Intensity modulated radiotherapy (IMRT) is a form of radiation therapy that conforms closely to the targeted tumor shape and allows higher doses of radiation to be delivered while minimizing toxicity to surrounding healthy tissues.

Background

For certain stages of many cancers, including breast and lung, randomized controlled trials have shown that postoperative RT 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 Radiotherapy

Over the past several decades, methods to plan and deliver 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, 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 Radiotherapy

IMRT, which uses computer software, CT images, and magnetic resonance imaging (MRI), 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 adjoining organs at risk (OAR). 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 overdosaging. Alternatively, IMRT provides the opportunity to construct heterogenous dose deposition within the target volume thus tailoring differential dose in keeping with physician assessment of differential cancer cell density, etc. This may diminish local failure within the overall target volume.

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.

Whole and Partial Breast Irradiation

Definitive or adjunctive irradiation to the breast may initially include the entire breast with or without subsequent “boost” to the lumpectomy cavity or be targeted solely to the lumpectomy cavity plus small safety margin (i.e. partial breast irradiation). Both formats of breast irradiation may be provided via a mixture of external irradiation techniques (i.e. teletherapy and/or insertion of needles or balloon like devices containing radioactive substances and implanted in the breast tissue), thus providing irradiation therapy from within the targeted tissues (i.e. brachytherapy). Whole breast irradiation is typically scheduled once a day for 3-7 weeks while partial breast treatment is commonly delivered twice a day for five days.
MEDICAL POLICY CRITERIA

I. IMRT may be considered **medically necessary** to deliver irradiation to the thorax when one or more of the following criteria are met:

   A. Documented prior radiation treatment to the planned target volume; or
   
   B. Documented significant pulmonary function impairment; or
   
   C. Documented curative treatment for any of the following indications:
      1. Esophageal cancer
      2. Lung cancer
      3. Pleural mesothelioma
      4. Thymic carcinoma
      5. Thymoma
   
   D. Breast cancer treatment when one or more of the following is met:
      1. Post breast conserving surgery, when 10% or greater reduction in either mean heart dose or dose to the left descending artery can be achieved through IMRT planning; or
      2. Post mastectomy for consolidation irradiation to the chest wall (with or without regional nodes) when dose/volume histogram analysis (3-D versus IMRT) demonstrates that published dose/volume constraints can *only* be met with IMRT (i.e., Quantec) (see Policy Guidelines); or
      3. For individuals with large breasts, avoidance or minimization of hot spots (focal regions with dose variation greater than 10% of prescribed dose).
   
   E. Treatment for any other tumor when all of the following criteria are met:
      1. The tumor is in close proximity to organs at risk (see Policy Guidelines); and
      2. Comparative dose/volume histograms analysis (3-D versus IMRT) demonstrates that published dose/volume constraints can *only* be met with IMRT (i.e., Quantec) (see Policy Guidelines).

II. IMRT is **not medically necessary** for the treatment of all indications when criteria I. above is not met.

III. IMRT of the breast is considered **investigational** as a technique of partial-breast irradiation after breast-conserving surgery.
POLICY GUIDELINES

In order to determine the medical necessity for IMRT, the following information must be submitted for review with the request for coverage (Note: histograms are not initially required but may be requested for the indications of esophageal cancer, lung, pleural mesothelioma, thymoma, or thymic carcinoma):

- For the indications of esophageal or lung cancer, pleural mesothelioma, thymoma, or thymic carcinoma, histograms are not initially required, but may be requested.
- For all other indications (other than esophageal or lung cancer, pleural mesothelioma, thymoma, or thymic carcinoma), comparative dose/volume histograms of 3-D and IMRT treatment planning approaches including a narrative summary of the medical necessity for IMRT to meet published dose constraints (i.e., QUANTEC) and organ(s) at risk as specified in the policy criteria.[1]
- For left breast irradiation, summary analysis demonstrating that 10% or greater reduction in either mean heart dose, or dose to the left descending artery can be achieved through IMRT planning. The following is a clinical example of documentation for medical necessity:
  - The target volume coverage with 3D planning predicts that the mean heart dose will be 18 Gy while IMRT planning predicts reduction by 10% to 16.8 Gy
- For individuals with large breasts, comparative dose/volume histograms (3-D and IMRT) and a narrative summary demonstrating the medical necessity for IMRT to avoid hot spots (i.e., focal volumes with dose variation in excess of 10% can be avoided or minimized).

Organs at Risk

Organs at risk are defined as normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed radiation dose.[2] These organs at risk may be particularly vulnerable to clinically important complications from radiation toxicity.

SCIENTIFIC EVIDENCE

Multiple-dose planning studies generate 3-dimensional conformal radiation (3D-CRT) and intensity-modulated radiotherapy (IMRT) treatment plans from the same scans, and then compare predicted dose distributions within the target area and adjacent organs. Results of such planning studies have shown that IMRT is better than 3D-CRT with respect to conformality to, and dose homogeneity within, the target. Results have also demonstrated that IRMT less radiation to nontarget areas. Dosimetry studies using stationary targets generally confirm these predictions. However, because patients move during treatment, dosimetry with stationary targets only approximate actual radiation doses received. Based on these dosimetry studies, radiation oncologists expect IMRT to improve treatment outcomes compared with those of 3D-CRT.

Comparative studies of radiation-induced adverse effects from IMRT versus alternative radiation delivery would constitute definitive evidence in establishing the benefit of IMRT. 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, absent such comparative trials, it is likely that benefit from IMRT is at least as good as with other types of delivery.
In general, when the indication for IMRT is to avoid radiation to sensitive areas, dosimetry studies have been considered sufficient evidence to demonstrate that harm would be avoided by using IMRT. For other IMRT indications, such as using IMRT to provide better tumor control, comparative studies of health outcomes are needed to demonstrate such a benefit.

**Breast Cancer**

The grading of acute radiation dermatitis is relevant to studies of IMRT for treatment of breast cancer. Acute radiation dermatitis is graded on a scale of 0 (no change) to 5 (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. Publications have also reported on the potential for IMRT to reduce radiation to the heart (left ventricle) in patients with left-sided breast cancer and unfavorable cardiac anatomy. This is a concern because of the potential development of late cardiac complications (e.g., coronary artery disease) following RT to the left breast.

**Whole-Breast Irradiation**

*Systematic Reviews*

In 2012, Dayes et al 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. Based on a review of 6 published reports through March 2009 (1 randomized controlled trial [RCT], 3 retrospective cohort studies, 1 historically controlled trial, 1 prospective cohort) including 2012 patients, the authors recommended IMRT over tangential RT after breast-conserving surgery to avoid acute adverse effects associated with radiation. There was insufficient data to recommend IMRT over standard tangential RT for reasons of oncologic outcomes or late toxicity. The RCT included in this review was the Canadian multicenter trial by Pignol et al reported next. In this RCT, IMRT was compared with 2D-RT. CT scans were used in treatment planning for both arms of the study. The types of conventional RT regimens were not reported for the other studies.

Two of the six cohort studies reviewed by Dayes et al reported on breast cancer-related outcomes. 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 six 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 et al (summarized below), for example, found a reduction in moist desquamation specific to the inframammary fold by 39%. Only two retrospective cohort studies reported on late toxicity effects; one cohort study reported a significant difference between IMRT and tangential RT 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.

*Randomized Controlled Trials*

The 2008 multicenter, double-blind RCT by Pignol et al evaluated whether breast IMRT would reduce the rate of acute skin reaction (moist desquamation), decrease pain, and improve quality of life (QOL) compared with RT using wedges. Patients were assessed each week up to 6 weeks after RT. 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 radiation treatment (31% with IMRT vs 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 presence of moist desquamation significantly correlated with pain and a reduced QOL.

Donovan et al reported on an RCT comparing outcomes with conventional 2D-RT with wedged, tangential beams or IMRT in 300 breast cancer patients.[6] In an abstract, investigators reported interim cosmetic outcomes at 2 years postrandomization for 233 evaluable patients. In 2007, Donovan et al published a subsequent report on this trial.[7] 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 (≤500 cm³), who generally have fairly good dosimetry with standard 2D compensators. All patients were treated with 6 or 10 megavolt photons to a dose of 50 gray (Gy) in 25 fractions in 5 weeks followed by an electron boost to the tumor bed of 11.1 Gy in 5 fractions. The primary end point was change in breast appearance scored from serial photographs taken before RT and at 1-, 2-, and 5-year follow-ups. Secondary end points included patient self-assessments of breast discomfort, breast hardness, QOL, 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 (58%) of 122 allocated standard 2D treatment compared with 47 (40%) of 118 patients allocated IMRT. Significantly fewer patients in the 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 minimization of unwanted radiation dose inhomogeneity in the breast reduced late adverse effects. While the change in breast appearance was statistically different, a beneficial effect on QOL was not demonstrated.

In 2009, Barnett et al published baseline characteristics and dosimetry results of a single-center RCT of IMRT for early breast cancer after breast-conserving surgery.[8] Subsequently, in 2012, Barnett et al reported on the 2-year interim results of the RCT.[9] In this trial, 1145 patients with early breast cancer were evaluated for external-beam radiotherapy. Twenty-nine percent had adequate dosimetry with standard RT. The other 815 patients were randomly assigned to receive either IMRT or 2D-RT. 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 21 cm or more, 90% of patients had received greater than V107 of the prescribed dose to greater than 2 cm³ with standard radiation planning. The incidence of acute toxicity did not differ significantly between groups. Additionally, photographic assessment scores for breast shrinkage were not significantly different between groups. The authors noted overall cosmesis after 2D-RT and IMRT was dependent on surgical cosmesis, suggesting breast shrinkage and induration were due to surgery rather than radiation, thereby masking the potential cosmetic benefits of IMRT.

Nonrandomized Comparative Studies

In 2012, Hardee et al compared the dosimetric and toxicity outcomes after treatment with IMRT or 3D-CRT for WBI in 97 consecutive patients with early-stage breast cancer, who were assigned to either approach after partial mastectomy based on insurance carrier approval for reimbursement for IMRT.[10]
IMRT significantly reduced the maximum radiation dose to the breast (Dmax median, 110% for 3D-CRT vs 107% for IMRT; p<0.001) and improved median dose homogeneity (median, 1.15 for 3D-CRT vs 1.05 for IMRT; p<0.001) 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) and grade 2 and 3 subacute hyperpigmentation (p=0.01). With a minimum of 6 months of follow-up, the treatment was reported to be similarly well-tolerated by both groups, including among women with large breast volumes.\[[10]\]

Freedman et al studied the time spent with radiation-induced dermatitis during a course of RT for women with breast cancer treated with 2D-RT or IMRT.\[[11]\] For this 2009 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 a single center. All patients were treated with whole-breast radiotherapy (WBRT) followed by a boost to the tumor bed. WBRT 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 weekly during treatment. The IMRT patients spent 82% of weeks during treatment with grade 0 or 1 dermatitis and 18% with grade 2 or 3 dermatitis, compared with 29% and 71% of patients, respectively, treated with 2D-RT (p<0.001). 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 or 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 comparators.

Hardee et al 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 on 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; Wilcoxon test, p<0.001) and improved median dose homogeneity (median, 1.15 for 3D-CRT vs 1.05 for IMRT; Wilcoxon test, p<0.001) 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 (χ² test, p=0.03) and grade 2 to 3 subacute hyperpigmentation (Fisher exact test, p=0.01). With a minimum of 6 months of follow-up, the treatment was reported to be similarly well-tolerated in either group, including among women with large breast volumes.\[[10]\]

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.

Randomized Controlled Trials

IMRT has also been investigated as a technique of partial-breast irradiation, as an alternative to 3D-WBRT after breast-conserving surgery. In 2010, Livi et al reported on preliminary results for 259 patients randomized in a phase 3 trial, which began in September 2008, that compared conventional fractionated WBI treatment (n=128) to accelerated partial-breast irradiation (APBI) with IMRT (n=131).\[[12]\] Radiation Therapy Oncology Group grade 1 and 2 skin toxicity were observed at rates 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 needed. Additionally, 18 months after RT, 1 case of contralateral breast cancer was diagnosed in the partial-breast irradiation group, raising authors’ concern that it may be related to the high dosage of IMRT.

Five-year survival analysis results of the Livi RCT were reported in 2015. A total of 520 patients were accrued, with 260 per group. The WBI arm received conventional RT at total dose of 50 Gy in 25 fractions, followed by a boost to the tumor bed of 10 Gy in 5 fractions. The APBI arm received a total dose of 30 Gy to the tumor bed in 5 daily fractions. The primary end point was occurrence of Ipsilateral breast tumor recurrence, with main analysis by intention-to-treat. At median follow-up of 5 years for all patients (interquartile range, 3.4-7.0), the Ipsilateral breast tumor recurrence rate was 1.5% (3 cases; 95% CI, 0.1 to 3.0) in the APBI group and 1.5% in the WBI group (3 cases; 95% CI, 0.0 to 2.8). Log-rank analysis showed no significant difference between the groups (p=0.86). The 5-year OS rate was 99% for the APBI group and 97% for the WBI group (p=NS). The APBI group had significantly better acute (p≤0.000) and late (p=0.004) skin adverse events (grade ≤2) compared with the WBI group and better cosmetic outcome (p=0.045). These results suggested APBI with IMRT is safe and effective in treatment of localized breast cancer. However, the evidence does not permit conclusions about the balance of benefits and harms given the small number of events observed in both groups and the lack of 10-year follow-up data.

Chest Wall Irradiation

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 lungs. Rudat compared IMRT treatment planning for chest wall irradiation with 3D-CRT in 20 postmastectomy patients. 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.

Summary

There is modest evidence from RCTs for a decrease in acute skin toxicity with IMRT compared with 2D-RT for WBI. One RCT reported improvements in moist desquamation of skin, but did not find differences in grade 3 or 4 skin toxicity, pain symptoms, or QOL. Another RCT found a change in breast appearance, but not QOL. A third RCT reported no differences in cosmetic outcomes at two years for IMRT compared with 2D-RT. Dosimetry studies have demonstrated that IMRT reduces inhomogeneity of radiation dose, thus potentially providing a mechanism for reduced skin toxicity. However, because WBRT is now delivered by 3D-CRT, these comparison data are of limited value. Studies on IMRT compared to 3D-CRT include one RCT on partial-breast IMRT and one nonrandomized comparative study on whole-breast IMRT. These studies have suggested that IMRT may improve short-term clinical outcomes. Ten-year follow-up is needed to evaluate the effect of partial-breast IMRT on recurrence and survival. 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.
Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

Current National Comprehensive Cancer Network (NCCN) guidelines (v.2.2016) 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.\textsuperscript{[15,16]} The guidelines state that “Greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated radiation therapy (IMRT).” 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 postmastectomy in select patients, but IMRT is not mentioned as a technique for irradiation in these circumstances.

American Society for Radiation Oncology (ASTRO)\textsuperscript{[17,18]}

The ASTRO task force’s consensus-based guideline recommended that radiation doses to the lung and heart during WBRT should be minimized, provided the coverage of the breast is not compromised. IMRT was included in the ASTRO summary of techniques for WBRT following breast conserving therapy (BCT) or mastectomy, irrespective of margin width.

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.\textsuperscript{[19]} 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)\textsuperscript{[20]} 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.\textsuperscript{[19]}

Nonrandomized Comparative Studies

The 2010 nonrandomized comparative study by Liao et al compared patients who received 1 of 3 forms of RT, along with chemotherapy, for inoperable NSCLC at 1 institution.\textsuperscript{[20]} This study retrospectively compared 318 patients who received CT plus 3D-CRT and chemotherapy from 1999 to 2004 (mean follow-up, 2.1 years) to 91 patients who received 4-dimensional CT plus IMRT and chemotherapy from 2004 to 2006 (mean follow-up, 1.3 years). Both groups received a median dose of 63 Gy. Disease end points were locoregional progression, distant metastasis, and OS. Disease covariates were gross tumor
volume (GTV), nodal status, and histology. The toxicity end point was grade 3, 4, or 5 radiation pneumonitis; toxicity covariates were GTV, smoking status, and dosimetric factors. Ising Cox proportional hazards models, the hazard ratios (HRs) for IMRT were less than 1 for all disease end points; the difference was significant only for OS. The median (SD) survival was 1.40 (1.36) years for the IMRT group and 0.85 (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 4D-CT plus IMRT was at least as good as that with 3D-CRT in terms of the rates of freedom from locoregional progression and metastasis. This retrospective study found a significant reduction in toxicity and improvement in survival. The nonrandomized, retrospective aspects of this study from 1 center limit the ability to draw definitive treatment conclusions about IMRT.

Harris et al (2014) compared the effectiveness of IMRT, 3D-CRT, or 2D-RT in treating stage III non-small-cell lung cancer (NSCLC) using a cohort of patients from the Surveillance, Epidemiology, and End Results–Medicare database treated between 2002 and 2009.[21] OS was better with IMRT and 3D-CRT than with 2D-CRT. In univariate analysis, improvements in OS (HR=0.90, p=0.02) and cancer-specific survival (HR=0.89, p=0.02) were associated with IMRT. However, IMRT was similar to 3D-CRT after controlling for confounders in OS and cancer-specific survival (HR=0.94, p=0.23; HR=0.94, p=0.28, respectively). On multivariate analysis, toxicity risks with IMRT and 3D-CRT were also similar. Results were similar for 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 treated with definitive RT.[22] In this study of 223 patients 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 27 months (range, 2-147 months) for 3D-CRT. 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 (5%) than 3D-CRT (17%; p=0.005).

Ling et al compared IMRT and 3D-CRT in patients with stage III NSCLC treated with definitive RT.[23] In this study of 145 consecutive patients treated between 1994 and 2014, the choice of treatment was at the treating physician’s discretion, but all IMRT treatments were performed in the last 5 years. Ling found no significant differences between the groups for any measure of acute toxicity (grade ≥2 esophagitis, grade ≥2 pneumonitis, percutaneous endoscopic gastrostomy, narcotics, hospitalization, or weight loss). There were no significant differences in oncologic and survival outcomes.

**Summary**

For the treatment of lung cancer, no RCTs were identified that compared IMRT with 3D-CRT. Dosimetry studies have reported that IMRT can reduce radiation exposure to critical surrounding structures, especially in large lung cancers. Based on nonrandomized comparative studies, IMRT appears to produce clinical outcomes comparable with those of 3D-CRT. Interpretation of these studies is limited by the potential for bias in treatment assignment and/or change in treatments over time.

**Clinical Practice Guidelines**

*National Comprehensive Cancer Network (NCCN)*
Current NCCN guidelines (v.4.2016) for non-small-cell lung cancer indicate that “More advanced technologies are appropriate when needed to deliver curative RT safely.”[24] These technologies include (but are not limited to) IMRT/VMAT. “Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.”

The current NCCN guidelines (v.1.2017) 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.”[25] IMRT is included in the technologies listed.

American Society for Radiation Oncology (ASTRO)

The American Society for Radiation Oncology published consensus guidance on radiation to the lung in 2010. The guidance recommended limiting the 20-gray (Gy) dose volume of radiation to the lung to less than or equal to between 30% and 35% or less and mean lung dose to 20 to 23 Gy or less (with conventional fractionation) to reduce the risk of radiation pneumonitis to 20% or less.[26]

Esophagus

The esophagus is considered to be an organ at risk as it may be particularly vulnerable to clinically important complications from radiation toxicity. In addition, the thoracic esophagus is in close proximity to vital structures including the heart and lungs. Therefore, conformal radiation therapy is an appropriate delivery method for radiation therapy for esophageal cancer. Case series and retrospective studies have reported superior dose conformity and homogeneity, as well as reduced radiation dose to the heart and lungs with IMRT compared with 3D-CRT for esophageal cancer.[27-29]

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)[30]

The NCCN guidelines for esophageal and esophagogastric junction cancers states that “IMRT is appropriate in clinical settings where reduction in dose to organs at risk (e.g., heart, lungs) is required that cannot be achieved by 3-D techniques.”

Malignant Pleural Mesothelioma (MPM)

Systematic Reviews

Chi and colleagues report on a systematic review of IMRT as part of trimodal therapy (surgery, chemotherapy and radiation) for treatment of MPM.[31] 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.[32] 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 conducted a systematic review on the use of any radiation therapy in the treatment of MPM. 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).

**Randomized Controlled Trials and Nonrandomized Studies**

Since the above systematic reviews, no randomized or nonrandomized comparative studies were identified that reported on primary health outcomes (e.g., overall-, disease-, or progression-free survival). In summary, there is insufficient evidence to establish the role of radiation therapy in general in the treatment of MPM, nor IMRT as a specific type of radiation therapy. Well-designed comparative studies 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**

**National Comprehensive Cancer Network (NCCN)**

Current guidelines from NCCN on treatment of malignant pleural mesothelioma state “CT simulation-guided planning using either intensity-modulated radiation therapy (IMRT) or conventional photon/electron radiation therapy is acceptable. When IMRT is used, the NCI and ASTRO/ACR IMRT guidelines should be strictly followed.”

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 Stage 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 or metastases in bone) 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**

Published literature on IMRT for the treatment of thymomas and thymic carcinoma was summarized in a 2013 systematic review.[35] Giannopoulou reported that the treatment of choice is tumor resection in patients who are surgical candidates. Postoperative radiotherapy is recommended based upon a 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 randomized controlled trials or comparative studies have been published since the systematic review.

**Clinical Practice Guidelines**

*National Comprehensive Cancer Network (NCCN)*

The NCCN guidelines for thymomas and thymic carcinomas state that “RT should be given by 3-D conformal technique to reduce surrounding normal tissue damage (e.g., heart, lungs, esophagus, spinal cord).[36] Intensity modulated RT (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 guidelines should be strictly followed.”

**Other Tumors of the Thorax**

Other tumors in the thorax that are not specifically addressed above may include, but are not limited to chest wall tumors other than those related to breast cancer such as metastatic tumors in the bones of the thorax, or primary, recurrent, or metastatic tumors in other areas of the thorax (e.g., supraclavicular fossa; mediastinum; axilla). The technique for delivering radiation therapy to these tumors is determined based on the risk of toxicity to local vital structures such as the heart. Other concerns are additional damage to tissues with previous radiation exposure. IMRT is known to offer better conformality than 3D-CRT and, therefore, is more likely to decrease the radiation dose to vital structures or previously damaged tissue.

**Summary**

**Breast Cancer**

*Whole Breast*

The available evidence on whole-breast intensity modulated radiotherapy (IMRT) for breast cancer suggests that IMRT may lead to clinical outcomes comparable with 3D-CRT. In addition, IMRT may reduce cardiac doses in left-sided breast cancer and may lead to a decrease in acute skin toxicity.
Therefore, IMRT to deliver either whole breast irradiation following breast-conserving surgery or irradiation following mastectomy, may be considered medically necessary in select patients when policy criteria is met.

For individuals with large breasts, avoidance or minimization of hot spots to the breast may be achieved using IMRT resulting in less toxicity to the surrounding tissue. Therefore, IMRT may be considered medically necessary to avoid or minimize hot spots in women with large breasts when policy criteria is met.

**Partial Breast Irradiation**

Evidence on intensity modulated radiotherapy (IMRT) for partial breast irradiation is limited and has not demonstrated improvements in net health outcomes. In addition, there are no evidence-based clinical practice guidelines that recommend partial breast IMRT outside of the clinical trial setting. Therefore, IMRT as a technique of partial breast irradiation following breast-conserving surgery is considered investigational.

**Lung Cancer**

The available evidence on intensity modulated radiotherapy (IMRT) for lung cancer suggests that IMRT may lead to clinical outcomes comparable with 3D-conformal radiation therapy (CRT) and may reduce radiation exposure to surrounding critical structures such as the heart. Therefore, IMRT may be considered medically necessary for the treatment of lung cancer in patients.

**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 radiotherapy (IMRT) for the treatment of esophageal cancer may be considered medically necessary to minimize exposure of normal tissue.

**Pleural Mesothelioma**

Evidence on the role of intensity modulated radiotherapy (IMRT) in the treatment of pleural mesothelioma is limited. However, considering the rarity of this disease, the lack of effective treatment options, and clinical practice guideline recommendations, IMRT may be considered medically necessary to treat pleural mesothelioma.

**Thymus**

Evidence on the role of intensity modulated radiotherapy (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 clinical practice guideline recommendations, IMRT may be considered medically necessary to treat thymomas and thymic carcinomas.

**Other Tumors of the Thorax**

Intensity modulated radiotherapy (IMRT) has a number of possible roles in the treatment of tumors of the thorax that are not specifically addressed in the medical policy criteria. IMRT may provide better
conformality than 3D-CRT and decrease radiation dose to vital structures or previously damaged tissue. Therefore, IMRT may be considered medically necessary to reduce the risk of toxicity to organs at risk (e.g., heart, spinal cord, esophagus) when policy criteria are met, areas with documented prior radiation treatment to the planned target region, or in patients with significantly impaired pulmonary function or limited pulmonary capacity. IMRT of tumors that do not meet the policy criteria are not medically necessary.

REFERENCES


CROSS REFERENCES

**Intensity Modulated Radiotherapy (IMRT) of the Prostate**, Medicine, Policy No. 137

**Intensity Modulated Radiotherapy (IMRT) of the Head and Neck**, Medicine, Policy No. 138

**Intensity-Modulated Radiotherapy (IMRT) of the Abdomen and Pelvis**, Medicine, Policy No. 139

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

**Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy**, Surgery, Policy No. 16

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