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**Medical Policy Manual**

**Topic:** Intensity Modulated Radiation Therapy (IMRT) of the Thorax

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## IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

## DESCRIPTION

Intensity-modulated radiation therapy (IMRT), which uses computer software, CT, and magnetic resonance imaging (MRI) images, offers better conformality 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 conformality 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.

**MEDICAL POLICY CRITERIA**

I. Breast Cancer

A. Intensity modulated radiation therapy (IMRT) may be considered **medically necessary** to deliver either *whole breast* irradiation following breast-conserving surgery or irradiation following mastectomy, when at least one of the following criteria are met:

1. There is prior documented radiation to the planned target area; or
2. The radiation treatment field includes the heart.

B. Except as defined in I.A.1 and I.A.2 above, IMRT as a technique of *whole breast* irradiation or irradiation following mastectomy is considered **not medically necessary**. The clinical outcomes with this treatment have not been shown to be superior to other approaches such as 3D-conformal radiation therapy, yet IMRT is generally more costly than these alternatives.

C. IMRT as a technique of *partial breast* irradiation following breast-conserving surgery is considered **investigational**.

II. Lung Cancer

A. IMRT may be considered **medically necessary** as a treatment for lung cancer when at least one of the following criteria are met:

1. There is documented prior radiation treatment to the planned target area(s)
2. A critical anatomical structure (such as the spinal cord or heart) is located in the radiation field
3. There is documented significantly impaired pulmonary function or limited pulmonary capacity

B. Except as defined in II.A, IMRT is considered **not medically necessary** for the treatment of lung cancer. The clinical outcomes with this treatment have not been shown to be superior to other approaches such as 3D-conformal radiation therapy, yet IMRT is generally more costly than these alternatives.

III. Other Tumors

IMRT may be considered **medically necessary** for the treatment of the following tumors:

A. Esophageal cancer
B. Malignant pleural mesothelioma
C. Thymoma or thymic carcinoma

## SCIENTIFIC EVIDENCE[1]

### Background

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 conformality 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.

### Breast Cancer

Evidence from randomized controlled trials comparing intensity-modulated radiation therapy (IMRT) with 3D-CRT, the current standard of care, is needed in order to establish safety and efficacy of IMRT in the treatment of breast cancer.

IMRT has not been evaluated in reliable, randomized controlled trials using current technology as comparators or in long-term prospective studies. Specifically, no randomized trials comparing IMRT to 3D-CRT that report clinical outcomes have been published.

Whole Breast Irradiation

*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. [2] Based on a review of six published reports through March 2009 (one randomized clinical trial [RCT], three 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. [3] 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.

*Randomized and Non-randomized Trials*

- Kestin et al reported they had treated 32 patients with early-stage breast cancer using multiple static MLC segments to deliver IMRT for whole-breast irradiation.[4] With at least 1 month of follow-up on all patients, they observed no grade >III acute skin toxicity (using RTOG criteria). However, follow-up was inadequate to assess other health outcomes.
- A subsequent report from the same group included 281 early breast cancer patients treated with the same IMRT technique.[5] 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.
- Donovan et al reported the treatment planning and dosimetry results from an ongoing randomized controlled trial (RCT) comparing outcomes of radiation therapy (RT) for breast cancer using conventional EBRT with wedged, tangential beams or IMRT (n=300).[6] In an abstract, these investigators reported interim cosmetic outcomes at 2 years after randomization for 233 evaluable patients.[7] Changes in breast appearance were noted in 60 of 116 (52%) randomized to conventional EBRT and in 42 of 117 (36%) randomized to IMRT (p=0.05). Other outcomes were not reported.
- Selvaraj described changes in radiation dose delivered for IMRT compared to other techniques. Twenty patients with breast cancer who received IMRT or 3D conformal radiation therapy (3D CRT) were randomly selected for comparison.[8] In this study, the mean dose for the ipsilateral lung and the percentage of volume of contralateral volume lung receiving > 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. [9] 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.
- Donovan et al reported on a randomized controlled trial of 2D radiotherapy vs. IMRT in patients prescribed whole breast radiotherapy.[10] However, this study does not compare IMRT to the current standard radiation technology.
- Pignol et al reported the results of a multicenter randomized trial of breast IMRT vs. EBRT to reduce acute radiation dermatitis.[3] However, both 2D and 3D missing tissue compensation methods were used and the focus was on short-term (6 weeks) outcomes only.
- McDonald et al reported on a retrospective chart comparison of patients at one institution with Stages 0-III breast cancer who underwent irradiation after conservative surgery from January 1999 to December 2003.[11] Computed tomography simulation was used to design standard tangential breast fields with enhanced dynamic wedges for EBRT and both enhanced dynamic wedges and dynamic multileaf collimators for IMRT. In this report, 121 breasts were treated with IMRT and 124 with RT. Median breast dose was 50 Gy in both groups. Median follow-ups were 6.3 years for patients treated with IMRT and 7.5 years for those treated with EBRT. Treatment with IMRT decreased acute skin toxicity of Radiation Therapy Oncology Group Grade 2 or 3 compared with RT

(39% vs. 52%; 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 cRT (p = 0.36). Comparing IMRT with RT, there were no statistically significant differences in overall survival, disease-specific survival, or freedom from IBTR, contralateral breast tumor recurrence, distant metastasis, late toxicity, or second malignancies. Interpretation of this study is limited by its retrospective design and limited outcome measures (no quality of life measures).

- Barnett and colleagues published baseline characteristics and dosimetry results of a trial of IMRT vs. standard RT for early breast cancer.[12] Subsequent publications will report on late toxicity and quality of life.
- Freedman et al. studied the time spent with radiation-induced dermatitis during a course of radiation therapy for women with breast cancer treated with conventional or intensity-modulated radiation therapy (IMRT).[13] 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. [14] 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.
- Radiation to the heart (left ventricle) in patients with left-sided breast cancer is a concern because of the potential development of late cardiac complications, such as coronary artery disease following radiation therapy to the left breast. Coon et al reported that both TOMO and IMRT can significantly reduce cardiac doses, with modest increases in dose to other tissues in left-sided breast cancer patients with unfavorable cardiac anatomy.[15] However, the study is a dosimetric comparison of treatment plans based on 15 patients, and no clinical outcomes were reported.
- Barnett et al. reported no significant difference in breast shrinkage at 2 years between patients randomized to the forward-planned IMRT and conventional radiation therapy (2D CRT).[16] The secondary study endpoints included overall cosmesis, acute skin toxicity, clinical assessment of late normal tissue effect, and quality-of-life self-assessment. Although the interim findings suggest that the patients in the conventional radiation therapy group were more likely to develop telangiectasia at 2 years than those in the IMRT group, these findings are unreliable due to the significant loss to follow-up in the study population (>10% by year 2).
- A review of 354 stage 0 to III breast cancer patients treated with SIB-IMRT after conservative surgery reported favorable acute toxicity, low cardiac dose for left breast treatment, and excellent locoregional control.[17] However, the findings from this study need to be interpreted with caution due to the retrospective, non-comparative study design.

Partial Breast Irradiation

IMRT has also been investigated as a technique of partial breast irradiation, as an alternative to whole breast irradiation therapy after breast conserving surgery.

- A randomized intergroup trial comparing whole-breast and accelerated partial-breast irradiation, including IMRT, sponsored by the U.S. National Cancer Institute and led by National Surgical Adjuvant Breast and Bowel Project and the Radiation Therapy Oncology Group opened in early 2005 (NSABP B-39/RTOG-0413). The trial is randomizing 3,000 patients 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 by 29 months from the trial's start date. Lacking data with adequate follow-up from this or similar randomized, controlled trials, there is inadequate published evidence to permit scientific conclusions about partial breast irradiation.
- A literature review also identified pilot studies using IMRT for delivering accelerated partial breast irradiation. For example, Leonard reported on 55 patients treated with IMRT who had mean follow-up of 10 months.[18] At the short term follow-up, the dose delivery and clinical outcomes were considered acceptable. In a continuation of this study, outcomes were reported on 140 breasts in 136 consecutive patients with Stage 0/I breast cancer with negative margins.[19] Median follow-up was 53.1 months (range, 8.9-83.2). While this study reported positive outcomes for tumor recurrence, overall survival and cancer-specific survival, comparative studies with long-term follow-up are needed.

In a preliminary analysis, a randomized controlled trial in a selected group of patients with early-stage breast cancer reported that accelerated partial breast irradiation with IMRT is feasible, with low acute toxicity. However, the findings from this preliminary report need to be interpreted with caution as the analysis was carried out on only the first 259 patients of the 520 that are planned to be recruited.[20]

Irradiation of the Chest Wall in Postmastectomy Breast Cancer

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. For example:

- Rudat et al. compared IMRT treatment planning for chest wall irradiation with 3D-CRT in 20 postmastectomy patients.[21] The authors reported that IMRT resulted in significantly decreased heart and lung high dose-volume with a significantly improved conformity index when compared with 3D-CRT. However, there was no significant difference reported in the homogeneity index. The authors noted that longer-term prospective studies are needed to further assess cardiac toxicity and secondary lung cancer risk with multifield IMRT, which while reducing high dose-volume, increases mean heart and lung dose.

Clinical Practice Guidelines

Per the current National Comprehensive Cancer Network (NCCN) guidelines for breast cancer:[22]

*Whole Breast Radiation*

The goals for the whole breast radiation therapy are a uniform dose distribution and minimal normal tissue toxicity which can be accomplished using compensators, such as IMRT.

*Chest Wall Radiation*

Several techniques using photons and/or electrons are appropriate for chest wall radiation; however the guideline does not include specific examples of these technologies.

*Partial Breast Radiation*

The evidence on accelerated partial breast irradiation (APBI) is limited and patients are encouraged to participate in clinical trials.

**Lung Cancer**

Evidence from randomized controlled trials comparing intensity-modulated radiation therapy (IMRT) with 3D-CRT, the current standard of care, is needed in order to establish safety and efficacy of IMRT in the treatment of lung cancer.

Data related to outcomes and comparative studies for the treatment of lung cancer are limited. No randomized trials were identified that compared IMRT to 3D-CRT.

*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. [23] This review consisted of two 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 and colleagues [24] acknowledged that patients included in their cohort (n=409) were previously reported on in the earlier cohort by Yom and colleagues (n=290). However, 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.

*Non-randomized Trials*

- Holloway et al reported on a phase I dose escalation study that was terminated after the first 5 patients received 84 Gy in 35 fractions (2.4 Gy per fraction).[25] 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 2 dysphasia, 1 with grade 1 odynophagia, and 1 with grade 1 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.

- Sura and colleagues[26] 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 et al reported on 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 four-dimensional computed tomography (4DCT)/IMRT and chemotherapy from 2004-2006 (mean follow-up of 1.3 years).[24] Both groups received a median dose of 63 Gy. Disease endpoints were locoregional progression (LRP), distant metastasis (DM), and overall survival (OS). Disease covariates were gross tumor volume (GTV), nodal status, and histology. The toxicity endpoint was grade 3 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 <1 for all disease endpoints; the difference was significant only for overall survival. 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 non-randomized, retrospective design of this study from one center limits the ability to draw definitive conclusions from this report.
- In a 2012 follow-up study, the same investigators published long-term follow-up data from the MD Anderson Cancer Center on the use of definitive IMRT, with or without chemotherapy, for newly diagnosed, pathologically confirmed, inoperable NSCLC from 2005 to 2006. [27] 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. [28,29]
- A retrospective review in 2013 compared IMRT (n=104) with 3D-CRT (n=119) in 223 patients who were treated for limited-stage small cell lung cancer. Median follow-up was 27 months (ranges 4-83 months for IMRT; 2-147 months for 3D-CRT). The investigators found no significant between group differences in overall survival or disease-free survival. However, IMRT patients required significantly fewer percutaneous feeding tube placements (5% vs. 17%, p=0.005) suggesting lower esophageal toxicity.

Although the literature on IMRT treatment of lung cancer continues to develop, the recent publications still consist of small, retrospective, and/or non-comparative study designs.[30,31]

Clinical Practice Guidelines

The current National Comprehensive Cancer Network (NCCCN) guidelines for both *non-small and small cell lung cancer* indicate that "use of more advanced technologies is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints." Such technologies include, among others, IMRT.[32,33]

**Malignant Pleural Mesothelioma (MPM)**

Literature Appraisal

Currently published literature on IMRT for the treatment of MPM consists of prospective non-comparative trials. No comparative clinical trials were identified which studied primary health outcomes such as overall-, disease-, or progression-free survival, or which clearly identify patient selection criteria. The following systematic reviews were identified:

- Chi and colleagues report on a systematic review of IMRT as part of trimodal therapy (surgery, chemotherapy and radiation) for treatment of MPM.[34] However, search criteria were not expressed a priori and the quality of studies was not critically appraised; therefore, interpretation of results from this review is limited.

- Another systematic review of radiotherapy in general and IMRT specifically was published in 2011 by Price.[35] No randomized controlled trials (RCTs) were identified involving use of these therapies after surgical resection. Available evidence for IMRT consisted of case series, and reports of pulmonary toxicity with IMRT lead the author to conclude that additional studies are needed to establish the factors which differentiate those pre-disposed to adverse effects from radiation therapy from those not at risk. Based upon the available state of evidence, the review stated, "Much work has gone into exploring methods of radical treatment in the few thought suitable for this treatment, again without any evidence that such treatment is of any value, and very little into the palliation of symptoms for what remains an incurable disease in all who present with it." Therefore, the review concluded that, "There is currently no evidence to support the routine role of radiotherapy in patients with mesothelioma."

- In 2006, Chapman and colleagues conducted a Cochrane review on the use of any radiation therapy in treatment of MPM.[36] The authors were unable to find any literature that met the prespecified inclusion criteria (randomized controlled trial comparing patients treated with radiation therapy with a control group).

- Ung and colleagues, also in 2006, reported on a systematic review conducted on radiation therapy in MPM which found 3 RCTs on the prophylactic use of external beam radiation therapy of the surgical site.[37] No RCTs were identified on the use of radiation therapy as adjunctive treatment in MPM.

In summary, evidence to date is not sufficient to establish the role of radiation therapy in general in treatment of MPM, nor IMRT as a specific type of radiation therapy. RCTs are needed to isolate the treatment effect of radiation therapy from other components of care, and to firmly establish treatment timing and dosing guidelines.

Clinical Practice Guidelines

Current guidelines from National Comprehensive Cancer Network (NCCN) on treatment of malignant pleural mesothelioma recommend use of IMRT in "experienced centers or on protocol" based upon a standard level of evidence (Level 2A, indicating a consensus recommendation based upon lower-level evidence).[38] The guidelines caution that treatment with IMRT is associated with excessively high risk of fatal pneumonitis when strict limits are not applied, and that the mean lung dose should be minimized (< 8.5 Gray [Gy]).

In general, the guidelines state that indications for radiation include prophylactic radiation of the surgical site (to prevent seeding of malignant tumors through use of needle biopsy and other invasive diagnostic procedures), and radiation therapy in the curative or palliative settings. According to these guidelines, recommended uses of radiation therapy in MPM are as follows:

*Treatment Options in the Curative Setting*

Recommended treatment options for the disease include surgery, adjuvant radiation therapy and chemotherapy. The following are their recommendations based upon clinical stage and other patient characteristics:

Patients With Clinical Stages I through III MPM who are Medically Operable:

- Surgical resection (pleurectomy/decortication or extrapleural pneumonectomy) alone, or
- Trimodality therapy (i.e., chemotherapy, surgery, and radiotherapy)

All Others:

- For those for whom surgery is not an option, who are in clinical stage IV, or who have sarcomatoid histology, chemotherapy alone is recommended.

The guidelines go on to state that due to poor evidence of survival benefit, and risk of toxicity, "RT alone is not recommended."

*Palliative Radiation*

Radiation therapy with a palliative intent (for treatment of chest pain) is recommended. Optimal dosage and timing of radiation therapy for palliative intent are not known. A total dose of 21 Gy (3 x 7 Gy) is recommended. The guidelines conclude that radiation dosage and timing should be guided by intent (treatment or palliative care) and decided upon by a multidisciplinary team.

**Thymus Tumors**

Literature Appraisal

Published literature on IMRT for the treatment of thymomas and thymic carcinoma was summarized in a 2013 systematic review.[39] Giannopoulou et al. reported that the treatment of choice is tumor resection in patients who are surgical candidates. Postoperative radiotherapy is recommended based upon the 5-year survival of 50-60%. For unresectable disease concurrent chemotherapy and radiation therapy is recommended. The optimal tumor target definition was found with 3D RT, 4D RT, IMRT, image-guided RT, and computed tomography fusion with PET scan.

No new clinical trials have been published since the systematic review.

Clinical Practice Guidelines

Current NCCN guidelines state that "RT should be given by 3-D conformal technique to reduce surrounding normal tissue damage (e.g., heart, lungs, esophagus, spinal cord).[40] [IMRT] may further improve the dose distribution and decrease the dose to the normal tissue as indicated. If IMRT is applied, the ASTRO/ACR IMRT and ATC/NCI guidelines should be strictly followed."

**Summary**

Breast Cancer

*Whole Breast:*

Intensity modulated-radiation therapy (IMRT) has not been compared in randomized controlled trials (RCTs) with 3D-CRT, the current standard of care. The available evidence on IMRT for breast cancer comes from observational studies with methodological limitations. This evidence suggests that IMRT may lead to clinical outcomes comparable with 3D-CRT. In addition, it appears that IMRT reduces cardiac doses in left-sided breast cancer and may lead to some decrease in acute skin toxicity. However, it is not known whether IMRT leads to improvement in health outcomes (e.g., overall survival) compared with 3D-CRT. Therefore, IMRT to deliver either whole breast irradiation following breast-conserving surgery or irradiation following mastectomy, may be considered medically necessary in select patients meeting the policy criteria.

*Partial Breast Irradiation:*

Evidence on intensity-modulated radiation therapy (IMRT) for partial breast irradiation is very limited and has not demonstrated improvements in health outcomes. Therefore, IMRT as a technique of partial breast irradiation following breast-conserving surgery is considered investigational.

*Postmastectomy Chest Wall Irradiation*

The evidence on intensity-modulated radiation therapy (IMRT) for chest wall irradiation following mastectomy in breast cancer patients is very limited. Available studies have only focused on treatment planning and techniques, and have not demonstrated improvements in health outcomes compared with conventional 3D conformal radiation therapy. The risk of secondary lung cancers and cardiac toxicity due to radiation exposure needs to be further evaluated. Therefore, IMRT for chest wall irradiation in postmastectomy breast cancer patients is considered investigational.

Lung Cancer

Intensity modulated-radiation therapy (IMRT) has not been compared in randomized controlled trials (RCTs) with 3D-CRT, the current standard of care. The available evidence on IMRT for lung cancer is limited and comes from observational studies with methodological limitations. This evidence suggests that IMRT may lead to clinical outcomes comparable with 3D-CRT and reduced radiation exposure to surrounding critical structures. However, it is not known whether IMRT leads to improvement in health outcomes (e.g., overall survival) compared with 3D-CRT. Therefore, IMRT may be considered medically necessary for the treatment of lung cancer in patients meeting the policy criteria. In patients who fail to meet these criteria, IMRT is considered not medically necessary as the clinical outcomes

with this treatment have not been shown to be superior to other approaches such as 3D-conformal radiation therapy, yet IMRT is generally more costly than these alternatives.

Esophageal Cancer

The esophagus is considered to be an organ at risk as it may be particularly vulnerable to clinically important complications from radiation toxicity. Therefore, intensity modulated-radiation therapy (IMRT) may be considered medically necessary for the treatment of esophageal cancer.

Pleural Mesothelioma

Scientific evidence on the role of intensity-modulated radiation therapy (IMRT) in the treatment of malignant pleural mesothelioma (MPM) is limited. However, considering the rarity of this disease, the lack of effective treatment options, and the recommendations from the National Comprehensive Cancer Network (NCCN), IMRT may be considered medically necessary to treat MPM.

Thymus

Scientific evidence on the role of intensity-modulated radiation therapy (IMRT) in the treatment of thymomas and thymic carcinomas is limited. However, considering the rarity of these tumors, the location of the thymus near the heart and esophagus, and the recommendations from the National Comprehensive Cancer Network (NCCN), IMRT may be considered medically necessary to treat thymomas and thymic carcinomas.

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Intensity-Modulated Radiation Therapy (IMRT): Central Nervous System (CNS) and Vertebral Tumors, Medicine, Policy No. 147

| CODES | NUMBER | DESCRIPTION |
|---|---|---|
| CPT | 77301 | Intensity modulated radiotherapy plan, including dose volume histograms for target and critical structure partial tolerance specification |
| | 77338 | Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan (new code 1/1/10) |
| | 77418 | Intensity modulated treatment deliver, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary dynamic MLC, per treatment session |
| | 0073T | Compensator-based beam modulation treatment delivery of inverse planned treatment using three or more high resolution compensator convergent beam modulated fields, per treatment session |
| HCPCS | None | |