deliver IMRT for whole-breast irradiation. (18) With at least 1 month of follow-up on all patients, they observed no grade III or greater acute skin toxicity (using RTOG criteria). However, follow-up was inadequate to assess other health outcomes.

A subsequent report from Vicini and colleagues included 281 patients with early breast cancer treated with the same IMRT technique. (19) Of these, 102 (43%) experienced RTOG grade II, and 3 (1%) experienced grade III skin toxicity. Cosmetic results at 1 year after treatment were reported for 95 patients and were good to excellent in 94 (99%). No patients had skin telangiectasias, significant fibrosis, or persistent breast pain. Other primary or secondary outcomes were not reported.

Many reports in the literature described changes in radiation dose delivered for IMRT compared to other techniques. For example, Selvaraj reported on 20 patients with breast cancer randomly selected for comparison who received IMRT or 3D-CRT. (20) In this study, the mean dose for the ipsilateral lung and the percentage of volume of contralateral volume lung receiving greater than 5% of prescribed dose with IMRT were reduced by 9.9% and 35% compared to 3D CRT. The authors note that the dosimetric data suggest improved dose homogeneity in the breast and reduction in the dose to lung and heart for IMRT treatments, which may be of clinical value in potentially contributing to improved cosmetic results and reduced late treatment-related toxicity.

Hardee and colleagues compared the dosimetric and toxicity outcomes after treatment with IMRT or 3D-CRT for whole-breast irradiation in a consecutive series of 97 patients with early-stage breast cancer, who were assigned to either approach after segmental mastectomy based upon insurance carrier approval for reimbursement for IMRT. (21) IMRT significantly reduced the maximum dose to the breast (Dmax median, 110% for 3D-CRT vs. 107% for IMRT; p<0.0001, Wilcoxon test) and improved median dose homogeneity (median, 1.15 for 3D-CRT vs. 1.05 for IMRT; p<0.0001, Wilcoxon test) when compared with 3D-CRT. These dosimetric improvements were seen across all breast volume groups. Grade 2 dermatitis occurred in 13% of patients in the 3D-CRT group and 2% in the IMRT group. IMRT moderately decreased rates of acute pruritus (p=0.03, chi-square test) and grade 2 to 3 sub-acute hyperpigmentation (p=0.01, Fisher exact test). With a minimum of 6 months’ follow-up, the treatment
was reported to be similarly well-tolerated in either group, including among women with large breast volumes. (21)

Freedman and colleagues studied the time spent with radiation-induced dermatitis during a course of radiation therapy for women with breast cancer treated with conventional radiation therapy (2D-RT) or IMRT. (22) For this study, the population consisted of 804 consecutive women with early-stage breast cancer treated with breast-conserving surgery and radiation from 2001 to 2006 at the Fox Chase Cancer Center. All patients were treated with whole-breast radiation followed by a boost to the tumor bed. Whole-breast radiation consisted of conventional wedged photon tangents (n=405) earlier in the study period, and mostly of photon IMRT (n=399) in later years. All patients had acute dermatitis graded each week of treatment. The breakdown of cases of maximum toxicity by technique was as follows: 48%, grade 0/1, and 52%, grade 2/3, for IMRT; and 25%, grade 0/1, and 75%, grade 2/3, for conventional radiation therapy (p<0.0001). The IMRT patients spent 82% of weeks during treatment with grade 0/1 dermatitis and 18% with grade 2/3 dermatitis, compared with 29% and 71% of patients, respectively, treated with conventional radiation (p<0.0001). From this pre/post study, the authors concluded that breast IMRT is associated with a significant decrease both in the time spent during treatment with grade 2/3 dermatitis and in the maximum severity of dermatitis compared with that associated with conventional radiation. Interpretation of these results is limited by lack of a contemporaneous comparison. The investigators have subsequently reported on 5-year outcomes of the Fox Chase Cancer Center experience using whole-breast IMRT for the treatment of early-stage breast cancer; the 5-year actuarial ipsilateral breast tumor recurrence and locoregional recurrence rates were 2.0% and 2.4%, respectively. In terms of treatment-related effects, edema and erythema were consistently noted early after breast IMRT and peaked at 3-6 months from the start of whole-breast IMRT. Infection was rare, with <1.5% of the patient population experiencing this side effect; telangiectasia was noted to develop in approximately 8% of patients, and fibrosis in 7% of patients, at ≥36 months from the start of whole-breast IMRT. (23) Publications also report on the potential ability of IMRT to reduce radiation to the heart (left ventricle) in patients with left-sided breast cancer and unfavorable cardiac anatomy. (24) This is a concern because of the potential development of late cardiac complications, such as coronary artery disease, following radiation therapy to the left breast.

IMRT has also been investigated as a technique of partial-breast irradiation, as an alternative to whole-breast irradiation therapy after breast-conserving surgery. Breast brachytherapy (see policy No. 8.01.13) is another technique of partial-breast irradiation therapy. Leonard et al. reported on 55 patients treated with partial-breast IMRT who had mean follow-up of 10 months. (25) At the short-term follow-up, the dose delivery and clinical outcomes were considered acceptable; however, long-term follow-up is needed.

In 2010, Livi et al. reported on preliminary results of 259 patients randomized in a Phase III trial, that began in September 2008, to compare conventional fractionated whole-breast treatment (n=128) to accelerated partial-breast irradiation plus IMRT (n=131). (26) RTOG grade 1 and 2 skin toxicity was observed at a rate of 22% and 19% in the whole breast treatment group versus 5% and 0.8% in the partial breast treatment group, respectively. The authors concluded partial-breast irradiation with IMRT is feasible but noted long-term results on health outcomes are still needed. Additionally, 18 months after radiation therapy (RT), 1 case of contralateral breast cancer was diagnosed in the partial-breast irradiation group, creating concern from the authors that it may be related to the high dosage of IMRT.

Few studies have examined the use of IMRT for chest wall irradiation in postmastectomy breast cancer patients and no studies were identified that reported on health outcomes for this indication. Available studies have focused on treatment planning and techniques to improve dose distributions to targeted tissues while reducing radiation to normal tissue and critical surrounding structures, such as the heart and lung. An example of one available study was published by Rudat and colleagues, in which treatment planning for chest wall irradiation with IMRT was compared to 3D-CRT in 20 postmastectomy patients. (27) The authors reported IMRT resulted in significantly decreased heart and lung high-dose-volume with a significantly improved conformity index when compared to 3D-CRT. However, there was no significant difference reported in the homogeneity index. The authors noted longer-term prospective
studies are needed to further assess cardiac toxicity and secondary lung cancer risk with multi-field IMRT, which while reducing high dose-volume, increases mean heart and lung dose. As noted, health outcomes were not reported in this study.

**Lung Cancer**

**Systematic reviews**

In 2012, Bezjak and colleagues published a systematic review that examined the evidence for the use of IMRT in the treatment of lung cancer in order to quantify its potential benefits and make recommendations for radiation treatment programs considering adopting this technique within Ontario, Canada. (28) 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 2 cohort studies reported on data from the same institution (M.D. Anderson Cancer Center); the study by Liao and colleagues (2010, reported below) (29) acknowledged that patients included in their cohort (n=409) were previously reported on in the earlier cohort by Yom and colleagues (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. (28)

**Randomized and nonrandomized studies**

Holloway et al. reported on a Phase I 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). (30) 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 non-small cell lung cancer (NSCLC) had not been well-studied, Sura and colleagues reviewed their experience with IMRT for patients with inoperable NSCLC. (31) They reported a retrospective review of 55 patients with Stage I-IIIB inoperable NSCLC treated with IMRT between 2001 and 2005. The study endpoints were toxicity, local control, and overall survival. With a median follow-up of 26 months, the 2-year local control and overall survival rates for Stage I/II patients were 50% and 55%, respectively. For the Stage III patients, 2-year local control and overall survival 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 and colleagues report on a nonrandomized comparative study of patients who received one of these forms of radiation therapy, along with chemotherapy, for inoperable NSCLC at one institution (M.D. Anderson Cancer Center). (29) 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 2004–2006 (mean follow-up of 1.3 years). Both groups received a median dose of 63 Gy. Disease endpoints were locoregional progression, distant metastasis, and overall survival (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 and colleagues (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. (32) 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 overall survival time was 1.8 years; the 2-year
and 3-year overall survival rates were 46% and 30%, respectively. Rates of grade ≥3 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 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. (33, 34)

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. (35) Overall survival was better with IMRT and 3D-CRT
than 2D-CRT. In univariate analysis, improvements in overall survival 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 overall survival and cancer-specific survival
(HR 0.94, p=.23 and HR 0.94, p=.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. (36) 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, overall survival 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**

A search of the online site Clinicaltrials.gov on March 20, 2014 identified at least 3 randomized Phase
III studies comparing IMRT to 3D-CRT for breast cancer after breast-conserving surgery. One study
addresses partial-breast radiotherapy (NCT01185132), and 2 studies address whole-breast
radiotherapy (NCT01322854 and NCT01349322). In addition, a follow-up study of the Canadian RCT
by Pignol and colleagues (2008) is being undertaken to assess the long-term outcomes of breast
irradiation using IMRT (NCT01803139). In this study the investigators will recall all patients (n=358)
enrolled in the original trial at 8 years to assess whether this technique also reduces permanent side
effects including pain and cosmesis. This study will be open for recruitment in April 2013, with the
estimated completion date of June 2014.

A randomized intergroup trial that compared whole-breast and accelerated partial-breast irradiation,
including IMRT, sponsored by the U.S. National Cancer Institute and led by the National Surgical
Adjuvant Breast and Bowel Project and the RTOG opened in early 2005 (NCT00103181). The trial is
randomly assigning 4,300 patients (2,150 per treatment arm) to whole-breast or partial-breast
irradiation after lumpectomy with tumor-free margins verified by histologic examination. The primary objective is to compare in-breast tumor control (i.e., recurrence rates) for whole-breast versus partial-breast irradiation. Investigators anticipate accrual will be completed within 4.6 years (June 2015) from the trial’s start date. Lacking data with adequate follow-up from this or similar RCTs, there is inadequate published evidence to permit scientific conclusions about partial-breast irradiation, regardless of whether it is delivered by IMRT or breast brachytherapy.

One randomized Phase III trial for limited-stage small cell lung cancer treatment was identified comparing 3 different chest radiation therapy regimens, including IMRT, (NCT00632853). This U.S. multicenter trial has an estimated enrollment of 729 patients and is sponsored by the Cancer and Leukemia Group B, in collaboration with the Radiation Therapy Oncology Group and the National Cancer Institute. The primary outcome measure is overall survival time between 3 treatment arms. This study is currently recruiting participants with the estimated completion date of June 2023. In addition, a Phase III study from the M.D. Anderson Cancer Center is comparing 3D-CRT versus IMRT using 4-Dimensional CT Planning and image guided adaptive radiation therapy in 168 patients with locally-advanced NSCLC receiving concurrent chemo-radiation. The primary outcome measure is time to grade 3 pneumonitis. This study has closed but the results have not been published (NCT00520702).

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2010
In response to requests, input was received from 1 physician specialty society and 2 academic medical centers (3 reviewers) while this policy was under review in 2010. Those providing input suggested that IMRT should be utilized in select patients with breast cancer (e.g., some cancers involving the left breast) and lung cancer (e.g., some large cancers).

2012
In response to requests, input was received from 2 physician specialty societies and 3 academic medical centers (3 reviewers) while this policy was under review in 2011. There was near uniform consensus in responses that suggested whole-breast and lung IMRT are appropriate in select patients with breast and lung cancer. Respondents noted IMRT may reduce the risk of cardiac, pulmonary, or spinal cord exposure to radiation in some cancers such as those involving the left breast or large cancers of the lung. Respondents also indicated whole-breast IMRT may reduce skin reactions and potentially improve cosmetic outcomes. Partial breast IMRT was not supported by the respondents, and the response was mixed on the value of chest wall IMRT postmastectomy.

Summary

For the treatment of breast cancer, based on randomized and nonrandomized comparative studies, whole-breast intensity-modulated radiation therapy (IMRT) appears to produce clinical outcomes comparable to that of 3D-conformal radiation therapy (CRT). In addition, there is some evidence for decrease in acute skin toxicity with IMRT compared to 2D radiotherapy. Dosimetry studies have demonstrated that IMRT reduces inhomogeneity of radiation dose, thus potentially providing a mechanism for reduced skin toxicity. One RCT reported improvements in moist desquamation of skin, but did not report differences in grade 3-4 skin toxicity, pain symptoms, or quality of life. Another RCT reported no differences in cosmetic outcome at 2 years for IMRT compared with 2D radiotherapy. There was strong support through clinical vetting for the use of IMRT in breast cancer for left-sided breast lesions in which alternative types of radiotherapy cannot avoid toxicity to the heart. Based on the available evidence and results of input from clinical vetting, in conjunction with a strong indirect chain of evidence and the potential to reduce harms, IMRT may be considered medically necessary for whole-
breast irradiation when 1) alternate forms of radiotherapy cannot avoid cardiac toxicity, and 2) IMRT dose planning demonstrates a substantial reduction in cardiac toxicity.

Studies on IMRT for partial-breast irradiation are limited and have not demonstrated improvements in health outcomes. Therefore, partial-breast IMRT in the treatment of breast cancer is considered investigational.

No studies have reported on health outcomes after IMRT for chest wall irradiation in postmastectomy breast cancer patients. Available studies have only focused on treatment planning and techniques. The risk of secondary lung cancers and cardiac toxicity needs to be further evaluated. Therefore, IMRT for chest wall irradiation in postmastectomy breast cancer patients is considered investigational.

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 lung cancers. Results of clinical vetting indicate 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 and clinical vetting, 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) radiotherapy is given with curative intent, 2) alternate radiotherapy 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 conformal radiation therapy (e.g., 40% reduced to 30%). IMRT for the palliative treatment of lung cancer is considered not medically necessary since conventional radiation techniques are adequate for palliation.

Practice Guidelines and Position Statements

The current National Comprehensive Cancer Network (NCCN) guidelines for breast cancer indicate that for whole-breast irradiation, uniform dose distribution and minimization of toxicity to normal tissue are the objectives and list various approaches to achieve this, including IMRT. (37) The guidelines note accelerated partial-breast irradiation is generally considered investigational and should be limited to use in clinical trials. Additionally, IMRT is not mentioned as a technique in partial-breast irradiation. The guidelines indicate chest wall and regional lymph node irradiation may be appropriate post-mastectomy in select patients, but IMRT is not mentioned as a technique for irradiation in these circumstances.

The current NCCN guidelines for non-small cell lung cancer 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.” (38)

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. (39)

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 30–35% and mean lung dose to less than or equal to 20-23 Gy (with conventional fractionation) to reduce the risk of radiation pneumonitis to less than or equal to 20%. (40)

Medicare National Coverage

No national coverage determination (NCD) was identified. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
Some local medical review policies (LMRP), published by Medicare Part B carriers, have indicated that IMRT for the lung is considered medically necessary. These documents do not provide a detailed rationale for this conclusion.

References
Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator convergent beam modulated fields, per treatment session.

Placement of interstitial device(s) for radiation therapy guidance (eg, fiducial markers, dosimeter), percutaneous, intra-thoracic, single or multiple.

Therapeutic radiology treatment planning; simple.

Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications.

Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan.

Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session.

Stereoscopic X-ray guidance for localization of target volume for the delivery of radiation therapy.

N/A

New policy; considered investigational. This policy was implemented 8/15/2007.

Coding updated. Policy number changed from 2.03.08 to 8.01.46.

Policy statements for use in whole breast irradiation and lung cancer changed from investigational to not medically necessary. This change is effective November 1, 2010.

Policy statement added indicating chest wall IMRT postmastectomy is investigational. Policy statement added indicating whole breast IMRT may be medically necessary in large-sized breasts. Policy statements on whole breast and lung IMRT changed from not medically necessary to may be considered medically necessary. Policy statement on partial breast IMRT remains investigational. Change made effective retroactively to 3/1/2012 on 10/23/2012.

Policy statement added stating other indications not meeting the criteria for medical necessity are considered not medically necessary. Updated Considerations.

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