Name of Policy:
Intensity-Modulated Radiation Therapy (IMRT)

Policy #: 088                                      Latest Review Date: June 2013
Category: Radiology                                Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. 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 that patient’s illness, injury or disease.
Description of Procedure or Service:
Radiation therapy may be an integral component in the treatment of cancers of the abdomen and pelvis. Intensity-modulated radiation therapy (IMRT) has been proposed as a method of radiation therapy that allows adequate radiation therapy to the tumor while minimizing the radiation dose to surrounding normal tissues and critical structures.

Radiation techniques

Conventional external-beam radiation therapy
Over the past several decades, methods to plan and deliver radiation therapy have evolved in ways that permit more precise targeting of tumors with complex geometries. Most early trials used 2-dimensional treatment planning, based on flat images and radiation beams with cross-sections of uniform intensity that were sequentially aimed at the tumor along two or three intersecting axes. Collectively, these methods are termed “conventional external-beam radiation therapy.”

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

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

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

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

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

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

**Policy:**
**Breast and Lung**
Intensity-modulated radiation therapy (IMRT) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as a technique to deliver whole-breast irradiation in patients receiving treatment for left-sided breast cancer after breast-conserving surgery when all the following conditions have been met:

- Significant cardiac radiation exposure cannot be avoided using alternative radiation techniques; and
- IMRT dosimetry demonstrates significantly reduced cardiac target volume radiation exposure as follows:
  - The target volume coverage results in cardiac radiation exposure that is expected to be greater than or equal to 25 Gy to 10 cc or more of the heart (V25 greater than or equal to 10 cc) with 3D conformal RT, despite the use of a complex positioning device (such as Vac-Lok™); and
  - With the use of IMRT, there is a reduction in the absolute heart volume receiving 25 Gy or higher by at least 20% (e.g., volume predicted to receive 25 Gy by 3D RT is 20 cc and the volume predicted by IMRT is 16 cc or less).

Or

- In individuals with large breasts (cup size D or larger)
Intensity-modulated radiation therapy (IMRT) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in individuals with large breasts (cup size D or larger) for treatment right sided breast cancer.

Intensity-modulated radiation therapy (IMRT) of the breast does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational as a technique of partial-breast irradiation after breast-conserving surgery.

Intensity-modulated radiation therapy (IMRT) of the chest wall does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational as a technique of postmastectomy irradiation.

Intensity-modulated radiation therapy (IMRT) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as a technique to deliver radiation therapy in patients with lung cancer when ALL of the following conditions are met:
- Radiation therapy is being given with curative intent; and
- 3D conformal will expose >35% of normal lung tissue to more than 20 Gy dose-volume (V20); and
- IMRT dosimetry demonstrates reduction in the V20 to at least 10% below the V20 that is achieved with the 3D plan (e.g. from 40% down to 30% or lower).

Intensity-modulated radiation therapy (IMRT) does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as a technique to deliver radiation therapy in patients receiving palliative treatment for lung cancer.

Central Nervous System Tumors
Intensity-modulated radiation therapy (IMRT) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the treatment of tumors of the central nervous system when the tumor is in close proximity to organs at risk (brain stem, spinal cord, cochlea and eye structures including optic nerve and chiasm, lens and retina).

Prostate cancer
Intensity-modulated radiation therapy (IMRT) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in the treatment of localized prostate cancer at radiation doses of 75 to 80 Gy.

Head and Neck Cancer/Neoplasms or Thyroid Cancer
Intensity-modulated radiation therapy meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the treatment of *head and neck cancers.
* Head and neck cancers are cancers arising from the oral cavity and lip, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses and nasal cavity, salivary glands, and occult primaries in the head and neck region.

**Intensity-modulated radiation therapy meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in the treatment of patients with *benign head and neck neoplasms* such as glomus tumors or X nerve schwannomas when necessary for protection of the parotid gland or spinal cord.

**Intensity-modulated radiation therapy meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in the treatment of *thyroid cancers in close proximity to organs at risk* (esophagus, salivary glands, and spinal cord).

**Abdominal, Gastrointestinal, and Pelvic Cancer (excluding Prostate Cancer)**

**Intensity-modulated radiation therapy meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as an approach to delivering radiation therapy for patients with *cancer of the anus/anal canal*.

**Intensity-modulated radiation therapy meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in the treatment of *esophageal cancer*.

**Intensity-modulated radiation therapy meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in patients with cancer of the *abdomen and pelvis* when dosimetric planning with standard 3-D conformal radiation predicts that the radiation dose to an adjacent organ would result in unacceptable normal tissue toxicity, including but not limited to:

- Stomach (gastric)
- Hepatobiliary tract
- Pancreas
- Rectal locations
- Gynecologic tumors (including cervical, endometrial, and vulvar cancers)

**Radiation Tolerance doses for normal tissues of the abdomen and pelvis**

<table>
<thead>
<tr>
<th>Site</th>
<th>Portion of organ involved</th>
<th>TD 5/5 (Gy)</th>
<th>TD 50/5 (Gy)</th>
<th>Complication endpoint</th>
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<tbody>
<tr>
<td>Heart</td>
<td></td>
<td>60</td>
<td>70</td>
<td>50 (Pericarditis)</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>45</td>
<td>65</td>
<td>40 (Pneumonitis)</td>
</tr>
<tr>
<td>Spinal cord</td>
<td></td>
<td>50</td>
<td>70</td>
<td>NP (Myelitis/necrosis)</td>
</tr>
</tbody>
</table>

Proprietary Information of Blue Cross and Blue Shield of Alabama
Medical Policy #088
### Kidney
- 50
- 30
- 23
- NP
- 40
- 28
- Clinical nephritis

### Liver
- 50
- 35
- 30
- 55
- 45
- 40
- Liver failure

### Stomach
- 60
- 55
- 50
- 70
- 67
- 65
- Ulceration/perforation

### Small intestine
- 50
- NP
- 40
- 60
- NP
- 55
- Obstruction/perforation

### Femoral head
- NP
- NP
- 52
- NP
- NP
- 65
- Necrosis

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**Other Indications**

**Intensity-modulated radiation therapy (IMRT) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in patients with **soft tissue sarcoma of the extremities**.

**Intensity-modulated radiation therapy (IMRT) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in patients who **require repeat irradiation of a field that has received prior irradiation**.

**Effective for dates of service on or after January 1, 2013 through June 23, 2013:**

**Intensity-modulated radiation therapy (IMRT) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage:

- In the treatment of patients with **non-metastatic prostate cancer** for **dose escalation from 70 – 79 Gy or equivalent hypofractionated regimen**; or
- In the treatment of patients with **head and neck cancer (including thyroid cancer) and cancer at the base of the skull** except for patients with early stage larynx cancer (Stage I and II); or
- In the treatment of patients with **benign head and neck neoplasms** such as glomus tumors or X nerve schwannomas when necessary for protection of the parotid gland or spinal cord; or
- In the treatment of other CNS lesions with close proximity to the optic nerve, brain stem, or spinal cord **in which conventional conformal radiation therapy is either not feasible or inadequate**; or
- In the treatment of patients with **breast cancer** with **pre-existing clinical cardiac dysfunction where the heart should not be radiated**, breast cancer patients with **large**
breasts (cup size D or larger), breast cancer patients that received treatment with potentially cardiotoxic drugs including, but not limited to anthracyclines and anthraquinone; or

- In patients with soft tissue sarcoma of the extremities; or
- In patients with squamous cell cancer of the anus/anal canal; or
- In patients who require repeat irradiation of a field that has received prior irradiation; or
- In patients with esophageal cancer; or
- In patients with cancer of the abdomen and pelvis when dosimetric planning with standard 3-D conformal radiation predicts that the radiation dose to an adjacent organ would result in unacceptable normal tissue toxicity, including but not limited to:
  - Stomach (gastric)
  - Hepatobiliary tract
  - Pancreas
  - Rectal locations
  - Gynecologic tumors (including cervical, endometrial, and vulvar cancers)

### Radiation Tolerance doses for normal tissues of the abdomen and pelvis

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<td>Heart</td>
<td>60</td>
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</tr>
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<tr>
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<tr>
<td>Small intestine</td>
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<td>NP</td>
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<tr>
<td>Femoral head</td>
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</tbody>
</table>
IMRT does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational when performed for the treatment of patients with types of cancer not listed above including, but not limited to, lung cancer, gastric cancer, and colon cancer.

Effective for dates of service on or after June 1, 2012 through December 31, 2012:
Intensity-modulated radiation therapy (IMRT) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage:

- In the treatment of patients with non-metastatic prostate cancer for dose escalation from 70 – 79 Gy or equivalent hypofractionated regimen; or
- In the treatment of patients with head and neck cancer (including thyroid cancer) and cancer at the base of the skull except for patients with early stage larynx cancer (Stage I and II); or
- In the treatment of patients with benign head and neck neoplasms such as glomus tumors or X nerve schwannomas when necessary for protection of the parotid gland or spinal cord; or
- In the treatment of other CNS lesions with close proximity to the optic nerve, brain stem, or spinal cord in which conventional conformal radiation therapy is either not feasible or inadequate; or
- In the treatment of patients with breast cancer with pre-existing clinical cardiac dysfunction where the heart should not be radiated, breast cancer patients with large breasts (cup size D or larger), breast cancer patients that received treatment with potentially cardiotoxic drugs including, but not limited to anthracyclines and anthraquinone; or
- Used to treat gynecological tumors (uterus, cervix, ovary, fallopian tube) where brachytherapy is not feasible due to patient’s anatomy or local extent of tumor or if the conventional radiation therapy dose required to control the tumor would result in unacceptable risk of small intestine injury (V45>10% or V49>5%), or
- Used to treat abdominal tumors such as retroperitoneal sarcomas, primary pelvic sarcomas, and para-aortic nodal metastasis from cervical cancer, if the conventional radiation therapy dose required to control the tumor would result in unacceptable risk of small intestine injury (V45>10% or V49>5%); or
- In patients with locally advanced rectal adenocarcinoma when if the conventional radiation therapy dose required to control the tumor would result in unacceptable risk of small intestine injury (V45>10% or V49>5%); or
- In patients with soft tissue sarcoma of the extremities; or
- In patients with squamous cell cancer of the anus/anal canal; or
• In patients who require repeat irradiation of a field that has received prior irradiation; or
• In patients with esophageal cancer.

IMRT does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational when performed for the treatment of patients with types of cancer not listed above, including but not limited to, lung cancer, gastric cancer, anal cancer, and colon cancer.

Effective for dates of service January 18, 2012, through May 31, 2012

Intensity-modulated radiation therapy (IMRT) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage:

• In the treatment of patients with non-metastatic prostate cancer for dose escalation from 70 – 79 Gy or equivalent hypofractionated regimen; or
• In the treatment of patients with head and neck cancer and cancer at the base of the skull except for patients with early stage larynx cancer (Stage I and II); or
• In the treatment of patients with benign head and neck neoplasms such as glomus tumors or X nerve schwannomas when necessary for protection of the parotid gland or spinal cord; or
• In the treatment of other CNS lesions with close proximity to the optic nerve, brain stem, or spinal cord in which conventional conformal radiation therapy is either not feasible or inadequate; or
• In the treatment of patients with breast cancer with pre-existing clinical cardiac dysfunction where the heart should not be radiated, breast cancer patients with large breasts (cup size D or larger), breast cancer patients that received treatment with potentially cardiotoxic drugs including, but not limited to anthracyclines and anthraquinone; or
• Used to treat gynecological tumors (uterus, cervix, ovary, fallopian tube) where brachytherapy is not feasible due to patient’s anatomy or local extent of tumor or if the conventional radiation therapy dose required to control the tumor would result in unacceptable risk of small intestine injury (V45>10% or V49>5%), or
• Used to treat abdominal tumors such as retroperitoneal sarcomas, primary pelvic sarcomas, and para-aortic nodal metastasis from cervical cancer, if the conventional radiation therapy dose required to control the tumor would result in unacceptable risk of small intestine injury (V45>10% or V49>5%), or
• In patients with locally advanced rectal adenocarcinoma when if the conventional radiation therapy dose required to control the tumor would result in unacceptable risk of small intestine injury (V45>10% or V49>5%), or
• In patients with soft tissue sarcoma of the extremities; or
• In patients with squamous cell cancer of the anus/anal canal.

IMRT does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational when performed for the treatment of patients with types of
cancer not listed above, including but not limited to, lung, cancer, gastric cancer, anal cancer, colon cancer, esophageal cancer.

**Effective for dates of service November 18, 2009 through January 17, 2012:**

**Intensity-modulated radiation therapy (IMRT) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage:

- In the treatment of patients with **non-metastatic prostate cancer** for **dose escalation from 70 – 79 Gy or equivalent hypofractionated regimen**; or
- In the treatment of patients with **head and neck cancer and cancer at the base of the skull** except for patients with early stage larynx cancer (Stage I and II); or
- In the treatment of patients with **benign head and neck neoplasms** such as glomus tumors or X nerve schwannomas when necessary for protection of the parotid gland or spinal cord; or
- In the treatment of other CNS lesions with close proximity to the optic nerve, brain stem, or spinal cord in which **conventional conformal radiation therapy is either not feasible or inadequate**; or
- In the treatment of patients with **breast cancer with pre-existing clinical cardiac dysfunction where the heart should not be radiated**, breast cancer patients with **large breasts (cup size D or larger)**, breast cancer patients that received treatment with potentially cardiotoxic drugs including, but not limited to anthracyclines and anthraquinone; or
- Used to treat **gynecological tumors (uterus, cervix, ovary, fallopian tube)** where **brachytherapy is not feasible** due to patient’s anatomy or local extent of tumor or if the **conventional radiation therapy dose required to control the tumor would result in unacceptable risk of small intestine injury (V45>10% or V49>5%)**; or
- Used to treat **abdominal tumors such as retroperitoneal sarcomas, primary pelvic sarcomas, and para-aortic nodal metastasis from cervical cancer**, if the **conventional radiation therapy dose required to control the tumor would result in unacceptable risk of small intestine injury (V45>10% or V49>5%)**; or
- In patients with **locally advanced rectal adenocarcinoma** when if the **conventional radiation therapy dose required to control the tumor would result in unacceptable risk of small intestine injury (V45>10% or V49>5%)**; or
- In patients with **soft tissue sarcoma of the extremities**.

**IMRT does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** when performed for the treatment of patients with types of cancer not listed above, including but not limited to, lung, cancer, gastric cancer, anal cancer, colon cancer, esophageal cancer.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best*
medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

**Key Points:**
This policy is updated with literature search through April 2013.

Methods to plan and deliver intensity-modulated radiation therapy (IMRT) methods are not uniform. IMRT may use beams that remain on as the multileaf collimator (MLC) moves around the patient (dynamic MLC), or that are turned off during movement and turned on when the MLC reaches prespecified positions (“step and shoot” technique). A third alternative uses a very narrow single beam that moves spirally around the patient (tomotherapy). Each of these methods uses different computer algorithms to plan treatment and yields somewhat different dose distributions in and outside the target. Patient position can alter target shape and thus affect treatment plans. IMRT may be delivered with the patient in the prone or supine position. However, data are unavailable to compare clinical outcomes for patients treated in prone versus supine positions, and consensus is lacking. Respiratory motion of the internal organs during radiation treatments is another concern when using IMRT to treat lesions in those compartments. Treatment plans are usually based on one imaging scan, a static 3-dimensional computed tomography (CT) image. They partially compensate for day-to-day (inter-fraction) variability in patient set-up, and for (intra-fraction) motion of the target and organs at risk, by expanding the target volume with uniform margins around the tumor (generally 0.5–1 cm for all positional uncertainty).

Current methods seek to reduce positional uncertainty for tumors and adjacent normal tissues by various techniques. Patient immobilization cradles and skin or bony markers are used to minimize day-to-day variability in patient positioning. An active breathing control device combined with moderately deep inspiration breath-holding techniques may be used to improve conformality and dose distributions during IMRT. Other techniques being studied with internal tumors include gate beam delivery to the patient’s respiratory movement or continuous monitor of tumor (by in-room imaging) or marker (internal or surface) positions to aim radiation more accurately at the target. The impact of these techniques on outcomes of IMRT for any cancer is unknown. However, it appears likely that respiratory motion alters the dose distributions actually delivered while treating patients from those predicted by plans based on static CT scans, or measured by dosimetry, using stationary (non-breathing) targets. In addition, many tumors have irregular edges that preclude drawing tight margins on CT scan slices when radiation oncologists contour the tumor volume. It is unknown whether omitting some tumor cells or including some normal cells in the resulting target affects outcomes of IMRT. Finally, tumor size may change over the course of treatment as tumors respond or progress, which has potential effects on radiation dose delivery and distribution. Whether outcomes might be improved by repeating scans and modifying treatment plans accordingly (termed adaptive radiation therapy) is unknown.

The Advanced Technology Consortium (ATC) has helped to develop general guidelines for protocols that incorporate IMRT as an option. These guidelines were communicated to all clinical trial groups by the National Cancer Institute (NCI) and clearly stated that respiratory
motion could cause far more problems for IMRT than for traditional radiotherapy treatments (ATC Guidelines for use of IMRT for intra-thoracic treatments).

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

The most common techniques for delivering IMRT treatments on lineal accelerators use multileaf collimators (MLCs). The MLC leaves move automatically during the treatment of each field to form the intensity modulation and between fields to define treatment ports. An alternative way to deliver IMRT is by using a physical compensator. Compensators have been used in radiotherapy for decades to produce simple forms of intensity modulation. In the last decade compensator techniques have been used for delivering IMRT designed by dose optimization algorithms. Customized compensators are shaped to attenuate the open-field photo fluence such that the transmitted fluence map is as designed by the dose optimization algorithm. The advantage of the IMRT delivery method is simplicity.

The literature search found no reports directly comparing health outcomes of IMRT with those of 3D-CRT for either breast or lung cancer treatment. There were no prospective comparative trials (randomized or nonrandomized).

**Breast Cancer**

*Systematic reviews*

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

Two (of six) cohort studies reviewed by Dayes and colleagues 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 and colleagues (reported 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 radiotherapy in favor of IMRT for breast edema (IMRT, 1% vs. 25%, p<0.001), and the other study found a trend toward a
reduction in lymphedema rates (p=0.06). No differences were observed across both studies in other late effects including fat necrosis or second malignancies.

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

Randomized and nonrandomized studies
Donovan et al reported the treatment planning and dosimetry results from an ongoing RCT comparing outcomes of radiation therapy for breast cancer using conventional 2D-RT with wedged, tangential beams or IMRT (n=300) in 2002. In an abstract, these investigators reported interim cosmetic outcomes at two years after randomization for 233 evaluable patients. Changes in breast appearance were noted in 60 of 116 (52%) randomly assigned to conventional external-beam radiation therapy (EBRT) and in 42 of 117 (36%) randomly assigned to IMRT (p=0.05). Other outcomes were not reported. In 2007, Donovan et al published a subsequent report on this trial. Enrolled patients had ‘higher than average risk of late radiotherapy-adverse effects’, which included patients having larger breasts. The authors stated that while breast size is not particularly good at identifying women with dose inhomogeneity falling outside current International Commission on Radiation Units and Measurements guidelines, their trial excluded women with small breasts (less than or equal to 500 cc), who generally have fairly good dosimetry with standard 2D compensators. All patients were treated with six or ten MV photons to a dose of 50 Gy in 25 fractions to 100% in five weeks followed by an electron boost to the tumor bed of 11.1 Gy in five fractions to 100%. The primary endpoint was change in breast appearance scored from serial photographs taken before radiotherapy and at one, two, and five years follow-up. Secondary endpoints included patient self-assessments of breast discomfort, breast hardness, quality of life, and physician assessments of breast induration. Two-hundred forty (79%) patients with 5-year photographs were available for analysis. Change in breast appearance was identified in 71/122 (58%) allocated standard 2D treatment compared to 47/118 (40%) patients allocated 3D IMRT. Significantly fewer patients in the 3D IMRT group developed palpable induration assessed clinically in the center of the breast, pectoral fold, inframammary fold and at the boost site. No significant differences between treatment groups were found in patient-reported breast discomfort, breast hardness, or quality of life. The authors concluded that the analysis suggests that minimization of unwanted radiation dose inhomogeneity in the breast reduces late adverse effects. While the change in breast appearance was statistically different, a beneficial effect on quality of life was not demonstrated. Since whole-breast radiation therapy is now delivered by 3D-conformal techniques, these comparison data are of limited value. As the authors note, quality-of-life changes were not noted. No other clinical outcomes were reported.
In a 2008 study, Donovan and colleagues evaluated methods for breast cancer IMRT planning and compared IMRT methods to conventional wedge planning in 14 patients. The majority of IMRT plans were found to improve dose homogeneity over wedge-only treatment plans. In patients with a breast size of 500 cm³ or greater, the dose distribution improved between 5.6% and 11.1% (p<0.05), regardless of the planning method used. The authors noted in the discussion that IMRT may be inappropriate for patients with a breast volume of less than 1000 cm³.

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

Barnett and colleagues have published baseline characteristics and dosimetry results of a single-center randomized trial of IMRT for early breast cancer after breast-conserving surgery. In this trial, 1,145 patients with early breast cancer were evaluated for EBRT. Twenty-nine percent had adequate dosimetry with standard radiotherapy. The other 815 patients were randomly assigned to receive either IMRT or conventional 2D-RT. In this study, inhomogeneity occurred most often when the dose-volume was greater than 107% (V107) of the prescribed dose to greater than 2 cm³ breast volume with conventional radiation techniques. When breast separation was greater than or equal to 21 cm, 90% of patients had received greater than V107 greater than 2 cm³ with standard radiation planning. Subsequently, in 2012, Barnett and colleagues reported on the two-year interim results of the trial. The incidence of acute toxicity was not significantly different between groups. Additionally, photographic assessment scores for breast shrinkage were not significantly different between groups. The authors noted overall cosmesis after RT or IMRT was dependent upon surgical cosmesis; suggesting breast shrinkage and induration were due to surgery rather than RT, thereby masking the potential cosmetic benefits of IMRT.

Several other publications report findings from single institutions from patients who received IMRT compared to patients who received 2D-RT (nonrandomized studies). The grading of acute radiation dermatitis is relevant to these studies. Acute radiation dermatitis is graded on a scale of 0 to 5, with 0 as no change and 5 as death. Grade 2 is moderate erythema and patchy moist desquamation, mostly in skin folds; Grade 3 is moist desquamation in other locations and bleeding with minor trauma.
McDonald et al reported on a single institution retrospective review of patients who received radiation therapy after conservative surgery for Stages 0-III breast cancer from January 1999 to December 2003. Computed tomography simulation was used to design standard tangential breast fields with enhanced dynamic wedges for 2D-RT and both enhanced dynamic wedges and dynamic multileaf collimators for IMRT. In this report, 121 breasts were treated with IMRT and 124 with 2D-RT. Median breast dose was 50 Gy in both groups. Median follow-ups were 6.3 years (range: 3.7–104 months) for patients treated with IMRT and 7.5 years (range: 4.9–112 months) for those treated with 2D-RT. Decreased acute skin toxicity of Radiation Therapy Oncology Group (RTOG) Grade II or III was observed with IMRT treatment compared with 2D-RT (39% vs. 52%, respectively; p=0.047). For patients with Stages I-III (n=199), seven-year Kaplan-Meier freedom from ipsilateral breast tumor recurrence (IBTR) rates were 95% for IMRT and 90% for 2D-RT (p=0.36). For patients with stage 0 (ductal carcinoma in situ, n=46), seven-year freedom from IBTR rates were 92% for IMRT and 81% for 2D-RT (p=0.29). There were no statistically significant differences in overall survival (OS), disease-specific survival, or freedom from IBTR, contralateral breast tumor recurrence, distant metastasis, late toxicity, or second malignancies between IMRT and 2D-RT. The authors concluded that patients treated with breast IMRT had decreased acute skin toxicity, and long-term follow-up showed excellent local control. Interpretation of this study is limited by its retrospective design and limited outcome measures (no quality of life measures).

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

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

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

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

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

IMRT has also been investigated as a technique of partial-breast irradiation, as an alternative to whole-breast irradiation therapy after breast-conserving surgery. Breast brachytherapy is another technique of partial-breast irradiation therapy. Leonard et al reported on 55 patients treated with partial-breast IMRT who had mean follow-up of ten months. At the short-term follow-up, the dose delivery and clinical outcomes were considered acceptable; however, long-term follow-up is needed.
In 2010, Livi et al reported on preliminary results of 259 patients randomized in a Phase III trial, that began in September 2008, to compare conventional fractionated whole-breast treatment (n=128) to accelerated partial-breast irradiation plus IMRT (n=131). RTOG Grade 1 and 2 skin toxicity was observed at a rate of 22% and 19% in the whole breast treatment group versus 5% and 0.8% in the partial breast treatment group, respectively. The authors concluded partial-breast irradiation with IMRT is feasible but noted long-term results on health outcomes are still needed. Additionally, 18 months after radiation therapy (RT), one case of contralateral breast cancer was diagnosed in the partial breast irradiation group, creating concern from the authors that it may be related to the high dosage of IMRT.

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

**Lung Cancer**

*Systematic reviews*

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

*Randomized and nonrandomized studies*

Holloway et al reported on a Phase I dose escalation study of IMRT for patients with lung cancer that was terminated after the first five patients received 84 Gy in 35 fractions (2.4 Gy per fraction). Treatment planning used combined CT and positron emission tomography for volumetric imaging, and treatment beams were gated to patients’ respiration. Acute toxicities...
included one patient with RTOG Grade II dysphasia, one with Grade I odynophagia, and one with Grade I skin desquamation. In addition, one patient died of lung toxicity and was shown on autopsy to have bilateral diffuse pulmonary fibrosis with emphysema and diffuse alveolar damage. Of those who survived, one remained disease-free at 34 months, two developed metastases, and one developed an in-field recurrence.

Noting that the use of IMRT for inoperable non-small cell lung cancer (NSCLC) had not been well-studied, Sura and colleagues reviewed their experience with IMRT for patients with inoperable NSCLC. They reported a retrospective review of 55 patients with Stage I-IIIB inoperable NSCLC treated with IMRT between 2001 and 2005. The study endpoints were toxicity, local control, and overall survival. With a median follow-up of 26 months, the two-year local control and overall survival rates for Stage I/II patients were 50% and 55%, respectively. For the Stage III patients, two-year local control and overall survival rates were 58% and 58%, respectively, with a median survival time of 25 months. Six patients (11%) experienced Grade 3 acute pulmonary toxicity; two patients (4%) had Grade 3 or worse late treatment-related pulmonary toxicity. The authors concluded that these results were promising.

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

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

Central Nervous System Tumors

High-grade malignant tumors

Amelio and colleagues (2010) conducted a systematic review on the clinical and technical issues of using IMRT in newly diagnosed glioblastoma multiforme (GBM). The articles included in the review were through December 2009 and included 17 studies (nine related to dosimetric data and technical considerations, seven to clinical results, and one to both dosimetric and clinical results) for a total of 204 treated patients and 148 patient datasets used in planning studies. No randomized controlled studies (RCTs) were identified, and a meta-analysis was not performed.

For the six papers related to planning studies that compared either 3D-CRT versus IMRT, one study showed a noticeable difference between 3D-CRT and IMRT for the planning target volume (PTV) (13% benefit in V95 [volume that received 95% of the prescribed dose] from IMRT, (p<0.001); the remaining studies suggested that IMRT and 3D-CRT provide similar PTV coverage, with differences between 0 and 1%. Target dose conformity was found to be improved with IMRT.

The organs at risk (OAR) typically under consideration in the studies were the brainstem, optic chiasm, optic nerves, lens and retina. In general, IMRT allowed better sparing of the OAR than 3D-CRT but with considerable variation from study to study.

The eight studies that included clinical results included three retrospective, one prospective Phase I and IV prospective Phase II single institution studies. Of these eight studies, two used conventional total dose and dose per fraction, two used a hypofractionated regimen, and in the remaining, a hypofractionated scheme using a simultaneous integrated boost. Chemotherapy was administered in six of eight series, concomitantly with radiation and in the adjuvant phase. Median follow-up ranged from 8.8 and 24 months. Almost all patients (96%) were able to complete the treatment without interruption/discontinuation due to toxicity. Acute toxicity was reported as negligible with Grade-3 side effects observed in only two studies at rates of 7% and 12%. Grade-4 toxicity was recorded in only one series with an absolute rate of 3%. Data for late toxicities were available in 6/8 studies, with one study recording Grade-4 side effects with an incidence of 20%. One-year and two-year overall survival (OS) varied between 30% and 81.9% and between 0% and 55.6%, respectively. When OS was reported as a median time, its value ranged from seven to 24 months. Progression-free survival (PFS) ranged from 0% and 71.4% at one year and 0% and 53.6% at two years. Median PFS was reported as ranging from 2.5 to 12 months.

The authors also carried out a comprehensive qualitative comparison with data reported in the literature on similar non-IMRT clinical studies and offered the following conclusions. The results of the planning comparisons showed 3D-CRT and IMRT techniques provide similar results in terms of target coverage, IMRT is somewhat better than 3D-CRT in reducing the maximum dose to the OAR, although the extent varied from case to case, IMRT is clearly better.
than 3D-CRT in terms of dose conformity and sparing of the healthy brain at medium to low doses and that (in general) there were no aspects where IMRT seemed worse than 3D-CRT.

This evidence is limited by a number of factors. There is an absence of comparative studies with clinical outcomes, all of the studies were small in size, from a single institution, a majority of patients (53%) were retrospectively analyzed, and the administration of chemotherapy was variable across studies.

A representative sample of the comparative studies on dose planning and the single-arm studies with clinical outcomes are discussed below.

MacDonald and colleagues (2007) compared the dosimetry of IMRT and 3D-CRT in 20 patients treated for high-grade glioma. Prescription dose and normal-tissue constraints were identical for the 3D-CRT and IMRT treatment plans. The IMRT plan yielded superior target coverage as compared with the 3D-CRT plan. The IMRT plan reduced the percent volume of brainstem receiving a dose greater than 45 Gy by 31% (p=0.004) and the percent volume of brain receiving a dose greater than 18 Gy, 24 Gy, and 45 Gy by 10% (p=0.059), 14% (p=0.015), and 40% (p< or=0.0001), respectively. With IMRT, the percent volume of optic chiasm receiving more than 45 Gy was reduced by 30.4% (p=0.047). As compared with 3D-CRT, IMRT significantly increased the tumor control probability (p< or=0.0005) and lowered the normal-tissue complication probability for brain and brain stem (p<0.033).

Narayana and colleagues (2006) reported the outcomes of 58 consecutive patients with high-grade gliomas treated with IMRT. GBM accounted for 70% of cases and anaplastic gliomas for the remainder. Surgery consisted of biopsy alone in 26% of patients and of those who underwent resection, 63% had total or near total resection and 37% had partial resection. Eighty percent of patients received adjuvant chemotherapy. Median follow-up was 24 months. Acute neurotoxicities were Grade 1/2 in 36% of patients, grade 3 in 7%, and Grade 4 in 3%. Late toxicities were Grade 1/2 in 10%, Grade 3 in 7%, and no Grade 4 or 5. Freedom from late neurotoxicity at 24 months was 85%. Median OS for the anaplastic astrocytomas was 36 months and nine months for the GBM group. From these data, the authors concluded that the use of IMRT in high-grade gliomas does not appear to improve survival.

Narayana et al also performed a comparison of the IMRT treatment plans with 3D plans performed in 20 patients out of 58 total in that case series. Regardless of tumor location, IMRT did not improve PTV target coverage compared to 3D planning. IMRT decreased the maximum dose to the spinal cord, optic nerves, and eye by 16%, 7%, and 15%, respectively. These data indicate that IMRT may result in decreased late toxicities.

Huang and colleagues (2002) compared ototoxicity with use of conventional (2D) radiotherapy (n=11) versus IMRT (n=15) in 26 pediatric patients with medulloblastoma. All of the patients also received chemotherapy. When compared to conventional radiotherapy, IMRT delivered 68% of the radiation dose to the auditory apparatus, but full doses to the desired target volume. Median follow-up for audiometric evaluation was 51 months (9-107 months) for the conventional radiotherapy group and 18 months (8-37 months) for the group that received IMRT. Thirteen percent of the IMRT group had Grade-3 or -4 hearing loss, compared to 64% of the conventional radiotherapy group (p<0.014).
**Benign tumors**

Milker-Zabel and colleagues (2007) reported the results of the treatment of complex-shaped meningiomas of the skull base with IMRT in 94 patients. Patients received radiotherapy as primary treatment (n=26) postoperatively for residual disease (n=14) or after local recurrence (n=54). Tumor histology was World Health Organization Grade 1 in 54.3%, Grade 2 in 9.6%, and Grade 3 in 4.2%. Median follow-up was 4.4%. Overall local tumor control was 93.6%. Sixty-nine patients had stable disease (by computed tomography [CT]/magnetic resonance imaging [MRI]), and 19 had a tumor volume reduction after IMRT. Six patients had local tumor progression on MRI a median of 22.3 months after IMRT. In 39.8% of patients, preexisting neurologic deficits improved. Treatment-induced loss of vision was seen in one of 53 re-irradiated patients with a Grade-3 meningioma nine months after retreatment with IMRT.

Mackley and colleagues (2007) reported outcomes of treating pituitary adenomas with IMRT. A retrospective chart review was conducted on 34 patients treated between 1998 and 2003 at the Cleveland Clinic. Median follow-up was 42.5 months. Radiographic local control was 89%, and among patients with secretory tumors, 100% had a biochemical response. One patient required salvage surgery for progressive disease, resulting in a clinical PFS of 97%. One patient who received more than 46 Gy experienced optic neuropathy eight months after radiation.

Sajja and colleagues (2005) reported the outcomes of 35 patients with 37 meningiomas treated with IMRT. Tumor histology was benign in 35 and atypical in two tumors. The median CT/MRI follow-up was 19.1 months (range 6.4-62.4 months). Fifty-four percent of the meningiomas had been previously treated with surgery/radiosurgery prior to IMRT, and 46% were treated with IMRT, primarily after a diagnosis was established by CT/MRI. Three patients had local failure after treatment. No long-term complications from IMRT were documented among the 35 patients.

Uy and colleagues (2002) assessed the safety and efficacy of IMRT in the treatment of intracranial meningioma in 40 patients treated between 1994 and 1999. Twenty-five patients received IMRT after surgery either as adjuvant therapy for incomplete resection or for recurrence, and 15 patients received definitive IMRT after a presumptive diagnosis of meningioma on imaging. Thirty-two patients had skull base lesions and eight had non-skull base lesions. Follow-up ranged from six to 71 months (median 30 months). Defined normal structures generally received a significantly lower dose than the target. The most common acute CNS toxicity was mild headache, usually relieved with steroids. One patient experienced Radiation Therapy Oncology Group (RTOG) Grade-3 acute CNS toxicity, and two experienced Grade 3 or higher late CNS toxicity, with one possible treatment-related death. No toxicity was observed with mean doses to the optic nerve/chiasm up to 47 Gy and maximum doses up to 55 Gy. Cumulative five-year local control, PFS, and OS were 93%, 88%, and 89%, respectively.

**Brain metastases**

Edwards and colleagues (2010) reported outcomes on the use of whole-brain radiotherapy (WBRT) with an IMRT boost in 11 patients with metastatic disease to the brain ranging from 25-80 mm in maximum diameter. Patients were excluded if they had more than four metastases. Histologies of the metastases included primary lung (n=5), breast (n=4), colon
(n=1), and kidney (n=1). There were no acute or subacute complications. All tumors showed response on a one-month post-radiotherapy scan. Median follow-up was four months. Four of the 11 patients died of systemic disease 6-9 months after radiotherapy. The remaining patients were alive with no evidence of progression of the treated brain disease or local recurrence at 2-9 months after radiotherapy. No brain complications occurred to date.

**Prostate Cancer**

In 2012, Bauman and colleagues published a systematic review that examined the evidence for IMRT in the treatment of prostate cancer in order to quantify its potential benefits and to make recommendations for radiation treatment programs considering adopting this technique within the province of Ontario, Canada. Based on a review of 11 published reports through March 2009 (nine retrospective cohort studies and two randomized clinical trials [RCTs]) including 4,559 patients, the authors put forth the recommendation for IMRT over 3D-CRT for aggressive treatment of localized prostate cancer where an escalated radiation (>70 Gy) dose is required. There were insufficient data to recommend IMRT over 3D-CRT in the postoperative setting.

Nine of 11 studies reviewed by Bauman and colleagues reported on adverse effects. Six of nine studies reported on acute gastrointestinal (GI) effects. Four studies (three retrospective cohort studies and one RCT) reported differences in adverse effects between IMRT and 3D-CRT. The RCT included a total of 78 patients and reported that acute GI toxicity was significantly less frequent in the IMRT group compared to 3D-CRT. This was true for Grade 2 or higher toxicities (20% vs. 61%, p=0.001), Grade 3 or higher toxicity (0 vs. 13%, p=0.001) and for acute proctitis (15% vs. 38%, p=0.03). In contrast, the second RCT included in this systematic review reported that there were no differences in toxicity between IMRT and 3D-CRT.

Six of nine studies reported on acute genitourinary (GU) effects. One study, which was a retrospective cohort study including 1,571 patients, reported a difference in overall acute GU effects in favor of 3D-CRT (37% IMRT vs. 22% 3D-CRT, p=0.001). For late GI toxicity, four of nine studies, all retrospective cohort studies with a total of 3,333 patients, reported differences between IMRT and 3D-CRT. One RCT reported on late GI toxicity and did not find any differences between IMRT and 3D-CRT. Five of nine studies reported on late GU effects, and only one reported a difference in late GU effects in favor of 3D-CRT (20% vs. 12%, p=0.01). Two retrospective cohort studies reported mixed findings on quality-of-life outcomes. A subsequent economic analysis (based on this systematic review data) demonstrated that for radical radiation treatment (>70 Gy) of prostate cancer, IMRT seems to be cost-effective when compared with an equivalent dose of 3D-CRT from the perspective of the Canadian health care system for 2009.

In 2008, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review comparing the relative effectiveness and safety of various treatment options for clinically localized prostate cancer. Studies on IMRT were included in the assessment under the category of EBRT. Based on review of RCTs and nonrandomized studies published from 2000 to September 2007, there was no direct evidence (i.e., from RCTs) that IMRT resulted in better survival or disease-free survival than other therapies for localized prostate cancer. Based on case-series data, the absolute risks of clinical and biochemical outcomes (including tumor recurrence), toxicity, and quality of life after IMRT were comparable with conformal radiation. For IMRT, the percent of patients with Grade 1 and 2 acute GI toxicity was 22% and 4%.
respectively; the percent of patients with rectal bleeding was 1.6-10%; and the percent of patients with Grade 2 GU toxicity was 28-31%. This review concluded that there was low-level evidence that IMRT provides at least as good a radiation dose to the prostate with less radiation to the surrounding tissues compared with conformal radiation therapy.

In 2010, an update of the 2008 AHRQ systematic review was undertaken by the AHRQ Technology Assessment Program. As with the 2008 review, this review concluded that the available data were insufficient to compare the effectiveness of the various forms of radiation treatments. Studies on IMRT were included in the assessment under the category of external-beam radiation therapy (EBRT) and thus reported data were not specific to IMRT. While higher EBRT dosages may result in longer-term biochemical control than lower EBRT dosages, overall and disease-specific survival data were inconclusive. Additionally, GU and GI toxicities experienced with EBRT did not seem to differ when standard fractionation was compared to moderate hypofractionation. The authors noted the need for further studies to evaluate outcomes of IMRT for the treatment of prostate cancer. In addition, a subsequent report undertaken by the AHRQ Comparative Effectiveness Review Surveillance Program using the search strategy employed for the 2008 systematic review found no new data on IMRT following a limited literature search of the MEDLINE database through March 2012.

Similar findings were observed in a systematic review of the clinical effectiveness of IMRT for the radical treatment of prostate cancer undertaken by the U.K. Health Technology Assessment Programme in 2010. The authors also performed an economic analysis which demonstrated IMRT to be cost-effective from the perspective of the U.K. National Health Service for 2008/09 if this treatment modality can be used to prolong survival.

An earlier review by the Institute for Clinical and Economic Review reached the following conclusions in 2007:

“The literature on comparative rates of toxicity has serious methodological weaknesses. There are no prospective randomized trials or cohort trials, and the case series that exist are hampered by the lack of contemporaneous cohorts and/or by a failure to describe the selection process by which patients were assigned to IMRT vs. 3D-CRT. Published case series demonstrate consistent findings of a reduced rate of GI toxicity for IMRT at radiation doses from approximately 75–80 Gy [grays]. Data on GU [genitourinary] toxicity have not shown superiority of IMRT over 3D-CRT, nor do the existing data suggest that IMRT provided a lower risk of erectile dysfunction.”

“The literature suggests that the risk of Grade 2 GI toxicity is approximately 14% with 3D-CRT and 4% with IMRT. Thus, the number of patients needed to treat to prevent one case of moderate-severe proctitis is ten, and for every 100 patients treated with IMRT instead of 3D-CRT, ten cases of GI toxicity would be expected to be prevented.”

**Primary studies reporting on outcomes and adverse effects**

While the use of IMRT for prostate cancer has increased significantly, only a few institutions have reported long-term data on biochemical control rates and toxicity. Vora and colleagues reported on nine-year tumor control and chronic toxicities observed in 302 patients treated with IMRT for clinically localized prostate cancer at one institution. The median dose delivered was 76 Gy (range 70-77 Gy), and 35% of patients received androgen deprivation therapy. Local and distant recurrence rates were 5% and 8.6%, respectively. At nine years, biochemical control
rates were close to 77% for low-risk, 70% for intermediate-risk, and 53% for high-risk patients (log rank p=0.05). At last follow-up, only 0%/0.7% had persistent Grade ≥3 GI/GU toxicity. The high-risk group was associated with a higher distant metastasis rate (p=0.02) and death from prostate cancer (p=0.001).

Alicikus and colleagues reported on ten-year outcomes in 170 patients treated after high-dose IMRT (81 Gy). The ten-year actuarial prostate-specific antigen (PSA) relapse-free survival rates were 81% for the low-risk group, 78% for the intermediate-risk group, and 62% for the high-risk group. The ten-year distant metastases–free rates were 100%, 94%, and 90%, respectively, and cause-specific mortality rates were 0%, 3%, and 14%, respectively. The ten-year likelihood of developing Grade 2 and 3 late genitourinary toxicity was 11% and 5%, respectively, and the likelihood of developing Grade 2 and 3 late gastrointestinal toxicity was 2% and 1%, respectively. No Grade 4 toxicities were observed. These findings indicate that IMRT is associated with good long-term tumor-control and low rates of serious toxicity in patients with localized prostate cancer.

In 2008, Zelefsky and colleagues reported on the incidence and predictors of treatment-related toxicity at 10 years after 3D-CRT and IMRT for localized prostate cancer. Between 1988 and 2000, 1,571 patients with stages T1-T3 prostate cancer were treated with 3D-CRT or IMRT, with doses ranging from 66 to 81 Gy. Twenty-two percent were considered to be at low risk, as based on National Comprehensive Cancer Network (NCCN) guidelines. The median follow-up was ten years. The actuarial likelihood at ten years for the development of Grade 2 or higher GI toxicities was 9%. The use of IMRT significantly reduced the risk of GI toxicities compared with patients treated with conventional 3D-CRT (13% to 5%; p<0.001). Among patients who experienced acute symptoms, the ten-year incidence of late toxicity was 42%, compared with 9% for those who did not experience acute symptoms. The ten-year incidence of late Grade 2 or higher GU [genitourinary] toxicity was 15%. Patients treated with 81 Gy (IMRT) had a 20% incidence of GU symptoms at ten years, compared with 12% for patients treated with lower doses (p=0.01). Among patients who had developed acute symptoms during treatment, the incidence of late toxicity at ten years was 35%, compared with 12%. The incidence of Grade 3 GI and GU toxicities was 1% and 3%, respectively. The authors concluded that serious late toxicity was unusual despite the delivery of high radiation dose levels in these patients. They also noted that higher doses were associated with increased GI and GU Grade 2 toxicities, but the risk of proctitis was significantly reduced with IMRT.

Cahlon and colleagues reported on preliminary biochemical outcomes and toxicity with high-dose IMRT to a dose of 86.4 Gy for localized prostate cancer. For this study, 478 patients were treated between August 1997 and March 2004 with 86.4 Gy using a 5- to 7-field IMRT technique. The median follow-up was 53 months. Thirty-seven patients (8%) experienced acute Grade 2 GI toxicity; none had acute Grade 3 or 4 GI toxicity; 105 patients (22%) experienced acute Grade 2 GU toxicity; and three patients (0.6%) had Grade 3 GU toxicity. Sixteen patients (3%) developed late Grade 2 GI toxicity; two patients (<1%) developed late Grade 3 GI toxicity; 60 patients (13%) had late Grade 2 GU toxicity; and 12 (<3%) experienced late Grade 3 GU toxicity. The five-year actuarial PSA [prostate-specific antigen] relapse-free survival, according to the nadir plus 2 ng/mL definition, was 98%, 85%, and 70% for the low-, intermediate-, and high-risk NCCN prognostic groups. The authors concluded that treatment with ultra-high radiation dose levels of 86.4 Gy using IMRT for localized prostate cancer is
well-tolerated., and the early excellent biochemical control rates are encouraging. These results based on a case series should be considered as preliminary.

In 2009, Wong and colleagues reported on a retrospective study of radiation dose escalation in 853 patients with localized (T1c-T3N0M0) prostate cancer. Radiation therapies used included conventional dose (71 Gy) 3D-CRT (n=270), high-dose (75.6 Gy) IMRT (n=314), permanent transperineal brachytherapy (n=225), and external-beam radiotherapy (EBRT) plus brachytherapy boost (n=44). All patients were followed for a median of 58 months (range, 3 to 121 months). The authors reported:

“The 5-year overall survival for the entire group was 97%. The 5-year [biochemical control] bNED rates, local control rates, and distant control rates were 74%, 93%, and 96%, respectively, for 3D-CRT; 87%, 99%, and 97%, respectively, for IMRT; 94%, 100%, and 99%, respectively, for BRT alone; and 94%, 100%, and 97%, respectively, for EBRT + BRT. The bNED rates for 3D-CRT were significantly less than those of the other higher dose modalities (P<.0001).”

Intermediate- and high-risk prostate cancer patients in this study had significantly improved 5-year bNED rates with dose escalation. However, in low-risk prostate cancer patients, bNED rates with dose escalation were not improved compared to conventional dose 3D-CRT. The authors also found acute and late Grade-2 and -3 GU toxicities were fewer with IMRT than brachytherapy or EBRT plus brachytherapy.

**Head and Neck Cancers**

**Systematic Reviews**

This review identified 20 studies (one randomized controlled trial [RCT] and 19 case series) for IMRT in treatment of head and neck cancers. However, the RCT was for 2-dimensional (2D) RT compared to IMRT. Four studies (including the RCT) were for treatment of nasopharyngeal carcinoma, three for sinonasal cancer, and 13 were for cancer involving the oropharynx, hypopharynx, larynx, and oral cavity. The majority of the studies reviewed showed a decrease in xerostomia with use of IMRT. However, there was variability in measurement, e.g., flow rate versus symptoms. The case series of sinonasal cancers showed less ocular toxicity (e.g., blindness) after use of IMRT. The authors of this review recognize the limitations and biases of the studies used in their analysis. With this limitation, they support the finding of decreased xerostomia (as well as improved salivary gland function) with use of IMRT in head and neck cancers involving the oral cavity, larynx, oropharynx, and hypopharyngeal area.

A comparative effectiveness review was published in 2010 on radiotherapy treatment for head and neck cancers by Samson and colleagues from BCBSA’s Technology Evaluation Center under contract with the Agency for Healthcare Research and Quality (AHRQ). This report noted that based on moderate evidence, IMRT reduces late xerostomia and improves quality-of-life domains related to xerostomia compared with 3D-CRT. The report also noted that no conclusions on tumor control or survival could be drawn from the evidence comparing IMRT to 3D-CRT.

In 2011, Tribius and Bergelt reviewed 14 studies that compared the quality-of-life outcomes of head and neck cancer treatment with IMRT versus 2D-RT or 3D-CRT. The most commonly used quality-of-life questionnaire was the European Organization for Research and Treatment
Quality-of-Life Questionnaire (EORTC QLQ-C30) which was sometimes paired with the head and neck cancer module H&N35. Statistically significant improvements were observed with IMRT over 2D-RT and 3-dimensional conformal radiation (3D-CRT) in xerostomia, dry mouth, sticky saliva, and eating-related functions. However, the authors noted the study populations were heterogeneous and quality-of-life assessment tools varied. Therefore, further prospective randomized studies were recommended. Other evidence reviews, in 2010, came to similar conclusions in that treatment with IMRT resulted in reductions in acute and/or late xerostomia than other radiotherapies for head and neck cancer.

**Randomized controlled trials**

An RCT by Pow and colleagues on IMRT for nasopharyngeal carcinoma was published in 2006. However, as noted above, this RCT compared IMRT to conventional, 2-dimensional (2D) RT. In 2011, Nutting and colleagues reported on the PARSPORT randomized Phase III trial, which also compared conventional RT to parotid-sparing IMRT in 94 patients with T1-4, N0-3, M0 pharyngeal squamous-cell carcinoma. One year after treatment, Grade 2 or worse xerostomia was reported in 38% of patients in the IMRT group, which was significantly lower than the reported 74% in the conventional RT group. Xerostomia continued to be significantly less prevalent two years after treatment in the IMRT group (29% vs. 83%, respectively). At 24 months, rates of locoregional control, non-xerostomia late toxicities, and overall survival were not significantly different.

**Non-randomized comparative studies**

In 2009, Vergeer et al published a report that compared IMRT and 3D-CRT for patient-rated acute and late xerostomia, and health-related quality of life (HRQoL) among patients with head and neck squamous cell carcinoma (HNSCC). The study included 241 patients with HNSCC (cancers arising from the oral cavity, oropharynx, hypopharynx, nasopharynx, or larynx and those with neck node metastases from squamous cell cancer of unknown primary) treated with bilateral irradiation with or without chemotherapy. All patients were included in a program that prospectively assessed acute and late morbidity and HRQoL at regular intervals. Before October 2004, all patients were treated with 3D-CRT (n=150); starting in October 2004, 91 patients received IMRT. The use of IMRT resulted in a significant reduction of the mean dose to the parotid glands (27 Gy vs. 43 Gy; p<0.001). During radiation, Grade 3 or higher xerostomia at six weeks was significantly less with IMRT (approximately 20%) than with 3D-CRT (approximately 45%). At six months, the prevalence of Grade 2 or higher xerostomia was significantly lower after IMRT (32%) versus 3D-CRT (56%). Treatment with IMRT also had a positive effect on several general and head and neck cancer-specific HRQoL dimensions. The authors concluded that IMRT results in a significant reduction of xerostomia, as well as other head and neck symptoms, compared with standard 3D-CRT in patients with HNSCC.

de Arruda and colleagues reported on their experience treating 50 patients with oropharyngeal cancer (78% stage IV) with IMRT between 1998 and 2004. Eighty-six percent also received chemotherapy. This study found two-year progression-free survival of 98% and regional progression-free survival of 88%, results similar to the 85% to 90% rates for locoregional control reported in other published studies. The rate for Grade 2 xerostomia was 60% for acute and 33% for chronic (after nine months or more of follow-up); these rates are lower than the 60% to 75% generally reported with RT.
Hoppe et al reported on experience treating 37 patients with cancer of the paranasal sinuses, nasal cavity, and lacrimal glands with postoperative IMRT between 2000 and 2007. (10) In this report with 28-month median follow-up, there was no early or late Grade 3 or 4 radiation–induced ophthalmologic toxicity. Two-year local progression-free survival was 75%, and overall survival (OS) was 80%.

Braam et al reported on a Phase II study that compared IMRT to conventional RT in oropharyngeal cancer. This study appeared to use 2D RT. The mean dose to the parotid glands was 48 Gy for RT and 34 Gy for IMRT. Both stimulated parotid flow rate, and parotid complications (more than 25% decrease in flow rate) were greater in the RT group. At six months after treatment, 56% of IMRT patients and 81% of RT patients were found to have parotid complications.

Rusthoven and colleagues compared outcomes with use of IMRT and 3D-CRT in patients with oropharyngeal cancer. In this study, in which 32 patients were treated with IMRT and 23 with 3D-CRT, late xerostomia occurred in 15% of the IMRT patients and 94% of the 3D-CRT patients. There was also a trend toward improved locoregional control of the tumor with IMRT.

Rades et al reported on 148 patients with oropharyngeal cancer treated with RT. In this study, late xerostomia was noted in 17% of those treated with IMRT compared with 73% of those who received 3D-CRT and 63% of those who received standard radiation therapy.

Thyroid Cancer
Studies on use of IMRT for thyroid cancers are few. In thyroid cancer, radiation therapy is generally used for two indications. The first indication is treatment of anaplastic thyroid cancer, and the second indication is potential use for locoregional control in patients with incompletely resected high-risk or recurrent differentiated (papillary, follicular, or mixed papillary-follicular) thyroid cancer. Anaplastic thyroid cancer occurs in a minority (less than 5%) of thyroid cancer. The largest series comparing IMRT to 3D-CRT was published by Bhatia and colleagues.

Rades et al reported on 148 patients with oropharyngeal cancer treated with RT. In this study, late xerostomia was noted in 17% of those treated with IMRT compared with 73% of those who received 3D-CRT and 63% of those who received standard radiation therapy.
patients with localized disease who tolerate full-dose irradiation can potentially enjoy prolonged survival. Schwartz and colleagues reviewed institutional outcomes for patients treated for differentiated thyroid cancer with postoperative conformal external beam radiotherapy.

This was a single-institution retrospective review of 131 consecutive patients with differentiated thyroid cancer who underwent RT between January 1996 and December 2005. Histologic diagnoses included 104 papillary, 21 follicular, and six mixed papillary-follicular types. Thirty-four patients (26%) had high-risk histologic types and 76 (58%) had recurrent disease. Extraglandular disease spread was seen in 126 patients (96%), microscopically positive surgical margins were seen in 62 patients (47%), and gross residual disease was seen in 15 patients (11%). Median RT dose was 60 Gy (range, 38-72 Gy). Fifty-seven patients (44%) were treated with IMRT to a median dose of 60 Gy (range, 56-66 Gy). Median follow-up was 38 months (range, 0-134 months). Kaplan-Meier estimates of locoregional relapse-free survival, disease-specific survival, and OS at four years were 79%, 76%, and 73%, respectively. On multivariate analysis, high-risk histologic features, M1 (metastatic) disease, and gross residual disease were predictors for inferior disease-specific and OS. IMRT did not impact survival outcomes but was associated with less frequent severe late morbidity (12% vs. 2%, respectively), primarily esophageal stricture. The authors concluded that conformal external beam radiotherapy provides durable locoregional disease control for patients with high-risk differentiated thyroid cancer if disease is reduced to microscopic burden and that IMRT may reduce chronic radiation morbidity, but additional study is required.

Abdominal, Gastrointestinal, and Pelvic Cancer (excluding Prostate Cancer)

Literature searches have identified no studies that directly compare health outcomes with IMRT versus those in patients treated concurrently with any other type of radiotherapy for tumors of the thorax (e.g., esophagus), upper abdomen (e.g., stomach, pancreas, bile duct, liver), or pelvis (e.g., rectal, anal, gynecologic). Case series and single-arm studies of IMRT have been identified, including some with historical controls treated with non-IMRT methods.

Gastrointestinal Tract

**Stomach**

As outlined in a recent review article, IMRT has been investigated for treatment of gastric cancer in several studies, but only one reported clinical outcomes. In a small (n=7) case series, patients with stage III gastric cancer received postoperative chemoradiotherapy with 5-fluorouracil (5FU) and leucovorin and IMRT delivered to a dose of 50.4 Gy in 1.8 Gy fractions. Chemoradiotherapy with IMRT was well-tolerated, with no acute gastrointestinal (GI) tract toxicities (nausea, diarrhea, and esophagitis) greater than Grade 2.

The efficacy and safety of two different adjuvant chemoradiotherapy regimens using 3-dimensional conformal radiation (3D-CRT) (n=27) or IMRT (n=33) were evaluated in two consecutive cohorts of patients who underwent primarily D2 resection for gastric cancer. The cohorts in this study were generally well-matched, with American Joint Committee on Cancer (AJCC) advanced stage (II-IV) disease. The majority (n=26, 96%) of those who received 3D-CRT were treated with 5-fluorouracil plus folinic acid (5FU/FA); the other patient received oxaliplatin plus capecitabine (XELOX). In the 3D-CRT cohort, 13 (50%) patients completed the 5FU/FA regimen, 13 halted early because of acute toxicity or progression and received a median 60% of planned cycles. Patients in the IMRT cohort received XELOX (n=23, 70%) or
5FU/FA (n=10, 30%). Five of ten (50%) patients completed all planned 5FU/FA cycles; the other five received only a median 60% of cycles because of acute toxicity. Thirteen (56%) treated with XELOX completed all planned cycles; the other ten received a median of 70% planned cycles because of toxicity. Radiation was delivered to a total prescribed dose of 45 Gy/1.8 Gy/fraction in 21 (81%) of the 3D-CRT cohort patients; five received less than 45 Gy because of intolerance to treatment. Thirty (91%) patients in the IMRT cohort received the planned 45 Gy dosage; two (6%) were unable to tolerate the full course, and one case planned for 50.4 Gy was halted at 47 Gy. The median overall survival (OS) was 18 months in the 3D-CRT cohort, and more than 70 months in the IMRT cohort (p=0.0492). The actuarial two-year OS rates were 67% in the IMRT cohort and 37% in the 3D-CRT group (p not reported). Acute renal toxicity based on creatinine levels was generally lower in the IMRT cohort compared to the 3D-CRT group, with a significant difference observed at six weeks (p=0.0210). In the 3D-CRT group, LENT-SOMA Grade 2 renal toxicity was observed in two patients (8%) whereas no Grade 2 toxicity was reported in the IMRT group.

**Hepatobiliary**

In a retrospective series with a historical control cohort, clinical results achieved with image-guided IMRT (n=24) were compared to results with CRT (n=24) in patients with primary adenocarcinoma of the biliary tract. The majority of patients underwent postsurgical chemoradiotherapy with concurrent fluoropyrimidine-based regimens. IMRT treatment plans prescribed 46 to 56 Gy to the planning target volume (PTV) that includes the tumor and involved lymph nodes, in daily fractions of 1.8–2 Gy. CRT involved 3-D planning that delivered 46–50 Gy in 1.8–2 Gy daily fractions. Both groups received boost doses of 4–18 Gy as needed. The median estimated overall survival (OS) for all patients who completed treatment was 13.9 months (range: 9.0–17.6); the IMRT cohort had median OS of 17.6 months (range: 10.3–32.3), while the CRT cohort had a median OS of 9.0 months (range: 6.6–17.3). Acute GI toxicities were mild to moderate, with no significant differences between patient cohorts. These results suggest that moderate dose escalation via conformal radiotherapy is technically and clinically feasible for treatment of biliary tract adenocarcinoma. However, while this series represents the largest group of patients with this disease treated with IMRT, generalization of its results is limited by the small numbers of patients, use of retrospective chart-review data, nonrepresentative case spectrum (mostly advanced/metastatic disease), and comparison to a non-concurrent control radiotherapy cohort.

Two single arm studies reported outcomes with IMRT in patients with hepatobiliary cancers. The first study involved 42 patients with advanced (33% AJCC stage IIIIC, 67% stage IV) hepatocellular carcinoma (HCC) with multiple extrahepatic metastases. Among the 42 cases, 33 (79%) had intrahepatic HCC with extrahepatic metastases, nine (21%) had only extrahepatic lesions. The extrahepatic locations of HCC metastatic lesions included lung (n=19), lymph node and adrenal (n=20), other soft tissues (n=6), and bone (n=5). Helical tomotherapy was performed simultaneously for all lesions in each patient, with a total radiation dose of 50 and 40 Gy to 95% of the gross tumor volume (GTV) and PTV in ten fractions divided over two weeks. All received capecitabine during the course of IMRT as a radiosensitizer. After completion of tomotherapy, additional transarterial or systemic chemotherapy was administered to patients eligible for it according to tumor location. Among 31 patients who underwent hepatic IMRT, a mean of three courses (range: 1-6) transarterial chemolipiodolization was performed in 23. Among nine patients with extrahepatic lesions only, three received an additional three to seven
cycles of systemic chemotherapy consisting of epirubicin, cisplatin, and 5FU. Median follow-up was 9.4 months (range: 1.9–25.3 months). Tumor response was reported separately for each organ treated with IMRT. The overall objective tumor response rate was 45% for intrahepatic HCC, 68% for pulmonary lesions, 60% for lymph node and adrenal cases, and 67% for soft tissue metastases. Three cases of local tumor progression occurred within the target radiation area, including two intrahepatic HCC and one abdominal lymph node metastasis. Median OS was 12.3 months, with 15% OS at 24 months. The most common acute adverse events were mild anorexia and constitutional symptoms that occurred one to two weeks after start of IMRT, regressed spontaneously or subsided with symptomatic care, and did not interfere with the scheduled delivery of IMRT. However, it is not possible to discern the impact of IMRT on adverse events because almost all occurred in patients who received chemotherapy following IMRT. However, most patients were reported to have tolerated therapy well, with no treatment-related mortality.

A second retrospective single-arm study involved 20 patients with primary, unresectable HCC who were treated with IMRT and concurrent capecitabine. Patients had AJCC Grade T1 (n = 7) and T3 (n = 13) HCC. IMRT was prescribed to a minimum tumor dose of 50 Gy in 20 fractions over four weeks, with the optimization goal of delivering the prescription dose to 95% of the PTV. Capecitabine was administered as radiosensitizer on the days of IMRT delivery. Eleven (55%) patients underwent at least one transarterial chemoembolization (range: 1-3 procedures) before radiotherapy planning. Eighteen of 20 (90%) patients completed the full course of IMRT, two died before follow-up imaging was obtained. The mean survival of 18 patients who completed IMRT was 9.6 months after its conclusion. Disease progression occurred in-field in three patients, two failed elsewhere in the liver. Four patients (25%) required hospitalization during therapy, due to encephalopathy (n=1), gastric ulcer (n=1), acute hepatitis (n=1), and sepsis (n=1). Four required a break from chemotherapy because of peripheral neuropathy (n=2), acute hepatitis (n=1), and sepsis (n=1). Grade 1 acute abdominal pain was observed in 15%, 30% reported Grade 1 nausea, 5% experienced Grade 2 nausea. No acute or late toxicity greater than Grade 2 was reported.

Esophageal
NCCN guidelines (2.2012) on Esophageal and Esophagogastric Junction Cancers state that IMRT may be appropriate to reduce dose to normal structures such as heart and lungs. In designing IMRT plans, for structures such as the lungs, attention should be given to the lung volume receiving low to moderate doses, as well as the volume receiving high doses. Retrospective planning studies comparing three dimensional (3D) conformal versus IMRT treatment plans for esophagus cancer have generally shown superior dos conformity and homogeneity with IMRT and reduction of radiation dose to the lungs and heart.

Pancreatic
Three reports of case series provide clinical results with IMRT for pancreatic carcinoma. The largest series involved a retrospective analysis of 41 patients who received image-guided IMRT alone, postsurgically (41%), or with a number of concurrent primarily fluoropyrimidine-based chemotherapy regimens (88%). The prescribed radiation dose to the PTV ranged from 41.4–60.4 Gy in daily fractions of 1.8–2 Gy. For all patients diagnosed with adenocarcinoma (85%), one- and two-year actuarial OS were 38% and 25%, respectively; median OS in resected patients was 10.8 months (range: 6.2–55.1), as compared to 10.0 months (range: 3.4–28.0) in inoperable cases. Four patients (9.7%) were unable to complete radiotherapy as prescribed. Any
upper GI acute toxicity (none Grade 4) was reported in 29 (70%) patients, most commonly nausea, vomiting, and abdominal pain; any lower GI acute toxicity (less than 5% Grade 4) was reported in 17 (42%) cases, primarily diarrhea.

In a second series of 25 patients with pancreatic and bile duct cancers (68% unresectable), 24 were treated with IMRT and concurrent 5FU, one refused chemotherapy. Resected patients received 45–50.4 Gy to the PTV, whereas unresectable patients received 50.4–59.4 Gy. For all cancers, the median OS was 13.4 months, with one and two year OS of 55% and 22%, respectively. One and two year median OS were 83% and 50%, respectively, among resected cases, and 40% and 8%, respectively, among unresected cases. IMRT was well-tolerated, with Grade 2 or less acute upper GI toxicity in 80% of patients; Grade 4 late liver toxicity was reported in one patient who survived more than five years.

A third retrospective series included 15 patients with pancreatic adenocarcinoma (seven resected, eight unresectable) who underwent IMRT plus concurrent capecitabine. Resected cases received 45–54 Gy to the gross tumor volume, unresected cases received 54–55 Gy to the gross tumor volume; all cases received 45 Gy to the draining lymph node basin. At a median follow-up of 8.5 months, no deaths were reported among the resected patients, compared to two deaths in the unresected cases, yielding a one-year OS rate of 69% among the latter. No Grade 4 toxicities were reported, with the vast majority of acute toxicities reported at Grade 1 (nausea, vomiting, diarrhea, neutropenia, and anemia).

Gynecologic
A series of reports from a single institution provided data on clinical outcomes achieved with IMRT in women with gynecologic malignancies. Patients from an initial series were included in a subsequent report that comprised 40 patients who underwent IMRT to treat cancers of the cervix, endometrium, and other sites (three patients). Patients in this series underwent postsurgical IMRT (70%), with (58%) or without (42%) cisplatin chemotherapy, with a majority (60%) also undergoing postradiotherapy intracavitary brachytherapy (ICB). IMRT was prescribed to the PTV at a dose of 45 Gy, delivered in 1.8 Gy daily fractions; ICB delivered an additional 30–40 Gy to cervical cancer patients and 20–25 Gy to those with endometrial cancer. A well-matched non-concurrent cohort of patients who underwent 4-field CRT (45 Gy to the PTV, 1.8 Gy daily fractions) using 3D planning and received cisplatin chemotherapy was used to compare acute GI and genitourinary (GU) toxicities between radiotherapy modalities. No Grade 3 acute GI or GU toxicities were reported in IMRT or CRT recipients. Grade 2 GI toxicity was noted in 60% of the IMRT cohort versus 91% of the CRT group (p=0.002). No significant differences were noted in the incidence of Grade 2 GU toxicity in IMRT recipients (10%) compared to the CRT cohort (20%). Three other reports from the same group provide data on acute hematologic toxicity, chronic GI toxicities, and acute GI toxicities among patients who underwent IMRT with or without chemotherapy. It is unclear whether or not the patients in these reports are those from the initial studies or are new patients.

A small case series involved ten patients who underwent IMRT with intracavitary brachytherapy boost for locally advanced (FIGO stage IIB and IIIB) cervical cancer. During radiotherapy, all patients received cisplatin. Whole pelvic IMRT was administered to a dose of 50.4 Gy in 28 fractions, and intracavitary brachytherapy (ICB) was delivered to a dose of 30 Gy in six fractions. The mean OS was 25 months (range: 3-27 months), with actuarial OS of 67%.
Acute toxicities included one patient with Grade 3 diarrhea, one with Grade 3 thrombocytopenia, and three with Grade 3 leukopenia. One case of subacute Grade 3 thrombocytopenia was noted. These data are insufficient to draw conclusions about the efficacy or safety of IMRT in cervical cancer.

Two subsequent studies examined the use of post-hysterectomy radiotherapy in women with high-risk cervical cancer. In the first study, 68 patients were treated with adjuvant pelvic radiotherapy, high dose-rate ICB, and concurrent chemotherapy. The initial 35 cases received 4-field box CRT delivered to the whole pelvis; a subsequent 33 patients underwent IMRT. All patients received 50.4 Gy of radiation in 28 fractions and 6 Gy of high dose-rate vaginal cuff ICB in three insertions; cisplatin was administered concurrently to all patients. All patients completed the planned course of treatment. At median follow-up of 34.6 months (range: 12–52) in CRT recipients and 14 months (range: 6–25) in IMRT recipients, the one-year locoregional control rate was 94% for CRT and 93% for IMRT. Grades 1 to 2 acute GI toxicities were noted in 36% and 80% of IMRT and CRT recipients, respectively (p=0.00012), while acute Grade 1 to 2 GU toxicities occurred in 30% versus 60%, respectively (p=0.022). There was no significant difference between IMRT and CRT in the incidence of acute hematologic toxicities. Overall, the IMRT patients had lower rates of chronic GI (p=0.002) toxicities than the CRT patients.

A subsequent report from the same group included the initial 33 patients in that experience with an additional 21 cases. At a median follow-up of 20 months, this study showed a three-year disease-free survival rate of 78% and an OS rate of 98% in IMRT recipients.

**Anorectal**

A single-institution series included 17 patients with stage I/II cancer who underwent IMRT alone (n=3) or concurrent with 5FU alone (n=1) or 5FU with mitomycin C (MMC, n=13). Patients generally received 45 Gy to the PTV at 1.8 Gy per fraction, followed by a 9 Gy boost to the gross tumor volume. Thirteen of 17 (76%) patients completed treatment as planned. None experienced acute or late Grade 3 or above nonhematologic (GI or GU) toxicity. Grade 4 acute hematologic toxicity (leukopenia, neutropenia, and thrombocytopenia) was reported in 5 of 13 (38%) patients who received concurrent chemoradiotherapy. At a median follow-up of 20.3 months, the two-year OS rate was 91%.

A multicenter series included a cohort of 53 consecutive patients who received concurrent chemotherapy and IMRT. Forty-eight (91%) received 5FU plus MMC; the rest received other regimens not including MMC. Radiation was delivered at 45 Gy to the PTV. Thirty-one (58%) patients completed therapy as planned, with breaks in the others because of Grade 4 hematologic toxicities (40% of patients), painful moist desquamation, or severe GI toxicities. At the 18-month follow-up, the local tumor control rate was 83.9% (range: 69.9–91.6%), with an OS rate of 93.4% (range: 80.6–97.8%). Univariate analyses did not reveal any factors significantly associated with tumor control or survival rates, whereas a multivariate analysis showed patients with stage IIIB disease experienced a significantly lower colostomy-free survival (hazard ratio 4.18; 95% CI: 1.062–16.417; p=0.041).

A gastrointestinal toxicity study was reported in 45 patients who received concurrent chemotherapy and IMRT for anal cancer. Chemoradiotherapy is becoming the standard treatment for anal cancer, in part due to preservation of sphincter function. Patients had T1
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Medical Policy #088

(n=1), T2 (n=24), T3 (n=16), and T4 (n=2) tumors; N stages included Nx (n=1), N0 (n=31), N1 (n=8), N2 (n=3), and N3 (n=2). Concurrent chemotherapy primarily comprised 5-FU plus mitomycin C (MMC). IMRT was administered to a dose of 45 Gy in 1.8 Gy fractions, with areas of gross disease subsequently boosted with 9–14.4 Gy. Acute genitourinary toxicity was Grade 0 in 25 (56%) cases, Grade 1 in 10 (22%) patients, Grade 2 in five (11%) patients, with no Grade 3 or 4 toxicities reported; five (11%) patients had no genitourinary tract toxicities reported. Grades 3-4 leukopenia was reported in 26 (56%) cases, neutropenia in 14 (31%), and anemia in four (9%). Acute GI toxicity included Grade 0 in 2 (4%) patients, Grade 1 in 11 (24%), Grade 2A in 25 (56%), Grade 2B in 4 (9%), Grade 3 in three (7%) and no Grade 4 toxicities. Univariate analysis of data from these patients suggests a statistical correlation between the volume of bowel that received 30 Gy or more of radiation and the risk for clinically significant (Grade 2 or higher) GI toxicities.

A retrospective analysis of toxicity and disease outcomes associated with IMRT was performed in 47 patients with anal cancer. Thirty-one patients had squamous cell carcinoma (SCC). Patients had AJCC Stage I (n=6, 13%), Stage II (n=16, 36%), Stage III (n=14, 31%), Stage IV (n=6, 13%), or recurrent disease (n=3, 7%). IMRT was prescribed to a dose of at least 54 Gy to areas of gross disease at 1.8 Gy per fraction. Forty patients (89%) received concurrent chemotherapy with a variety of agents including MMC, 5FU, capecitabine, oxaliplatin, etoposide, vincristine, doxorubicin, cyclophosphamide, and ifosfamide in various combinations. The two-year actuarial OS for all patients was 85%. Eight patients (18%) required treatment breaks. Toxicities included Grade 4 leukopenia (7%) and thrombocytopenia (2%); Grade 3 leukopenia (18%) and anemia (4%); and, Grade 2 skin (93%). These rates were much lower than previous trials of chemoradiation, where Grade 3 to 4 skin toxicity was noted in about 50% of patients and Grade 3 to 4 GI toxicity noted in about 35%. In addition, the rate of treatment breaks was lower than in many studies; and some studies of chemoradiation include a break from radiation therapy. Some investigators believe that treatment breaks reduce the efficacy of this combined approach.

A small (n=6) case series of IMRT and concurrent infusional 5FU plus cisplatin was reported in patients with anal cancer and para-aortic nodal involvement. IMRT was delivered to a median dose of 57.5 Gy to the CTV, with nodal areas of involvement treated to a median dose of 55 Gy. Five of six completed the entire prescribed course of IMRT. The three-year actuarial OS rate was 63%. Four patients developed Grade 3 acute toxicities that included nausea and vomiting, diarrhea, dehydration, small bowel obstruction, neutropenia, anemia, and leukopenia. Five of six had Grade 2 skin toxicity.

**Other Indications**

*Soft tissue sarcoma of the extremities*

NCCN Guidelines for soft tissue sarcoma (STS) indicate that advanced techniques such as IMRT have led to the improvement of treatment outcomes in patients with STS. The main advantage of IMRT is its ability to more closely contour the high dose radiation volume thereby minimizing the volume of high dose radiation to the surrounding normal tissues.

Postoperative IMRT following limb-sparing surgery is associated with excellent local control in selected patients with high risk features. In a retrospective analysis, the five-year local control
rate was 94% in patients with negative as well as positive or close margins. The risk of complications such as edema and joint stiffness were also favorable when compared with conventional radiation therapy. In a nonrandomized comparison of local control by IMRT versus brachytherapy in patients with high-grade primary nonmetastatic STS of extremity, local control was significantly better with IMRT than brachytherapy (five-year local control rates were 92% and 81% respectively; p=0.04) despite higher rates of adverse features for IMRT.

Previous Treatment with Radiation
There are several situations when patients may require a repeat course of radiation to a previously irradiated field. The enhanced precision of IMRT may be beneficial in these circumstances, since the extent to which prior tissue is exposed to radiation therapy can be considered as one of the parameters in treatment planning for that patient. In those circumstances where repeat irradiation is required and IMRT can deliver that radiation more safely by avoiding or minimizing radiation to critical structures which have been previously irradiated, the use of IMRT may be considered the most appropriate treatment for that individual.

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

The current NCCN guidelines for non-small cell lung cancer indicate that “more advanced technologies are appropriate when needed to deliver curative radiation therapy safely. These technologies include (but are not limited to) IMRT...Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.”

The current NCCN guidelines for small cell lung cancer indicate 3D-CRT techniques are preferred and IMRT may be considered in select patients.

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

The National Comprehensive Cancer Network (NCCN) guidelines on Central Nervous System Cancers state that: when radiation is given to patients with low-grade gliomas, it is administered with restricted margins. Every attempt should be made to decrease the radiation dose outside the target volume. This can be achieved with 3-dimensional planning or IMRT.
NCCN guidelines do not address the use of IMRT in high-grade tumors or metastases of the CNS.

The most recent National Comprehensive Cancer Network (NCCN) guidelines (v4.2011) for prostate cancer indicate, in the principles of radiation therapy, the external-beam radiotherapy techniques of 3-dimensional conformal (3D-CRT), or IMRT, should be employed. The NCCN guidelines also indicate 3D-CRT or IMRT may be considered as initial treatment options in all prostate cancer patients except for patients with a very-low risk of recurrence and less than 20 years’ expected survival.

The American College of Radiology Appropriateness Criteria indicates IMRT is appropriate for field shaping in patients being treated for clinically localized prostate cancer. Additionally, the ACR guidelines indicate IMRT is most appropriate for treatment planning for dose escalation.

The National Comprehensive Cancer Network (NCCN) guidelines on head and neck cancers comment that, in order to minimize dose to critical structures, either IMRT or 3D-CRT is recommended for cancers of the oropharynx and nasopharynx, and maxillary sinus or paranasal/ethmoid sinus tumors. The guidelines also indicate: “[t]he application of IMRT to other sites (e.g., oral cavity, larynx, hypopharynx, salivary glands) is evolving and may be used at the discretion of the treating physicians.” IMRT is not mentioned in the NCCN guidelines for thyroid cancer. However, the NCCN guidelines indicate external beam radiation therapy (EBRT) may be considered as primary treatment for anaplastic thyroid carcinoma. For papillary, follicular, Hurthle and medullary thyroid carcinoma, EBRT may be considered for postoperative gross residual or unresectable disease.

The American College of Radiology and the American Society for Therapeutic Radiation and Oncology note IMRT is a widely used treatment option for many indications including head and neck tumors.

The National Cancer Institute (NCI) indicates IMRT may be appropriate for head and neck cancers in several instances. For radiation of cervical lymph nodes (for primary cancer of unknown origin) and untreated primary occult metastatic squamous neck cancer, IMRT may have less short- and long-term toxicity than conventional radiation therapy in terms of xerostomia, acute dysphagia, and skin fibrosis. For nasopharyngeal cancer, the NCI indicates IMRT results in a lower incidence of xerostomia and may provide a better quality of life than conventional 3-D or 2-D radiation therapy. IMRT may also be appropriate in select cases of recurrent nasopharyngeal cancer per the NCI. Finally, to prevent or reduce the extent of salivary gland hypofunction and xerostomia, the NCI indicates parotid-sparing IMRT is recommended as a standard approach in head and neck cancers, if oncologically feasible.

The guidelines for anal carcinoma (www.nccn.org/professionals/physician_gls/PDF/anal.pdf, V.1.2013) state that IMRT “may be used in place of 3D conformal RT in the treatment of anal carcinoma;” and, that “Its use requires expertise and careful application to avoid reduction in local control probability.”

The guidelines also indicate that IMRT remains investigational for gastric cancer (www.nccn.org/professionals/physician_gls/pdf/gastric.pdf, V.2.2012). However, according to
the NCCN, “IMRT may be appropriate in selected cases to reduce dose to normal structures such as heart, lungs, kidneys and liver. In designing IMRT plans for structures such as the lungs, attention should be given to the volume receiving low to moderate doses, as well as the volume receiving high doses.”

In cervical cancer (www.nccn.org/professionals/physician_gls/PDF/cervical.pdf, V.1.2012), the guidelines mention that IMRT is “becoming more widely used” but issues with reproducibility, immobilization and definition of target “remain to be validated.”

Although IMRT is mentioned as an option in the guidelines for pancreatic adenocarcinoma, they indicate a lack of consensus on radiotherapy dose and appropriate setting for use of IMRT in this disease. (www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf, V.2.2012)

IMRT is not mentioned in the guidelines for hepatobiliary cancers. (www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf, V.2.2012)


Summary

Breast and Lung

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

Studies on IMRT for partial-breast irradiation are limited and have not demonstrated improvements in health outcomes.

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.

For the treatment of lung cancer, based on nonrandomized comparative studies, IMRT appears to produce clinical outcomes comparable to that of 3D-conformal radiation therapy. Dosimetry...
studies report that IMRT can reduce radiation exposure to critical surrounding structures, especially in large lung cancers. Results of clinical vetting indicate strong support for IMRT when alternative radiotherapy dosimetry exceeds a threshold of 20 Gy dose-volume (V20) to at least 35% of normal lung tissue. As a result of available evidence and clinical vetting, in conjunction with a strong indirect chain of evidence and potential to reduce harms, IMRT of the lung may be considered medically necessary for lung cancer when: 1) radiotherapy is given with curative intent, 2) alternate radiotherapy dosimetry demonstrates radiation dose exceeding 20 Gy dose-volume (V20) for at least 35% of normal lung tissue, and 3) IMRT reduces the 20-Gy dose-volume (V20) of radiation to the lung at least 10% below the V20 of 3-D conformal radiation therapy (e.g., 40% reduced to 30%).

Central Nervous System Tumors
The body of evidence available to evaluate intensity-modulated radiation therapy (IMRT) in the treatment of CNS tumors consists of dose planning studies and case series. The case series are limited by small numbers, heterogeneous patient populations, and different types of tumors. No randomized trials have been reported that compare results using IMRT to other conformal radiation therapy modalities, nor do any of the reported case series using IMRT include concurrently treated control groups.

In general, the limited evidence suggests that IMRT provides tumor control and survival outcomes comparable to existing radiotherapy techniques. The evidence from treatment planning studies has shown that the use of IMRT decreases radiation doses delivered to critical central nervous system (CNS) structures (e.g., optic chiasm, brainstem) and normal tissue adjacent to the tumor. This potentially lowers the risk of adverse events (acute and late effects of radiation toxicity), although the clinical benefit of reducing the radiation dose to critical structures and surrounding normal tissue using IMRT is theoretical. Determination of whether adverse event rates are reduced with IMRT is further complicated by a lack of high-quality literature defining the adverse effects using 3D-conformal radiation therapy for the CNS, the main comparator to IMRT. The single-arm case series are of limited usefulness in determining the benefits of IMRT over other conformal radiation modalities.

Prostate Cancer
The evidence base for intensity-modulated radiation therapy (IMRT) of the prostate consists largely of lower quality studies, with a lack of high-quality comparative studies reporting on clinical outcomes. In general, where the radiation doses are similar, the available evidence suggests that IMRT provides tumor control rates comparable to existing radiotherapy techniques. In addition, while results are not uniform and are based primarily on retrospective cohort trials, some studies show reductions in gastrointestinal and genitourinary toxicity. A reduction in clinically significant complications of radiation therapy is likely to lead to an improved quality of life for treated patients.

Head and Neck or Thyroid Cancer
Radiation therapy is an integral component in the treatment of head and neck cancers. IMRT has been proposed as a method of radiation therapy that allows adequate radiation therapy to the tumor while minimizing the radiation dose to surrounding normal tissues and critical structures.
In general, the evidence to assess the role of IMRT in the treatment of cancers of the head and neck suggests that IMRT provides tumor control rates comparable to existing radiotherapy techniques. In addition, while results are not uniform across all studies, the majority of the studies show a marked improvement in the rate of late xerostomia, a clinically significant complication of radiation therapy that leads to decreased quality of life for patients. Thus, based on the published literature that provides data on outcomes of treatment, IMRT is a radiation therapy technique that can be used in the treatment of head and neck cancers.

There are limited data on use of IMRT for thyroid cancer. The published literature consists of small case series with limited comparison among techniques for delivering radiation therapy. Due to the limitations in this evidence, clinical input was obtained. There was near-uniform consensus that the use of IMRT for thyroid tumors may be appropriate in some circumstances such as for anaplastic thyroid carcinoma or for thyroid tumors that are located near critical structures such as the salivary glands or spinal cord. When possible adverse events could result if nearby critical structures receive toxic radiation doses, the ability to improve dosimetry with IMRT should be accepted as meaningful evidence for its benefit.

**Abdominal, Gastrointestinal, and Pelvic Cancer (excluding Prostate Cancer)**
The body of evidence available to assess the role of intensity-modulated radiation therapy (IMRT) in the treatment of cancers of the abdomen and pelvis generally comprises case series, both retrospective and prospective. No randomized trials have been reported that compare results with IMRT to any other conformal radiation therapy (CRT), nor do any of the case series include concurrently treated control patients. The available results are generally viewed as hypothesis-generating for the design and execution of comparative trials of IMRT versus CRT that evaluate tumor control and survival outcomes in the context of adverse events and safety.

The comparative data on use of IMRT versus 3-dimensional conformal radiation (3D-CRT) in chemoradiotherapy for anal cancer shows marked differences in rates of acute toxicity. Thus, use of IMRT in cancer of the anus/anal canal may be considered medically necessary.

For other tumors of the abdomen and pelvis, the evidence from treatment planning studies has shown that the use of IMRT decreases radiation doses delivered to normal tissue adjacent to tumor. This potentially lowers the risk of adverse events (acute and late effects of radiation toxicity), although the clinical benefit of reducing the radiation dose to normal tissue using IMRT is theoretical. Due to the limitations in this evidence, this policy underwent clinical vetting by the Blue Cross and Blue Shield Association. There was support for the use of IMRT in tumors of the abdomen and pelvis when normal tissues would receive unacceptable doses of radiation. The results of the vetting, together with an indirect chain of evidence and the potential to reduce harms, led to the decision that IMRT may be considered medically necessary for the treatment of tumors of the abdomen and pelvis when dosimetric planning with standard 3-D conformal radiation predicts that the radiation dose to an adjacent organ would result in unacceptable normal tissue toxicity.
Key Words:
Computer-controlled conformal radiation therapy, Generalized 3-D conformal radiation therapy, Intensity modulated radiation therapy, IMRT, Intensity modulated radiotherapy, unconstrained 3-D conformal radiation therapy, multileaf collimators, solid compensator

Approved by Governing Bodies:
The U.S. Food and Drug Administration (FDA) has approved a number of devices for use in intensity-modulated radiation therapy (IMRT), including several linear accelerators and multileaf collimators. Examples of approved devices and systems are the NOMOS Slit Collimator (BEAK™) (NOMOS Corp.), the Peacock™ System (NOMOS Corp.), the Varian Multileaf Collimator with dynamic arc therapy feature (Varian Oncology Systems), the Saturne Multileaf Collimator (GE Medical Systems), the Mitsubishi 120 Leaf Multileaf Collimator (Mitsubishi Electronics America Inc.), the Stryker Leibinger Motorized Micro Multileaf Collimator (Stryker Leibinger), the Mini Multileaf Collimator, model KMI (MRC Systems GMBH), and the Preference® IMRT Treatment Planning Module (Northwest Medical Physics Equipment Inc.).

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: Effective January 1, 2010, IMRT for FEP contract must have pre-authorization. Refer to member’s benefit plan for details. Information should be forwarded to: Blue Cross and Blue Shield of Alabama, ATTN: Pre-determination Department, P.O. Box 362025, Birmingham, AL 35236 Or faxed to 205-402-9387
Please note that IMRT services are being Pre-Determined by Blue Cross and Blue Shield of Alabama and not Pre-Certified by CareCore National, LLC that manages our Advanced Imaging Services.
Pre-certification requirements: Not applicable

Coding:
CPT codes:

77301  Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
77338  Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
77418  Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session
Compensator-based beam modulation treatment delivery of inverse planned treatment using three or more high resolution (milled or cast) compensator convergent beam modulated fields, per treatment session

References:


61. Milano MT, Garofalo MC, Chumra SJ et al. Intensity-modulated radiation therapy in the
treatment of gastric cancer: early clinical outcome and dosimetric comparison with
62. Milano MT, Jani AB, Farrey KJ et al. Intensity-modulated radiation therapy (IMRT) in the
63(2):354-61.
63. Milker-Zabel S, Zabel-du BA, Huber P et al. Intensity-modulated radiotherapy for complex-
shaped meningioma of the skull base: long-term experience of a single institution. Int J
64. Mundt AJ, Roeske JG, Lujan AE et al. Initial clinical experience with intensity-modulated
whole-pelvise radiation therapy in women with gynecologic malignancies. Gynecol Oncol
66. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in
gynecology patients treated with intensity-modulated whole pelvic radiation therapy. Int J
64(3):892-7.
68. National Comprehensive Cancer Network. NCCN Practice Guidelines on Oncology Anal
Cancer v.2.2010.
69. National Comprehensive Cancer Network. NCCN Practice Guidelines on Oncology Colon
Cancer v.3.2010
70. National Comprehensive Cancer Network. NCCN Practice Guidelines on Oncology
Esophageal Cancer v.1.2009.
71. National Comprehensive Cancer Network. NCCN Practice Guidelines on Oncology Gastric
Cancer v.2.2010.
72. National Comprehensive Cancer Network. NCCN Practice Guidelines on Oncology Head
73. National Comprehensive Cancer Network. NCCN Practice Guidelines on Oncology Occult
Primary v.1.2010.
74. National Comprehensive Cancer Network. NCCN Practice Guidelines on Oncology
Pancreatic Adenocarcinoma v.1.2009.
75. National Comprehensive Cancer Network. NCCN Practice Guidelines on Oncology Rectal
76. National Comprehensive Cancer Network. NCCN Practice Guidelines on Oncology Soft
Tissue Sarcoma v.2.2009.
77. National Comprehensive Cancer Network. NCCN Practice Guidelines on Oncology
Esophageal and Esophagogastric Junction v 2.2012. Available at
Cancer Network Clinical Practice Guidelines in Oncology. V.2.2013. Available online at:


Policy History:
Medical Policy Group, July 2002 (2)
Medical Policy Group, August 2002
Medical Policy Committee, September 2002
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Medical Review Committee, February 2003
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Medical Policy Group, August 2003
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Medical Policy Group, September 2006 (2)
Medical Policy Administration Committee, September 2006
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Medical Policy Group, August 2007 (2)
Medical Policy Administration Committee, October 2007
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Medical Policy Administration Committee, June 2008
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Medical Policy Group, October 2008 (2)
Medical Policy Administration Committee, November 2008
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Medical Policy Group, March 2009 (2)
Medical Policy Group, September 2009 (2)
Medical Policy Administration Committee, October 2009
Available for comment October 3-November 17, 2009
Medical Policy Group, December 2009 (2)
Medical Policy Administration Committee, December 2009
Available for comment December 21, 2009-February 2, 2010
Medical Policy Group, January 2012 (2) Update description, policy—coverage for anal cancer,
Key Points, References
Medical Policy Administration Committee, February 2012
Available for comment February 9 – March 26
Medical Policy Group, September 2012 (2); Added coverage for patients who require repeat
irradiation of a field that has received prior irradiation and for esophageal cancer. Key Points and
References updated to support coverage statement
Medical Policy Administration Committee, October 2012
Available for comment November 1 through December 17, 2012
Medical Policy Panel, December 2012
Medical Policy Group, March 2013 (2) Policy statement changed to state that IMRT may be
considered medically necessary for all anal cancers (not limited to squamous cell carcinoma).
Policy statement changed to state that IMRT may be considered medically necessary for the
treatment of tumors of the abdomen and pelvis when dosimetric planning predicts the volume of
small intestine receiving doses >45 Gy with standard 3-D conformal radiation would result in
unacceptable risk of small intestine injury. Added a policy statement that IMRT would be
considered investigational for all other uses in the abdomen and pelvis. Paragraph added to
policy guidelines regarding toxic radiation dose to tissues and definition of a clinically
significant decrease in radiation dose. Key Points and Referenced updated to support policy
changes.
Medical Policy Administration Committee, April 2013
Available for comment March 25 through May 9, 2013
Medical Policy Panel, April 2013
Medical Policy Panel, June 2013
Medical Policy Group, May 2013 (2) Extensive revision of policy including Policy statements,
Key Points, and References
Medical Policy Administration Committee, July 2013
Available for comment June 24 through August 7, 2013
Medical Policy Group, June 2014 (3): Updated policy with link to CareCore National© medical policies effective August 1, 2014
Medical Policy Administration Committee, June 2014
Available for comment June 16 through July 31, 2014
Medical Policy Group, July 2014: Removed CareCore link and ‘Draft’. Transfer to CareCore is on hold until further notice.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.