Policy Statement

Intensity-modulated radiotherapy (IMRT) may be considered medically necessary as a technique to deliver whole-breast irradiation in patients receiving treatment when all of the following conditions are met:

I. Left-sided breast cancer
II. Prior breast-conserving surgery
III. Documentation of all of the following:
   A. Significant cardiac radiation exposure cannot be avoided using alternative radiotherapy
   B. IMRT dosimetry demonstrates significantly reduces cardiac target volume radiation exposure as documented by both of the following:
      1. With 3D-CRT, the target volume coverage results in cardiac radiation exposure that is expected to be greater than or equal to 25 gray (Gy) to 10 cm³ or more of the heart (V25 ≥10 cm³), despite the use of a complex positioning device (e.g., Vac-Lok™)
      2. With IMRT, there is a reduction in the absolute heart volume receiving 25 Gy or more by at least 20% (e.g., volume predicted to receive 25 Gy by 3D-CRT is 20 cm³, and the volume predicted by IMRT is ≤16 cm³)

IMRT may be considered medically necessary when all of the following conditions are met:

I. Individual has large breasts (> 500 cc)
II. 3-dimensional conformal radiotherapy dosimetry results in hot spots (focal regions with dose variation greater than 10% of target)
III. Hot spots can be avoided with IMRT

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

IMRT of the chest wall is considered investigational as a technique of postmastectomy irradiation.

IMRT may be considered medically necessary as a technique to deliver radiotherapy in patients with lung cancer when all of the following conditions are met:

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

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

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

Policy Guidelines

Organs at risk are defined as normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed radiation dose. These organs at risk may be particularly vulnerable to clinically important complications from radiation toxicity. Table PG1 outlines
radiation doses generally considered tolerance thresholds for these normal structures for the chest and abdomen. Dosimetry plans may be used to demonstrate that radiation by 3-dimensional conformal radiotherapy (3D-CRT) would exceed tolerance doses to structures at risk.

<table>
<thead>
<tr>
<th>Site</th>
<th>TD 5/5, Gray&lt;sup&gt;a&lt;/sup&gt;</th>
<th>TD 50/5, Gray&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Complication End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Portion of Organ Involved</td>
<td>Portion of Organ Involved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/3</td>
<td>2/3</td>
<td>3/3</td>
</tr>
<tr>
<td>Heart</td>
<td>60</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>Lung</td>
<td>45</td>
<td>30</td>
<td>17.5</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>50</td>
<td>50</td>
<td>47</td>
</tr>
</tbody>
</table>


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

Intensity modulated radiation therapy may be covered for a diagnosis that is listed as investigational, not medically necessary, or not identified, for unusual cases when at least one of the following conditions are present:

- The target volume is in close proximity to critical structures that must be protected and both of the following: *(see source below)*
  - Planned 3D-CRT exposure to critical adjacent structures is above normal tissue constraints
  - Planned IMRT exposure to these critical adjacent structures does not exceed normal tissue constraints
- An immediately adjacent area has been previously irradiated and abutting portals must be established with high precision

Requests for the above exceptions and all other indications not discussed in this policy will be reviewed on a case-by-case basis.

*The following Normal Tissue Constraint Guidelines are derived from the textbook: Radiation Oncology: A Question-Based Review published by Lippincott Williams & Wilkins, 2010 [author: Hristov et al., 2010]). According to the author, most dosages were derived from randomized studies or consensus guidelines however; pediatric dose constraints will vary greatly from protocol to protocol. Sources used in the development of the guidelines included the American Brachytherapy Society (ABS); Clinical practice guidelines from Johns Hopkins Hospital (J HH); the International Journal of Radiation Oncology *Biology* Physics (IJ ROBP); the National Comprehensive Cancer Network (NCCN), Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC); and the Radiation Therapy Oncology Group (RTOG) protocols at the time of publication.*

The following guidelines are only intended to serve as a guide and may not be applicable to all clinical scenarios.
### Central Nervous System (single fraction)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spinal Cord</strong></td>
<td>max 13 Gy (if 3 fx, max 20 Gy)</td>
</tr>
<tr>
<td><strong>Brain</strong></td>
<td>V12 Gy ≤5–10 cc</td>
</tr>
<tr>
<td><strong>Chiasm/Optic Nerves</strong></td>
<td>max 10 Gy</td>
</tr>
<tr>
<td><strong>Brainstem</strong></td>
<td>max 12.5 Gy</td>
</tr>
<tr>
<td><strong>Sacral plexus</strong></td>
<td>V18 ≤0.035 cc, V14.4 ≤5 cc</td>
</tr>
<tr>
<td><strong>Cauda equina</strong></td>
<td>V16 ≤0.035 cc, V14 ≤5 cc</td>
</tr>
</tbody>
</table>

### Head and Neck (1.8–2.0 Gy/fx)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parotid gland(s)</strong></td>
<td>mean &lt;25 Gy (both glands) or mean &lt;20 Gy (1 gland)</td>
</tr>
<tr>
<td><strong>Submandibular gland(s)</strong></td>
<td>mean &lt;35 Gy</td>
</tr>
<tr>
<td><strong>Larynx</strong></td>
<td>mean ≤44 Gy, V50 ≤=27%, max 63–66 Gy (when risk of tumor involvement is limited)</td>
</tr>
<tr>
<td><strong>TMJ/mandible</strong></td>
<td>max 70 Gy (if not possible, then V75 ≤1 cc)</td>
</tr>
<tr>
<td><strong>Oral cavity</strong></td>
<td>Non-oral cavity cancer: mean &lt;30 Gy, avoid hot spots &gt;60 Gy Oral cavity cancer: mean &lt;50 Gy, V55 ≤1 cc, max 65 Gy</td>
</tr>
<tr>
<td><strong>Esophagus (cervical)</strong></td>
<td>V45 &lt;33%</td>
</tr>
<tr>
<td><strong>Pharyngeal constrictors</strong></td>
<td>mean &lt;50 Gy</td>
</tr>
<tr>
<td><strong>Thyroid</strong></td>
<td>V26 &lt;20%</td>
</tr>
</tbody>
</table>

### Thoracic (1.8–2.0 Gy/fx)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brachial plexus</strong></td>
<td>max 66 Gy, V60 ≤5%</td>
</tr>
<tr>
<td><strong>Lung (combined lung for lung cancer treatment)</strong></td>
<td>mean &lt;20–23 Gy, V20 &lt;30%-35%</td>
</tr>
<tr>
<td><strong>Lung (ipsilateral lung for breast cancer treatment)</strong></td>
<td>V25 &lt;10%</td>
</tr>
<tr>
<td><strong>Single lung (after pneumonectomy)</strong></td>
<td>V5 &lt;60%, V20 &lt;4-10%, MLD &lt;8 Gy</td>
</tr>
<tr>
<td><strong>Bronchial tree</strong></td>
<td>max 80 Gy</td>
</tr>
<tr>
<td><strong>Heart (lung cancer treatment)</strong></td>
<td>Heart V45 &lt;67%; V60 &lt;33%</td>
</tr>
<tr>
<td><strong>Heart (breast cancer treatment)</strong></td>
<td>V25 &lt;10%</td>
</tr>
<tr>
<td><strong>Esophagus</strong></td>
<td>V50 &lt;32%; V60 &lt;33%</td>
</tr>
</tbody>
</table>

### Thoracic (hypofractionation)

Note: the max dose limits refer to volumes >0.035 cc (~3 mm³).

<table>
<thead>
<tr>
<th>Organ</th>
<th>Dose (fractions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spinal cord</strong></td>
<td>1 fraction: 14 Gy</td>
</tr>
<tr>
<td></td>
<td>3 fractions: 18 Gy (6 Gy/fx)</td>
</tr>
<tr>
<td></td>
<td>4 fractions: 26 Gy (6.5 Gy/fx)</td>
</tr>
<tr>
<td></td>
<td>5 fractions: 30 Gy (6 Gy/fx)</td>
</tr>
<tr>
<td><strong>Esophagus</strong></td>
<td>1 fraction: 15.4 Gy</td>
</tr>
<tr>
<td></td>
<td>3 fractions: 30 Gy (10 Gy/fx)</td>
</tr>
<tr>
<td></td>
<td>4 fractions: 30 Gy (7.5 Gy/fx)</td>
</tr>
<tr>
<td></td>
<td>5 fractions: 32.5 Gy (6.5 Gy/fx)</td>
</tr>
<tr>
<td><strong>Brachial plexus</strong></td>
<td>1 fraction: 17.5 Gy</td>
</tr>
<tr>
<td></td>
<td>3 fractions: 21 Gy (7 Gy/fx)</td>
</tr>
<tr>
<td></td>
<td>4 fractions: 27.2 Gy (6.8 Gy/fx)</td>
</tr>
<tr>
<td></td>
<td>5 fractions: 30 Gy (6 Gy/fx)</td>
</tr>
<tr>
<td><strong>Heart/Pericardium</strong></td>
<td>1 fraction: 22 Gy</td>
</tr>
<tr>
<td></td>
<td>3 fractions: 30 Gy (10 Gy/fx)</td>
</tr>
<tr>
<td></td>
<td>4 fractions: 34 Gy (8.5 Gy/fx)</td>
</tr>
<tr>
<td></td>
<td>5 fractions: 35 Gy (7 Gy/fx)</td>
</tr>
</tbody>
</table>
### Constraints

<table>
<thead>
<tr>
<th>Organ</th>
<th>Constraints</th>
</tr>
</thead>
</table>
| **Great vessels** | 1 fraction: 37 Gy  
3 fractions: 39 Gy (13 Gy/fx)  
4 fractions: 49 Gy (12.25 Gy/fx)  
5 fractions: 55 Gy (11 Gy/fx) |
| **Trachea/Large Bronchus** | 1 fraction: 20.2 Gy  
3 fractions: 30 Gy (10 Gy/fx)  
4 fractions: 34.8 Gy (8.7 Gy/fx)  
5 fractions: 40 Gy (8 Gy/fx) |
| **Rib** | 1 fraction: 30 Gy  
3 fractions: 30 Gy (10 Gy/fx)  
4 fractions: 32 Gy (8.7 Gy/fx)  
5 fractions: 32.5 Gy (6.5 Gy/fx) |
| **Skin** | 1 fraction: 26 Gy  
3 fractions: 30 Gy (10 Gy/fx)  
4 fractions: 36 Gy (9 Gy/fx)  
5 fractions: 40 Gy (8 Gy/fx) |
| **Stomach** | 1 fraction: 12.4 Gy  
3 fractions: 27 Gy (9 Gy/fx)  
4 fractions: 30 Gy (7.5 Gy/fx)  
5 fractions: 35 Gy (7 Gy/fx) |

#### Gastrointestinal (GI) (1.8-2.0 Gy/fx)

- **Stomach**
  - TD 5/5 whole stomach: 45 Gy
- **Small bowel**
  - V45 <195 cc
- **Liver (metastatic disease)**
  - mean liver <32 Gy (liver = normal liver minus gross disease)
- **Liver (primary liver cancer)**
  - mean liver <28 Gy (liver = normal liver minus gross disease)
- **Colon**
  - 45 Gy, max dose 55 Gy
- **Kidney (bilateral)**
  - mean <18 Gy, V28 <20%, V23 Gy <30%, V20 <32%, V12 <55%. If mean kidney dose to 1 kidney >18 Gy, then constrain remaining kidney to V6 <30%

#### Gastrointestinal (GI) (single fraction)

- **Duodenum**
  - V16 <0.035 cc, V11.2 <5 cc
- **Kidney (Cortex)**
  - V8.4 <200 cc
- **Kidney (Hilum)**
  - V10.6 <66%
- **Colon**
  - V14.3 <20 cc, V18.4 <0.035 cc
- **jejunum/ileum**
  - V15.4 <0.035 cc, V11.9 <5 cc
- **Stomach**
  - V16 <0.035 cc, V11.2 <10 cc
- **Rectum**
  - V18.4 <0.035 cc, V14.3 <20 cc

#### Genitourinary (GU) (1.8-2.0 Gy/fx)

- **Femoral heads**
  - V50 <5%
- **Rectum**
  - V75 <15%, V70 <20%, V65 <25%, V60 <35%, V50 <50%
- **Bladder**
  - V80 <15%, V75 <25%, V70 <35%, V65 <50%
- **Testis**
  - V3 <50%
- **Penile bulb**
  - Mean dose to 95% of the volume <50 Gy. D70 <=70 Gy, D50 <=50 Gy

#### Genitourinary (GU) (LDR prostate brachytherapy)

- **Urethra**
  - Volume of urethra receiving 150% of prescribed dose (Ur150) <30%
- **Rectum**
  - Volume of rectum receiving 100% of prescribed dose (RV100) <0.5 cc

#### Gynecological (GYN)

- **Bladder point (cervical brachytherapy)**
  - Max 80 Gy (LDR equivalent dose)
- **Rectal point (cervical brachytherapy)**
  - Max 75 Gy (LDR equivalent dose)
### Coding

The following CPT codes are used for simple and complex IMRT delivery:

- **77385**: Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
- **77386**: Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex

The Centers for Medicare & Medicaid Services did not implement these CPT codes and instead created HCPCS G codes with the language of the previous CPT codes. Therefore, the following codes may be used for IMRT:

- **G6015**: Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session
- **G6016**: 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

Code 77301 remains valid:

- **77301**: Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications

The following CPT code may also be used and is to be reported only once per IMRT plan:

- **77338**: Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan

### Description

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

### Related Policies

- Intensity-Modulated Radiotherapy of the Prostate
- Intensity-Modulated Radiotherapy: Abdomen and Pelvis
- Intensity-Modulated Radiotherapy: Cancer of the Head and Neck or Thyroid
- Intensity-Modulated Radiotherapy: Central Nervous System Tumors

### Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these
instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

### Regulatory Status

In general, IMRT systems include intensity modulators, which control, block, or filter the intensity of radiation; and RT planning systems, which plan the radiation dose to be delivered.

A number of intensity modulators have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process. Intensity modulators include the Innocure Intensity Modulating Radiation Therapy Compensators (Innocure) cleared in 2006, and the decimal tissue compensator (Southeastern Radiation Products), cleared in 2004. FDA product code: IXI. Intensity modulators may be added to standard linear accelerators to deliver IMRT when used with proper treatment planning systems.

RT planning systems have also been cleared for marketing by the FDA through the 510(k) process. They include the Prowess Panther (Prowess) in 2003, TiGRT (LinaTech) in 2009, and the Ray Dose (RaySearch Laboratories) in 2008. FDA product code: MUJ.

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

### Rationale

#### Background

For certain stages of many cancers, including breast and lung, randomized controlled trials (RCTs) have shown that postoperative radiotherapy (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.

#### Radiotherapy Techniques

Radiation therapy may be administered externally (i.e., a beam of radiation is directed into the body) or internally (i.e., a radioactive source is placed inside the body, near a tumor). External radiotherapy (RT) techniques include "conventional" or 2-dimensional (2D) RT, 3-dimensional (3D) conformal RT, and intensity-modulated radiation therapy (IMRT).

**Conventional External-Beam Radiotherapy**

Methods to plan and deliver RT have evolved that permit more precise targeting of tumors with complex geometries. Conventional 2D treatment planning utilizes X-ray films to guide and position radiation beams. Bony landmarks (bones visualized on X-ray) are used to locate a tumor and direct the radiation beams. The radiation is typically of uniform intensity.

**Three-Dimensional Conformal Radiotherapy**

Radiation treatment planning has evolved to use 3D images, usually from computed tomography (CT) scans, to more precisely delineate the boundaries of the tumor and to discriminate tumor tissue from adjacent normal tissue and nearby organs at risk for radiation damage. Three-dimensional conformal RT (3D-C RT) involves initially scanning the patient in the position that will be used for the radiation treatment. The tumor target and surrounding normal organs are then outlined in 3D on the scan. Computer software assists in determining the orientation of radiation beams and the amount of radiation the tumor and normal tissues receive to ensure coverage of the entire tumor in order to minimize radiation exposure for at risk normal tissue and nearby organs. Other imaging techniques and devices such as multileaf collimators (MLCs) may be used to "shape" the radiation beams. Methods have also been
Intensity-Modulated Radiotherapy

IMRT is the more recent development in external radiation. Treatment planning and delivery are more complex, time-consuming, and labor-intensive for IMRT than for 3D-CRT. Similar to 3D-CRT, the tumor and surrounding normal organs are outlined in 3D by a scan and multiple radiation beams are positioned around the patient for radiation delivery. In IMRT, radiation beams are divided into a grid-like pattern, separating a single beam into many smaller “beamlets”. Specialized computer software 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, surrounding tissues, and organs at risk, computer software optimizes the location, shape, and intensities of the beam ports to achieve the treatment plan’s goals.

Increased conformality may permit escalated tumor doses without increasing normal tissue toxicity and is proposed to 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.

Other advanced techniques that may further improve RT treatment by improving dose distribution. These techniques are considered variations of IMRT. Volumetric modulated arc therapy delivers radiation from a continuous rotation of the radiation source. The principal advantage of volumetric modulated arc therapy is greater efficiency in treatment delivery time, reducing radiation exposure and improving target radiation delivery due to less patient motion. Image-guided RT involves the incorporation of imaging before and/or during treatment to more precisely deliver RT to the target volume.

Investigators are exploring an active breathing control device combined with moderately deep inspiration breath-holding techniques to improve conformity and dose distributions during IMRT for breast cancer. Techniques presently being studied with other tumors (e.g., lung cancer) 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 the 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 (nonbreathing) targets.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and
confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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 conformity to, and dose homogeneity within, the target. Results have also demonstrated that IMRT delivers 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 events from IMRT vs alternative radiation delivery would constitute definitive evidence of establishing the benefit of IMRT. Single-arm series of IMRT can give insights into the potential for benefit, particularly if an adverse event 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 indications, such as using IMRT to provide better tumor control, comparative studies of health outcomes are needed to demonstrate such a benefit.

Breast Cancer
Clinical Context and Therapy Purpose
The purpose of the use of IMRT in patients who have breast cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of IMRT improve health outcomes in patients with breast cancer?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is women with breast cancer.

Interventions
The therapy being considered is IMRT. Radiotherapy (RT) is an integral component of the treatment of breast cancer. IMRT has been proposed as a method of RT that allows adequate radiation to the tumor while minimizing the radiation dose to surrounding normal tissues and critical structures. IMRT is performed by radiation oncologists in outpatient settings.

Comparators
The following therapy is currently being used to make decisions about breast cancer: 2D and 3D-CRT. 3D-CRT is performed by radiation oncologists in outpatient settings.

Outcomes
The general outcomes of interest are overall survival (OS), locoregional control, and treatment-related adverse events (e.g., radiation dermatitis).
The grading of acute radiation dermatitis is relevant to studies of IMRT for the 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 fractionated radiotherapy (FRT) to the left breast.

In addition, IMRT may reduce toxicity to structures adjacent to tumors, allowing dose escalation to the target area and fewer breaks in treatment courses due to a reduction in side effects. However, this may come with a loss of locoregional control and OS. Thus, outcomes of interest are toxicity, quality of life, locoregional control, and OS.

Follow-up after IMRT varies by the staging of breast cancer and patient age at diagnosis. Five-year to 10-year follow-up to monitor for recurrence have been recommended.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

**Whole-Breast Irradiation With Intensity-Modulated Radiotherapy vs 2-Dimensional Radiotherapy**

**Review of Evidence**

**Systematic Reviews**
Dayes et al (2012) conducted a systematic review of 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 studies (total n=2012 patients) published through March 2009 (1 RCT, 3 retrospective cohort studies, 1 historically controlled trial, 1 prospective cohort), reviewers recommended IMRT over conventional RT after breast-conserving surgery to avoid acute adverse events associated with radiation. There were insufficient data to recommend IMRT over conventional RT based on oncologic outcomes or late toxicity. The RCT included in this review was the Canadian multicenter trial by Pignol et al (2008), details of which are reported in the next section. In this RCT, IMRT was compared with 2D-RT. Computed tomography scans were used in treatment planning for both arms of the study. The types of conventional RT regimens used in the other studies were not reported.

**Randomized Controlled Trials**
Donovan et al (2007) evaluated IMRT as compared to 2D-RT (using standard wedge compensators) regarding late adverse effects after whole breast RT. Enrolled patients had a “higher than average risk of late radiotherapy-adverse effects,” which included patients with larger breasts. Trialists stated that while breast size was 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 endpoint (change in breast appearance) was scored from serial photographs taken before RT and at 1-
2-, and 5-year follow-ups. 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 (58%) of 122 patients 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 events. While the change in breast appearance differed statistically, a beneficial effect on quality of life was not demonstrated.

The multicenter, double-blind RCT by Pignol et al (2008, 2016) evaluated whether breast IMRT would reduce the rate of acute skin reaction (moist desquamation), decrease pain, and improve quality of life compared with 2D-RT using wedges. Patients were assessed each week up to 6 weeks after RT and then at 8 to 10 years. A total of 358 patients were randomized between 2003 and 2005 at 2 Canadian centers, and 331 were analyzed. Of these, 241 patients were available for long-term follow-up. The trialists 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 RT (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 quality of life. At a median follow-up of 9.8 years, there was no significant difference in chronic pain between treatment arms. Young age (p=0.013) and pain during RT (p<0.001) were associated with chronic pain. Poorer self-assessed cosmetic outcome (p<0.001) and quality of life (p<0.001) were also associated with pain during RT.

Barnett et al (2009) published baseline characteristics and dosimetry results of a single-center RCT assessing IMRT for early breast cancer after breast-conserving surgery. Subsequently, Barnett et al (2012) reported on the 2-year interim results of this RCT. In this trial, 1145 patients with early breast cancer were evaluated for external-beam RT. Twenty-nine percent had adequate dosimetry with standard RT. The other 815 patients were randomized to IMRT or 2D-RT. Inhomogeneity occurred most often when the dose-volume was greater than 107% (V107) of the prescribed dose to a breast volume greater than 2 cm³ with conventional RT. 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 did not differ significantly 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.

**Whole-Breast Irradiation With Intensity-Modulated Radiotherapy vs 3-Dimensional Conformal Radiotherapy**

**Review of Evidence**

**Randomized Controlled Trials**

In their RCT, Jagsi et al (2018) assessed whether IMRT with deep inspiration breath hold (DIBH) reduces cardiac or pulmonary toxicity of breast RT compared to 3D-CRT. The study included 62 women with node-positive breast cancer in whom RT was indicated for treating the left breast or chest-wall and the internal mammary, infracavicular and supraclavicular nodal regions. The primary outcome was the percentage decrease in heart perfusion at 1 year post-treatment compared to baseline, measured using attenuation corrected single-photon emission computed tomography. A secondary outcome was a change in left ventricular ejection fraction. The 3D-CRT group received ≥ 5 Gy to 15.8% of the left ventricle; the IMRT-DIBH group
received 5.6% to the left ventricle (p<0.001). At 1 year, no differences in perfusion of the heart were detected; however, significant differences were found in left ventricular ejection fraction. In the 3D-CRT arm, 6 patients had > 5% changes in left ventricular ejection fraction, and the IMRT-DIBH arm had 1 patient with > 5% change. The authors contend that their study is important because it demonstrates that the IMRT-DIBH technique’s reduction in cardiac dose could be associated with better preservation of cardiac left ventricle function—a potentially clinically meaningful finding. One limitation of this study is its small size, and only 1 follow-up scan was conducted at 1 year due to resource constraints. A 6-month scan might have shown greater differences between the 2 arms.

**Nonrandomized Comparative Studies**

Hardee et al (2012) compared the dosimetric and toxicity outcomes after treatment with IMRT or 3D-CRT for whole-breast irradiation 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.11 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) 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 in 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.

Guttmann et al (2018) published a single-center retrospective analysis of 413 women who received tangential whole-breast irradiation between 2011 and 2015 (Table 1).12 Of the patients, 212 underwent IMRT and 201 received 3D-CRT. The main endpoint was a comparison of acute radiation dermatitis (grade 2+), and secondary endpoints were acute fatigue and breast pain. Grade 2+ radiation dermatitis was experienced by 59% of 3D-CRT patients and 62% of IMRT patients (p=0.09). There was also no significant difference between 3D-CRT and IMRT for breast pain (grade 2+, 18% vs 18%, respectively; p=0.33) or fatigue (grade 2+, 18% vs 25.5%, respectively; p=0.24) (Table 2). A study limitation was that follow-up varied across patients because those treated with IMRT completed treatment 1 week sooner than those treated with 3D-CRT.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Comparator</th>
<th>FU</th>
</tr>
</thead>
</table>

**Table 1. Summary of Key Nonrandomized Trials Characteristics**

**Table 2. Summary of Key Nonrandomized Trials Results**

<table>
<thead>
<tr>
<th>Study</th>
<th>Acute Radiation Dermatitis</th>
<th>Acute Fatigue</th>
<th>Acute Breast Pain</th>
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</thead>
<tbody>
<tr>
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<td>Grade 0=46</td>
<td>Grade 0=26</td>
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<td>Grade 1=78</td>
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<td>Grade 2=129</td>
<td>Grade 2=39</td>
<td>Grade 2=39</td>
</tr>
<tr>
<td></td>
<td>Grade 3=3</td>
<td>Grade 3=0</td>
<td>Grade 3=0</td>
</tr>
</tbody>
</table>

| Grade | Grade 0=0 | Grade 0=44 | Grade 0=44 |
|-------| Grade 1=83 | Grade 1=121 | Grade 1=121 |
|       | Grade 2=109 | Grade 2=33 | Grade 2=33 |
|       | Grade 3=9 | Grade 3=3 | Grade 3=3 |

IMRT: intensity-modulated radiotherapy; 3D-CRT: 3-dimensional conformal radiotherapy.
**Chest Wall Irradiation**

Studies have examined the use of IMRT for chest wall irradiation in postmastectomy breast cancer patients. 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 (e.g., heart, lung). In a study by Rudat et al (2011), treatment planning for chest wall irradiation with IMRT was compared with 3D-CRT in 20 postmastectomy patients. The authors reported IMRT significantly decreased heart and lung high-dose volume with a significantly improved conformity index compared with 3D-CRT. However, there were no significant differences in the homogeneity index. The authors noted 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. As noted, health outcomes were not reported in this study.

Rastogi et al (2018) published a retrospective study of 107 patients receiving RT postmastectomy to the left chest wall. Patients were treated with 3D-CRT (n=64) or IMRT (n=43). The planning target volume, homogeneity index, and conformity index for both groups were compared. IMRT had a significantly improved conformity index score (1.127) compared with 3D-CRT (1.254; p<0.001), while results for both planning target volume (IMRT, 611.7 vs 3D-CRT, 612.2; p=0.55) and homogeneity index (IMRT, 0.094 vs 3D-CRT, 0.096; p=0.83) were comparable. Furthermore, secondary analyses showed that IMRT had significantly lower mean- and high-dose volumes to the heart and ipsilateral lung (p<0.001 and p<0.001, respectively), while 3D-CRT had superior low-dose volume (p<0.001). The study was limited by its small population size and short follow-up.

Ho et al (2019) published the long-term pulmonary outcomes of a feasibility study of inverse-planned, multibeam IMRT in node-positive breast cancer patients receiving regional nodal irradiation. While the authors' primary endpoint was feasibility, they also observed the incidence of radiation pneumonitis grade 3 or greater and changes in pulmonary function. The later endpoints were measured with the Common Terminology Criteria for Adverse Events and pulmonary function tests and community-acquired pneumonia questions. Of 104 completed follow-up procedures, the overall rate of respiratory toxicity was 10.6%, with 1 grade 3 radiation pneumonitis event.

Kivanc et al (2019) published a dosimetric comparison of 3D-CRT and IMRT for left-sided chest wall and lymphatic irradiation. The study compared 5 different techniques (i.e., 3D-CRT, forward-planned IMRT, inverse-planned IMRT[7- or 9-field], and hybrid inverse-planned/forward-planned IMRT) in 10 patients. Results revealed no differences among the techniques for doses received by 95% of the volume (D95%) of lymphatics. Forward-planned IMRT was associated with a significantly lower D95% dose to the chest wall-planning target volume as compared to the other techniques (p=0.002). Of the evaluated techniques, the 9-field inverse-planned IMRT achieved the lowest volumes receiving higher doses. Overall, the dose homogeneity in chest wall-clinical target volume was improved with IMRT techniques versus 3DCRT, especially 9-field inverse-planned IMRT. The hybrid IMRT plans had the advantages of both forward-planned and inverse-planned IMRT techniques.

**Section Summary: Breast Cancer**

There is evidence from RCTs that IMRT decreases acute skin toxicity more than 2D-RT for whole-breast irradiation. One RCT reported improvements in moist desquamation of skin but did not find differences in grade 3 or 4 skin toxicity, pain symptoms, or quality of life. Another RCT found a change in breast appearance but not quality of life. A third RCT reported no differences in cosmetic outcomes at 2 years for IMRT or 2D-RT. Dosimetry studies have demonstrated that IMRT reduces inhomogeneity of radiation dose, thus potentially providing a mechanism for reduced skin toxicity. However, because whole-breast RT is now delivered by 3D-CRT, these comparison data are of limited value.
Studies comparing IMRT with 3D-CRT include 1 RCT comparing IMRT with DIBH to 3D-CRT, 2 non-randomized comparative assessments of whole-breast IMRT, and studies on treatment planning for chest wall IMRT. These studies have suggested that IMRT might improve short-term clinical outcomes. No studies have reported on health outcomes after IMRT for chest wall irradiation in breast cancer patients postmastectomy. Available studies have only focused on treatment planning and techniques. The risk of secondary lung cancers needs further evaluation. Additionally, cardiac and pulmonary toxicity needs further evaluation. Despite this, evidence supports the use of IMRT for left-sided breast lesions in which alternative types of RT cannot avoid toxicity to the heart and lungs.

Lung Cancer
Clinical Context and Therapy Purpose
The purpose of IMRT in patients who have lung cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of IMRT improve health outcomes in patients with lung cancer?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is individuals with lung cancer.

Interventions
The therapy being considered is IMRT. RT is an integral component of the treatment of lung cancer. IMRT has been proposed as a method of RT that allows adequate radiation to the tumor while minimizing the radiation dose to surrounding normal tissues and critical structures. IMRT is performed by radiation oncologists in outpatient settings.

Comparators
The following therapy is currently being used to make decisions about lung cancer: 3D-CRT. 3D-CRT is performed by radiation oncologists in outpatient settings.

Outcomes
The general outcomes of interest are OS, locoregional control, and treatment-related adverse events.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
Bezjak et al (2012) conducted a systematic review that examined the evidence on the use of IMRT for the treatment of lung cancer to quantify its potential benefits and make recommendations for RT programs considering adopting this technique in Ontario, Canada. 
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; the study by Liao et al (2010; reported below) indicated that patients assessed in their cohort
Intensity-Modulated Radiotherapy of the Breast and Lung

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(n=409) were previously reported in another cohort involving 290 subjects, 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, reviewers recommended that IMRT be considered for lung cancer patients when the tumor is proximate to an organ at risk, where the target volume includes a large volume of an organ at risk, or where dose escalation would be potentially beneficial while minimizing normal tissue toxicity.17

Nonrandomized Comparative Studies

Liao et al (2010) compared patients who received RT, along with chemotherapy, for inoperable non-small-cell lung cancer (NSCLC) at a single institution.18 This study retrospectively compared 318 patients who received computed tomography plus 3D-CRT and chemotherapy from 1999 to 2004 (mean follow-up, 2.1 years) with 91 patients who received 4-dimensional computed tomography plus IMRT and chemotherapy from 2004 to 2006 (mean follow-up, 1.3 years). Both groups received a median dose of 63 Gy. Disease endpoints were locoregional progression, distant metastasis, and OS. Disease covariates were gross tumor volume, nodal status, and histology. The toxicity endpoint was grade 3, 4, or 5 radiation pneumonitis; toxicity covariates were gross tumor volume, smoking status, and dosimetric factors. Using Cox proportional hazards models, the hazard ratios (HRs) for IMRT were less than 1 for all disease endpoints; the difference was significant only for OS. The median survival was 1.40 years for the IMRT group and 0.85 years for the 3D-CRT group. The toxicity rate was significantly lower in the IMRT group than in the 3D-CRT group. The 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 4-dimensional computed tomography 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 significant reductions in toxicity and improvement in survival. The nonrandomized, retrospective aspects of this study from a single-center limit the ability to draw definitive treatment conclusions about IMRT.

Shirvani et al (2013) reported on a U.S. cancer center study that assessed the use of definitive IMRT in limited-stage small-cell lung cancer treated with definitive RT.19 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 both multivariable and 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 with 3D-CRT (17%; p=0.005).

Harris et al (2014) compared the effectiveness of IMRT, 3D-CRT, or 2D-RT in treating stage III NSCLC using a cohort of patients from the Surveillance, Epidemiology, and End Results-Medicare database treated between 2002 and 2009.20 Overall survival 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 (HR=0.94, p=0.23) and cancer-specific survival (HR=0.94, p=0.28). On multivariate analysis, toxicity risks with IMRT and 3D-CRT were also similar. Likewise, results were similar for the propensity score-matched models and the adjusted models.

Ling et al (2016) compared IMRT with 3D-CRT in patients who had stage III NSCLC treated with definitive RT.21 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. The authors 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.
Chun et al (2017) reported on a secondary analysis of a trial that assessed the addition of cetuximab to a standard chemotherapy regimen and radiation dose escalation. Use of IMRT or 3D-CRT was a stratification factor in the 2 x 2 design. Of 482 patients in the trial, 53% were treated with 3D-CRT and 47% were treated with IMRT, though treatment allocation was not randomized. Compared with the 3D-CRT group, the IMRT group had larger planning treatment volumes (486 mL vs 427 mL, p=0.005), larger planning treatment volume/volume of lung ratio (median, 0.15 vs 0.13; p=0.13), and more stage IIIB breast cancer patients (38.6% vs 30.3%, p=0.056). Even though there was an increase in treatment volume, IMRT was associated with less grade 3 or greater pneumonitis (3.5% vs 7.9%, p=0.039) and a reduced risk (odds ratio [OR], 0.41; 95% confidence interval [CI], 0.171 to 0.986; p=0.046), with no significant differences between the groups in 2-year OS, progression-free survival, local failure, or distant metastasis-free survival.

Koshy et al (2017) published a retrospective cohort analysis of patients with stage III NSCLC, comparing those treated with IMRT and with non-IMRT. Using the National Cancer Database, 7493 patients treated between 2004 and 2011 were assessed. Main outcomes were OS and the likelihood and effects of radiation treatment interruption, defined as a break in the treatment of 4 or more days. Overall survival for non-IMRT and IMRT patients, respectively, were 18.2 months and 20 months (p<0.001) (Table 4). Median survival with and without a radiation treatment interruption was 16.1 and 19.8 months, respectively (p<0.001), and IMRT significantly reduced the likelihood of a radiation treatment interruption (OR, 0.84; p=0.04). The study was limited by unavailable information regarding RT planning and potential mechanisms affecting survival, and by a possible prescription bias, causing patients with better performance status to be given IMRT.

Appel et al (2019) conducted another retrospective, single institution, cohort evaluating the impact of radiation technique on pathological and clinical outcomes in 74 patients with locally advanced NSCLC managed with a trimodality strategy. Key study characteristics and results are presented in Tables 3 and 4. The 2-year overall local control rate was 81.6% (95% CI, 69% to 89.4%), disease-free survival was 58.3% (95% CI, 45.5% to 69%), and 3-year OS was 70% (95% CI, 57% to 80%). When comparing radiation techniques for these outcomes, there were no significant differences in local control (p=0.94), disease-free survival (p=0.33), or OS (p=0.72). Grade 2 esophageal toxicity was non significantly reduced with IMRT as compared to 3D-CRT (32% versus 37%; p=0.66). As with other studies, the retrospective design and single-center nature of this cohort make generalizability of the results to other cancer centers limited.

### Table 3. Summary of Key Observational Comparative Study Characteristics

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Comparator</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort U.S.</td>
<td>2004-2011</td>
<td>7493</td>
<td>IMRT</td>
<td>Non-IMRT</td>
<td>32 mo</td>
<td></td>
</tr>
<tr>
<td>Cohort Israel</td>
<td>2012-2018</td>
<td>74</td>
<td>IMRT</td>
<td>3D-CRT</td>
<td>3.6 years (median)</td>
<td></td>
</tr>
</tbody>
</table>

3D-CRT; three-dimensional conformal radiotherapy; FU: follow-up; IMRT: intensity-modulated radiotherapy.

### Table 4. Summary of Key Observational Comparative Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>OS</th>
<th>Major Pathologic Response Rate</th>
<th>Pathologic Complete Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chun et al (2017)</td>
<td>Months</td>
<td>20.0</td>
<td>65.2%</td>
</tr>
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<td>IMRT</td>
<td></td>
<td></td>
<td>34.8%</td>
</tr>
<tr>
<td>Non-IMRT</td>
<td>18.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appel et al (2019)</td>
<td>2-year</td>
<td>IMRT % (95% CI)</td>
<td>85% (60 to 95)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>65.2%</td>
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<tr>
<td></td>
<td></td>
<td>3D-CRT % (95% CI)</td>
<td>82% (68 to 90)</td>
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<td>62.7%</td>
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</table>

3D-CRT; three-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; OS: overall survival.
Section Summary: Lung Cancer
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 for large lung tumors. Based on nonrandomized comparative studies, IMRT appears to produce survival outcomes comparable with those of 3D-CRT, with a reduction in adverse events.

Summary of Evidence
For individuals who have breast cancer who receive IMRT, the evidence includes systematic reviews, RCTs, and nonrandomized comparative studies. Relevant outcomes are OS, locoregional control, quality of life, and treatment-related morbidity. There is modest evidence from RCTs for a decrease in acute skin toxicity with IMRT compared with 2D-RT for whole-breast irradiation, and dosimetry studies have demonstrated that IMRT reduces inhomogeneity of radiation dose, thus potentially providing a mechanism for reduced skin toxicity. However, because whole-breast RT is now delivered by 3D-CRT, these comparative data are of limited value.

Studies comparing IMRT with 3D-CRT include 1 RCT comparing IMRT with DIBH to 3D-CRT, 2 nonrandomized comparative studies on whole-breast IMRT, and a few studies on chest wall IMRT. These studies suggest that IMRT requires less radiation exposure to nontarget areas and may improve short-term clinical outcomes. The available studies on chest wall IMRT for postmastectomy breast cancer patients have only focused on treatment planning and techniques. However, when dose-planning studies have indicated that RT will lead to unacceptably high radiation doses, the studies suggest IMRT will lead to improved outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Evidence supports the use of IMRT for left-sided breast lesions in which alternative types of RT cannot avoid toxicity to the heart. Based on available evidence, input from clinical vetting, a strong chain of evidence, and the potential to reduce harms, IMRT may be considered medically necessary for whole-breast irradiation when (1) alternative forms of RT cannot avoid cardiac toxicity, and (2) IMRT dose-planning demonstrates a substantial reduction in cardiac toxicity. IMRT for the palliative treatment of lung cancer is considered not medically necessary because conventional radiation techniques are adequate for palliation.

For individuals who have lung cancer who receive IMRT, the evidence includes nonrandomized, retrospective, comparative studies. Relevant outcomes are OS, locoregional control, and treatment-related morbidity. Dosimetry studies have shown that IMRT can reduce radiation exposure to critical surrounding structures, especially in large lung tumors. Based on nonrandomized comparative studies, IMRT appears to produce survival outcomes comparable to those of 3D-CRT and reduce toxicity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information
Clinical Input From 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.

2012 Input
In response to requests from Blue Cross Blue Shield Association, input was received from 2 physician specialty societies and 3 academic medical centers (3 reviewers) in 2011. There was a near-uniform consensus in responses that whole-breast and lung intensity-modulated radiotherapy (IMRT) is appropriate in select patients with breast and lung cancer. Respondents noted IMRT might 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 might reduce skin reactions and potentially improve cosmetic outcomes. Partial-breast IMRT was not supported by respondents, and the response was mixed on the value of chest wall IMRT postmastectomy.

2010 Input
In response to requests from Blue Cross Blue Shield Association, input was received from 1 physician specialty society and 2 academic medical centers (3 reviewers) in 2010. Input suggested that IMRT is used in select patients with breast cancer (e.g., some cancers involving the left breast) and lung cancer (e.g., some large cancers).

Practice Guidelines and Position Statements
National Comprehensive Cancer Network

Breast Cancer
Current NCCN guidelines (v.4.2020) for breast cancer indicate the importance of individualizing RT planning and delivery. CT based treatment planning is encouraged to delineate target volumes and adjacent organs at risk. Improved target dose homogeneity and sparing of normal tissues can be accomplished utilizing various "compensators such as wedges, forward planning using segments, and IMRT." Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose in adjacent normal tissues, such as the heart and lung. The guideline states that "the panel recommends whole breast irradiation to include breast tissue in entirety. CT-based treatment planning is recommended to limit irradiation exposure of the heart and lungs, and to assure adequate coverage of the breast and lumpectomy site." 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.

Lung Cancer
Current NCCN guidelines (v.5.2020) for non-small-cell lung cancer indicate that "More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) ... IMRT/VMAT (volumetric modulated arc therapy).... Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival." IMRT is included in the technologies listed. The guidelines also states that "IMRT is preferred over 3D conformal external-beam RT on the basis of reduced toxicity in the setting of concurrent chemotherapy/RT."

American Society for Radiation Oncology

Breast Cancer
In 2018, the American Society for Radiation Oncology published evidence-based guidelines on whole-breast irradiation with or without low axilla inclusion. The guidance recommended a "preferred" radiation dosage of "4000 cGy [centigray] in 15 fractions or 4250 cGy in 16 fractions." IMRT is included in the technologies listed. The guidelines also states that "IMRT is preferred over 3D conformal external-beam RT on the basis of reduced toxicity in the setting of concurrent chemotherapy/RT."

Lung Cancer
In 2018, the American Society for Radiation Oncology has also published evidence-based guidelines on RT for lung cancer. The guidelines recommended "moderately hypofractionated palliative thoracic radiation therapy" with chemotherapy as palliative care for stage III and IV incurable non-small-cell lung cancer.
American Society of Clinical Oncology/American Society for Radiation Oncology/Society of Surgical Oncology

Breast Cancer

In 2016, the American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology, and the Society of Surgical Oncology developed a focused update of a prior ASCO guideline related to the use of post-mastectomy RT. The Expert Panel unanimously agreed that “available evidence shows that post-mastectomy RT reduces the risk of locoregional failure, any recurrence, and breast cancer mortality for patients with T1-2 breast cancer with 1 to 3 positive axillary nodes. However, some subsets of these patients are likely to have such a low risk of locoregional failure that the absolute benefit of post-mastectomy RT is outweighed by its potential toxicities.” Additionally, the guideline noted that “the decision to recommend post-mastectomy RT requires a great deal of clinical judgment.”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Some local Medicare Part B carriers have indicated that IMRT for the lung is considered medically necessary. These documents do not detail the rationale for this conclusion.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 5.

Table 5: Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02635009</td>
<td>Randomized Phase II/III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small Cell Lung Cancer</td>
<td>304</td>
<td>Apr 2027</td>
</tr>
<tr>
<td>NCT01349322</td>
<td>A Phase III Trial of Accelerated Whole Breast Irradiation with Hypofractionation Plus Concurrent Boost Versus Standard Whole Breast Irradiation Plus Sequential Boost for Early-Stage Breast Cancer</td>
<td>2354</td>
<td>Aug 2024</td>
</tr>
<tr>
<td>NCT02003560</td>
<td>Accelerated Partial Breast Irradiation After Breast Conserving Surgery for Low-risk Invasive Breast Cancer: 3D Conformal Radiotherapy (3D-CRT) and Intensity Modulated Radiotherapy (IMRT) - Prospective Phase II Study</td>
<td>90</td>
<td>Mar 2024</td>
</tr>
<tr>
<td>NCT03786354</td>
<td>Prospective Evaluation of Shoulder Morbidity in Patients with Lymph-Node Positive Breast Cancer Receiving Regional Nodal Irradiation</td>
<td>60</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT01185132</td>
<td>A Phase III Randomized Study Comparing Intensity Modulated Planning vs 3-dimensional Planning for Accelerated Partial Breast Radiotherapy</td>
<td>660</td>
<td>Jul 2028</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02440191</td>
<td>Postoperative Radiotherapy With Intensity-modulated Radiation Therapy (IMRT) Using Simultaneous Integrated Boost Versus 3-Dimensional Conformal Radiotherapy (3D-CRT) in Early Breast Cancer: a Prospective Randomized Trial</td>
<td>690</td>
<td>Apr 2018 (ongoing)</td>
</tr>
<tr>
<td>NCT00520702</td>
<td>A Randomized Trial to Compare Time To Common Toxicity Criteria for Adverse Effect (CTC AEC) 3.0 Grade Treatment Related Pneumonitis (TRP) in Patients With Locally Advanced Non-Small Cell Carcinoma (NSCLC) Receiving Concurrent Chemoradiation Radiation Treated With 3-Dimensional Conformal Radiation Therapy (3D CRT, ARM 1) vs Intensity</td>
<td>168</td>
<td>Oct 2018</td>
</tr>
<tr>
<td>NCTNo.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------------</td>
<td>---------------------</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References


**Documentation for Clinical Review**

Please provide the following documentation:

- History and physical and radiation oncology consultation report including:
  - Medical necessity for performing IMRT rather than conventional or 3D treatment planning
  - Past history of radiation (site) (if applicable)
  - Past surgical procedures (pertaining to request)
  - Primary cancer type and location
- Goals/requirements of the IMRT treatment plan and proposed IMRT treatment dose (dose volume histogram [DVH] - in color preferred; organs at risk)
- Comparison 3D-CRT dose volume histogram (DVH) (in color preferred; organs at risk) (as applicable)
- Radiology report(s) for the past 2 months

**Post Service (in addition to the above, please include the following):**

- Procedure report(s)

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>77014</td>
<td>Computed tomography guidance for placement of radiation therapy fields</td>
</tr>
<tr>
<td></td>
<td>77261</td>
<td>Therapeutic radiology treatment planning; simple</td>
</tr>
<tr>
<td></td>
<td>77262</td>
<td>Therapeutic radiology treatment planning; intermediate</td>
</tr>
<tr>
<td></td>
<td>77263</td>
<td>Therapeutic radiology treatment planning; complex</td>
</tr>
<tr>
<td></td>
<td>77293</td>
<td>Respiratory motion management simulation (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td></td>
<td>77300</td>
<td>Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface and depth dose, as required during course of treatment, only when prescribed by the treating physician</td>
</tr>
<tr>
<td></td>
<td>77301</td>
<td>Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications</td>
</tr>
<tr>
<td></td>
<td>77306</td>
<td>Teletherapy isodose plan; simple (1 or 2 unmodified ports directed to a single area of interest), includes basic dosimetry calculation(s)</td>
</tr>
<tr>
<td></td>
<td>77307</td>
<td>Teletherapy isodose plan; complex (multiple treatment areas, tangential ports, the use of wedges, blocking, rotational beam, or special beam considerations), includes basic dosimetry calculation(s)</td>
</tr>
<tr>
<td></td>
<td>77331</td>
<td>Special dosimetry (e.g., TLD, microdosimetry) (specify), only when prescribed by the treating physician</td>
</tr>
<tr>
<td></td>
<td>77332</td>
<td>Treatment devices, design and construction; simple (simple block, simple bolus)</td>
</tr>
<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>77334</td>
<td>Treatment devices, design and construction; complex (irregular blocks, special shields, compensators, wedges, molds or casts)</td>
</tr>
<tr>
<td></td>
<td>77336</td>
<td>Continuing medical physics consultation, including assessment of treatment parameters, quality assurance of dose delivery, and review of patient treatment documentation in support of the radiation oncologist, reported per week of therapy</td>
</tr>
<tr>
<td></td>
<td>77338</td>
<td>Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan</td>
</tr>
<tr>
<td></td>
<td>77370</td>
<td>Special medical radiation physics consultation</td>
</tr>
<tr>
<td></td>
<td>77385</td>
<td>Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple</td>
</tr>
<tr>
<td></td>
<td>77386</td>
<td>Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex</td>
</tr>
<tr>
<td></td>
<td>77387</td>
<td>Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed</td>
</tr>
<tr>
<td></td>
<td>77417</td>
<td>Therapeutic radiology port image(s)</td>
</tr>
<tr>
<td></td>
<td>77427</td>
<td>Radiation treatment management, 5 treatments</td>
</tr>
<tr>
<td></td>
<td>77470</td>
<td>Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>G6001</td>
<td>Ultrasonic guidance for placement of radiation therapy fields</td>
</tr>
<tr>
<td></td>
<td>G6002</td>
<td>Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy</td>
</tr>
<tr>
<td></td>
<td>G6015</td>
<td>Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session</td>
</tr>
<tr>
<td></td>
<td>G6016</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>G6017</td>
<td>Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment</td>
</tr>
</tbody>
</table>

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/30/2015</td>
<td>Policy title change from Intensity Modulated Radiation Therapy (IMRT) BCBSA Medical Policy adoption</td>
</tr>
<tr>
<td>10/01/2016</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>09/01/2017</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>09/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>09/01/2019</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>06/01/2020</td>
<td>Administrative update. Policy statement, guidelines and literature updated.</td>
</tr>
<tr>
<td>10/01/2020</td>
<td>Annual review. No change to policy statement. Literature review updated. Coding update.</td>
</tr>
</tbody>
</table>
Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member’s illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.