INTENSITY-MODULATED RADIATION THERAPY

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Table of Contents

INSTRUCTIONS FOR USE ...................................................... 1
BENEFIT CONSIDERATIONS ............................................. 1
COVERAGE RATIONALE ..................................................... 1
DEFINITIONS ................................................................. 2
APPLICABLE CODES ........................................................ 2
DESCRIPTION OF SERVICES .............................................. 3
CLINICAL EVIDENCE ......................................................... 3
U.S. FOOD AND DRUG ADMINISTRATION .................................... 10
CENTERS FOR MEDICARE AND MEDICAID SERVICES ............. 10
REFERENCES ................................................................. 11
POLICY HISTORY/REVISION INFORMATION ............................ 15

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Medical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Medical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some benefit documents allow coverage of experimental/investigational/unproven services for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

This policy applies to persons 19 years of age and older. Intensity-modulated radiation therapy (IMRT) is covered without further review for persons 18 years and younger.

Intensity-Modulated Radiation Therapy
UnitedHealthcare Commercial Medical Policy

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IMRT is proven and medically necessary for **definitive therapy** of the primary site of the following diagnoses:

- Anal cancer
- Breast cancer when the patient has a separation of 25.5 cm or more in the intra-thoracic distance from the midpoint of the posterior light field border of the medial tangential field to the midpoint of the posterior light field of the lateral tangential field
- Cervical cancer in patients who have had a hysterectomy
- Esophageal cancer
- Head and neck cancers, including the following areas: pharynx (nasopharynx, oropharynx and hypopharynx), larynx, salivary glands, oral cavity (includes the tongue), nasal cavity and paranasal sinuses
- Mediastinal tumors
- Pancreatic cancer
- Primary or benign tumors of the central nervous system including the brain, brainstem and spinal cord
- Prostate cancer
- Tracheal cancer

**IMRT may be covered for a diagnosis that is not listed above as proven, including recurrences or metastases in selected cases, when at least one of the following conditions is present:**

- A non-IMRT technique would substantially increase the probability of clinically meaningful normal tissue toxicity.
- The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

Requests for these exceptions will be evaluated on a case-by-case basis.

**The use of compensator based beam modulation treatment is proven and medically necessary when done in combination with an IMRT indication that is listed above as proven.**

**IMRT used in conjunction with proton beam radiation therapy is unproven and not medically necessary.**

Clinical evidence is insufficient to support the combined use of these technologies in a single treatment plan. Comparative effectiveness studies including randomized controlled trials are needed to demonstrate the safety and long-term efficacy of combined therapy.

**DEFINITIONS**

**Definitive Therapy**: Definitive therapy is treatment with curative intent. Treatment of a local recurrence of the primary tumor may be considered definitive if there has been a long disease free interval (generally ≥2 years) and treatment is with curative intent.

**APPLICABLE CODES**

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>77301</td>
<td>Intensity-modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications</td>
</tr>
<tr>
<td>77338</td>
<td>Multi-leaf collimator (MLC) device(s) for intensity-modulated radiation therapy (IMRT), design and construction per IMRT plan</td>
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<tr>
<td>77385</td>
<td>Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple</td>
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<tr>
<td>77386</td>
<td>Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex</td>
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<tr>
<td>77387</td>
<td>Guidance for localization of target volume for delivery of radiation treatment delivery, includes intrafraction tracking, when performed</td>
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<tr>
<td>77520</td>
<td>Proton treatment delivery; simple, without compensation</td>
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<td>77522</td>
<td>Proton treatment delivery; simple, with compensation</td>
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### External beam radiation therapy

Delivers x-rays that are generated using a machine called a linear accelerator. Three-dimensional conformal radiation therapy (3D-CRT) uses very sophisticated computer software and advanced treatment machines to deliver radiation to very precisely shaped target areas. IMRT is an advanced form of conformal external beam radiation therapy that uses computer-controlled linear accelerators to deliver precise radiation doses to the target area while minimizing the dose to surrounding normal critical structures. IMRT allows for the radiation dose to conform more precisely to the shape of the tumor by modulating – or controlling – the intensity of the radiation beam. The ratio of normal tissue dose to tumor dose is reduced to a minimum with IMRT, allowing delivery of higher radiation doses with potentially fewer side effects than conventional radiation therapy techniques. IMRT differs from conventional conformal radiation therapy in that it has the ability to adjust the beam intensity by using multiple beamlets. This kind of dose modulation allows different areas of a tumor or nearby tissues to receive different doses of radiation (National Cancer Institute (NCI), 2010; American College of Radiology (ACR) website, 2015; ACR website, 2016a).

### Image-guided radiation therapy (IGRT)

Often used in conjunction with IMRT and other advanced forms of radiation therapy. IGRT uses frequent imaging during a course of radiation therapy to more precisely target radiation at the tumor and avoid healthy surrounding tissue. It is used to treat tumors in areas of the body that are prone to movement, such as the lungs, as well as tumors located close to critical organs. Using specialized computer software, these images are then compared to the reference images taken during treatment planning. IGRT may be performed prior to the start of treatment (interfraction) or continuously/real-time during treatment sessions (intrafraction). Computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and x-ray imaging may be used by visualizing boney or soft-tissue anatomy. Other methods use markers placed on the surface of the body or implanted in the body (e.g., optical surface imaging or electromagnetic localization) (ACR website, 2016b; ACR/American Society for Radiation Oncology [ASTRO], 2014).

### Clinical Evidence

A systematic review by De Neve et al. (2012) concluded that while some studies show lower toxicity in IMRT-treated patients, further studies are needed to evaluate efficacy endpoints, like overall survival, disease-specific survival or local control.

Veldeman et al. (2008) conducted a systematic review of the evidence behind the use of IMRT for various disease sites. Forty-nine comparative studies on head and neck, prostate, gynecological, CNS, breast and lung cancer were reviewed. The authors reported that the generally positive findings for toxic effects and quality of life (QOL) are consistent with the ability of IMRT to better control the dose distribution inside (i.e., dose homogeneity and simultaneous integrated boost) and outside (i.e., selective sparing of organs at risk (OAR)) the planning target volume.

NCI published guidelines for the utilization of IMRT treatment techniques in clinical trial protocols (NCI, 2005). These guidelines and protocol requirements were updated in 2006 to include IMRT in anatomical regions where target motion can have a significant effect (NCI, 2006).
Han et al. (2014) conducted a prospective cohort study to evaluate toxicity, QOL and clinical outcomes in 58 patients treated with IMRT and concurrent chemotherapy for anal and perianal cancer. Stage I, II, III, and IV disease was found in 9%, 57%, 26%, and 9% of patients, respectively. Radiation dose was 27 Gy in 15 fractions to 36 Gy in 20 fractions for elective targets and 45 Gy in 25 fractions to 63 Gy in 35 fractions for gross targets. The chemotherapy regimen was 5-fluorouracil and mitomycin C. The median follow-up time was 34 months. The authors reported that IMRT reduced acute grade 3+ hematologic and gastrointestinal toxicities compared with reports from non-IMRT series, without compromising locoregional control. The reported QOL scores most relevant to acute toxicities returned to baseline by 3 months after treatment.

Mitchell et al. (2014) evaluated toxicity, local control and survival in 65 patients with localized squamous cell carcinoma of the anal canal treated with IMRT and concurrent chemotherapy. The median dose to the primary tumor and pelvis were 54 Gy and 45 Gy, respectively. The most common concurrent chemotherapy regimens were 5-fluorouracil and cisplatin (75%), capecitabine and oxaliplatin (11%) and 5-fluorouracil and mitomycin C (5%). The percentage of patients with Tx, T1, T2, T3 and T4 disease were 8%, 17%, 49%, 15% and 11%, respectively. The percentage of patients with N0, N1, N2 and N3 disease were 46%, 17%, 9% and 28%, respectively. With a median follow-up of 19 months, the 2-year local and distant control rates were both 93%. The 2-year overall and disease-free survival rates were 96% and 86%, respectively.

Kachnic et al. (2013) conducted a prospective, multi-institutional phase II trial (RTOG 0529) assessing dose-painted intensity modulated radiation therapy (DP-IMRT) for anal cancer. The primary outcome was reducing grade 2+ combined acute gastrointestinal and genitourinary adverse events (AEs) of 5-fluorouracil (5FU) and mitomycin-C (MMC) chemoradiation for anal cancer by at least 15% compared with the conventional radiation/5FU/MMC arm from RTOG 9811. Of 52 evaluable patients, the grade 2+ combined acute adverse event rate was 77%. However, significant reductions were seen in acute grade 2+ hematologic events (73% vs. 85%), grade 3+ gastrointestinal events (21% vs. 36%) and grade 3+ dermatologic events (23% vs. 49%) with DP-IMRT. Although the trial did not meet its primary endpoint, the authors reported that DP-IMRT was associated with significant sparing of acute grade 2+ hematologic and grade 3+ dermatologic and gastrointestinal toxicity. The authors also emphasized the importance of real-time radiation quality assurance for IMRT trials.

In a retrospective comparative study, Dasgupta et al. (2013) compared IMRT (n=45) and conventional radiotherapy (CRT) (n=178) outcomes in patients with anal squamous cell carcinoma (ASCC). Primary outcomes were local recurrence-free survival (LRFS), distant metastases-free survival (DMFS) and overall survival (OS). The 2-year LRFS, DMFS and OS were 87%, 86% and 93%, respectively, for IMRT; and 82%, 88% and 90%, respectively, for CRT. The authors concluded that outcomes were not compromised by more conformal radiotherapy. In the absence of prospective, multi-institutional, randomized trials of IMRT in ASCC, retrospective data, using methods to minimize bias, help to establish the role of IMRT in the definitive therapy of ASCC.

DeFoe et al. (2012) reported the clinical outcomes of 78 patients with anal carcinoma treated with intensity-modulated radiation therapy (IMRT) and concurrent chemotherapy. The median follow-up for the entire cohort was 16 months (range 0-72 months). Acute grade ≥3 toxicity included 27.7% gastrointestinal and 29.0% dermatological. Acute grade 4 hematological toxicity occurred in 12.9% of patients. Sixty-four (88.9%) patients experienced a complete response. The 2 year colostomy-free survival, overall survival, freedom from local failure and freedom from distant failure rates were 81.2, 86.9, 83.6 and 81.8%, respectively.

Forty-three patients were treated with dose-painted IMRT (DP-IMRT) and concurrent chemotherapy for squamous cell carcinoma of the anal canal. Median follow-up was 24 months (range, 0.6-43.5 months). Acute Grade ≥3 toxicity included: hematologic 51%, dermatologic 10%, gastrointestinal 7% and genitourinary 7%. Two-year local control, overall survival, colostomy-free survival and metastasis-free survival were 95%, 94%, 90% and 92%, respectively (Kachnic et al., 2012).

A retrospective review by Bazan et al. (2011) compared IMRT (n=29) with conventional radiation therapy (n=17) for the treatment of anal cancer. Patients treated with conventional radiation required more treatment breaks and longer treatment duration. The 3-year overall survival (OS), locoregional control (LRC) and progression-free survival were 87.8%, 91.9% and 84.2%, respectively, for the IMRT groups and 51.8%, 56.7% and 56.7%, respectively, for the CRT group.

A study conducted by Saarilahti et al. (2008) compared the use of IMRT and 3D-CRT in 59 patients with anal squamous cell cancer. IMRT resulted in a significant reduction in skin and mucosal eruptions and late radiation proctitis.

Salama et al. (2007) reported a multicenter experience treating anal canal cancer patients with concurrent chemotherapy and IMRT. Eighteen-month colostomy-free survival, overall survival, freedom from local failure and...
Intensity-modulated radiation therapy (IMRT) is associated with a decrease in acute desquamation compared to conventional radiation therapy (CRT). IMRT reduces the dose to the contralateral breast significantly compared to conventional tangential field techniques. The authors also found that the primary breast size significantly affects the scatter dose to the contralateral breast but not the ipsilateral lung or heart dose when using IMRT for breast irradiation.

Freedman et al. (2006) evaluated 73 patients to determine the incidence and severity of acute skin toxicity with breast IMRT, and to compare the results with a matched cohort of patients treated by conventional radiation therapy. The authors concluded that IMRT for breast cancer was associated with a decrease in acute desquamation compared to conventional radiation therapy. The authors also concluded that further study of patient symptoms, QOL, and cosmesis is needed to evaluate the benefit of IMRT for breast cancer.

Several studies comparing IMRT to standard radiotherapy found that IMRT delivers substantially lower amounts of radiation to the contralateral breast (Prabhakar et al., 2007; Bhatnagar et al., 2006a; Bhatnagar et al., 2006b; Bhatnagar et al., 2004).

Woo et al. (2006) evaluated the radiation body exposure during breast radiotherapy in a prospective cohort of 120 women. The use of physical wedges as a compensation technique was the most significant factor associated with increased scattered dose, resulting in approximately three times more exposure compared with breast IMRT and...
dynamic wedge. The investigators concluded that the amount of radiation that is scattered to a patient's body is consistent with exposure reported to be associated with excess of leukemia, and recommend using breast IMRT or virtual wedging for the radiotherapy of breast cancer receiving high-dose anthracycline chemotherapy.

NCCN guidelines for breast cancer state that greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments and IMRT. Respiratory control techniques and prone positioning may be used to try to further reduce dose to adjacent normal tissues, particularly the heart and lungs (NCCN, Clinical Practice Guidelines in Oncology, Breast Cancer, 2016).

**Central Nervous System (CNS) Tumors**

Milker-Zabel et al. (2007) evaluated 94 patients with meningiomas of the skull base who were treated with IMRT. Median follow-up was 4.4 years and overall local control was 93.6%.

The potential benefits and limitations of different radiation techniques (stereotactic arc therapy (SRS/T), IMRT, helical tomotherapy (HT), Cyberknife and intensity-modulated multiple arc therapy (AMOA)) were assessed using comparative treatment planning methods on 12 patients presenting with benign brain tumors. For the class of tumors investigated, HT, AMOA and IMRT had better target coverage with HT providing the best combination of indices. Between AMOA and IMRT, target coverage was comparable and, considering OAR, AMOA was slightly preferable (Cozzi et al., 2006).

NCCN guidelines for central nervous system cancers state that every attempt should be made to decrease the radiation dose outside the target volume. This can be achieved with 3D planning or IMRT (NCCN, Clinical Practice Guidelines in Oncology, Central Nervous System Cancers, 2016).

**Cervical Cancer**

Hasselle et al. (2011) evaluated disease outcomes and toxicity in cervical cancer patients treated with pelvic IMRT. Patients treated with extended field or conventional techniques were excluded. IMRT plans were designed to deliver 45 Gy in 1.8-Gy daily fractions to the planning target volume while minimizing dose to the bowel, bladder and rectum. Toxicity was graded according to the Radiation Therapy Oncology Group system. The study included 111 patients with Stage I-IVA cervical carcinoma. Of these, 22 were treated with postoperative IMRT, 8 with IMRT followed by intracavitary brachytherapy and adjuvant hysterectomy, and 81 with IMRT followed by planned intracavitary brachytherapy. Of the patients, 63 had Stage I-IIA disease and 48 had Stage IIB-IVA disease. The median follow-up time was 27 months. The 3-year overall survival rate and the disease-free survival rate were 78% and 69%, respectively. The 3-year pelvic failure rate and the distant failure rate were 14% and 17%, respectively. Estimates of acute and late grade 3 toxicity or higher were 2% and 7%, respectively. The authors concluded that IMRT is associated with low toxicity and favorable outcomes, supporting its safety and efficacy for cervical cancer. Prospective clinical trials are needed to evaluate the comparative efficacy of IMRT vs. conventional techniques.

Chen et al. (2007a) assessed 68 patients at high risk of cervical cancer after hysterectomy who were treated with adjuvant pelvic radiotherapy and concurrent chemotherapy. Thirty-three patients received adjuvant radiotherapy by IMRT. Before the IMRT series was initiated, 35 other patients underwent conventional four-field radiotherapy (Box-RT). IMRT provided compatible local tumor control compared with Box-RT. The actuarial 1-year local control for patients in the IMRT and Box-RT groups was 93% and 94%, respectively. IMRT was well tolerated, with significant reduction in acute gastrointestinal (GI) and genitourinary (GU) toxicities compared with the Box-RT group (GI 36% vs. 80%; GU 30% vs. 60%). The IMRT group had lower rates of chronic GI and GU toxicities than the Box-RT patients. The investigators concluded that their results suggest that IMRT significantly improved the tolerance to adjuvant chemoradiotherapy with compatible locoregional control compared with conventional Box-RT. However, longer follow-up and more patients are needed to confirm the benefits of IMRT.

ACR Appropriateness Criteria state that IMRT has not been tested prospectively and is not recommended for the routine treatment of advanced cervical cancer at this time due to significant organ motion issues. However, IMRT may be appropriate to reduce acute toxicities in patients who have had a hysterectomy (ACR, 2012).

NCCN guidelines for cervical cancer state that IMRT and similar highly conformal methods of dose delivery may be helpful in minimizing the dose to the bowel and other critical structures in the post-hysterectomy setting and in treating the para-aortic nodes when necessary. These techniques can also be useful when high doses are required to treat gross disease in regional lymph nodes. IMRT should not be used as a routine alternative to brachytherapy for treatment of central disease in patients with an intact cervix. Very careful attention to detail and reproducibility (including consideration of target and normal tissue definitions, patient and internal organ motion, soft tissue deformation and rigorous dosimetric and physics quality assurance) is required for proper delivery (NCCN, Clinical Practice Guidelines in Oncology, Cervical Cancer, 2017).
**Esophageal Cancer**

Lin et al. (2012) performed an analysis of long-term clinical outcomes comparing 3D-CRT (n=413) vs. IMRT (n=263) for esophageal cancer. Primary outcomes were overall survival time, interval to local failure and interval to distant metastasis. Compared with IMRT, 3D-CRT patients had a significantly greater risk of dying (72.6% vs. 52.9%) and of locoregional recurrence. No difference was seen in cancer-specific mortality or distant metastasis. An increased cumulative incidence of cardiac death was seen in the 3D-CRT group, but most deaths were undocumented.

In a small study (n=19), Kole et al. (2012) reported that treating patients with distal esophageal cancer using IMRT significantly decreased the exposure of the heart and right coronary artery when compared with 3D-CRT.

Chandra et al. (2005) studied 10 patients in a retrospective treatment planning study to evaluate the feasibility whether IMRT can be used to reduce doses to normal lung than three-dimensional conformal radiotherapy (3D-CRT) in treating distal esophageal malignancies. The authors noted that dose-volume of exposed normal lung can be reduced with IMRT, although clinical investigations are warranted to assess IMRT treatment outcome of esophageal cancers.

NCCN guidelines for esophageal cancer state that IMRT is appropriate in clinical settings where reduction in dose to organs at risk (e.g., heart and lungs) is required that cannot be achieved by 3D techniques. Retrospective studies comparing 3D conformal versus IMRT for patients with esophageal cancer have generally shown superior dose conformity and homogeneity with IMRT and reduction of radiation dose to the lungs and heart (NCCN, Clinical Practice Guidelines in Oncology, Esophageal and Esophagogastric Junction Cancers, 2016).

**Head and Neck Cancer**

An Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review of radiotherapy for head and neck cancer found that while IMRT is more successful than traditional radiation therapy in avoiding side effects, such as xerostomia (dry mouth), it is unknown whether IMRT is better or worse at reducing tumor size (Samson et al., 2010). A 2014 update found moderate-strength evidence showing a reduction in the incidence of late grade 2 or higher xerostomia with IMRT compared with three-dimensional conformal radiotherapy (3DCRT). This increases the strength of evidence on this toxicity, raising it to “high.” Evidence in the update is insufficient to show a difference between IMRT and 3DCRT in overall survival or locoregional tumor control rates. No new evidence was found that would alter any conclusions of the earlier report for any other toxicity, oncologic outcomes or comparisons (Ratko et al., 2014).

Nutting et al. (2011) assessed whether parotid-sparing IMRT reduced the incidence of severe xerostomia, a common late side-effect of radiotherapy to the head and neck. Ninety-four patients with pharyngeal squamous cell carcinoma were randomly assigned to receive IMRT (n=47) or conventional radiotherapy (n=47). The primary endpoint was the proportion of patients with grade 2 or worse xerostomia at 12 months. Median follow-up was 44.0 months. Six patients from each group died before 12 months and seven patients from the conventional radiotherapy and two from the IMRT group were not assessed at 12 months. At 12 months, xerostomia side-effects were reported in 73 of 82 patients. Grade 2 or worse xerostomia at 12 months was significantly lower in the IMRT group (38%) than in the conventional radiotherapy group (74%). The only recorded acute adverse event of grade 2 or worse that differed significantly between the treatment groups was fatigue, which was more prevalent in the IMRT group. At 24 months, grade 2 or worse xerostomia was significantly less common with IMRT than with conventional radiotherapy. At 12 and 24 months, significant benefits were seen in recovery of saliva secretion with IMRT compared with conventional radiotherapy, as were clinically significant improvements in dry-mouth-specific and global QOL scores. At 24 months, no significant differences were seen between randomized groups in non-xerostomia late toxicities, locoregional control or overall survival. The authors concluded that sparing the parotid glands with IMRT significantly reduces the incidence of xerostomia and leads to recovery of saliva secretion and improvements in associated QOL.

Fifty-one patients with early-stage nasopharyngeal carcinoma took part in a randomized controlled clinical study and received IMRT or CRT. The investigators found that IMRT was significantly better than CRT in terms of parotid sparing and improved QOL for early-stage disease (Pow et al., 2006).

Sixty patients with early-stage nasopharyngeal carcinoma (NPC) were randomly assigned to receive either IMRT or two-dimensional radiation therapy (2DRT). At 1 year after treatment, patients in IMRT arm had lower incidence of observer-rated severe xerostomia than patients in the 2DRT arm (39.3% v 82.1%). The investigators concluded that IMRT is superior to 2DRT in preserving parotid function and results in less severe delayed xerostomia in the treatment of early-stage NPC. Incomplete improvement in patient's subjective xerostomia with parotid-sparing IMRT reflects the need to enhance protection of other salivary glands (Kam et al., 2007).

Lee et al. (2006) compare toxicity and efficacy of conventional radiotherapy using delayed accelerated concomitant boost radiotherapy (CBRT) vs. IMRT in the setting of concurrent chemotherapy (CT) for locally advanced oropharyngeal carcinoma in 293 patients. In total, 41 were treated with IMRT/CT and 71 were treated with CBRT/CT.
The investigators found that in the setting of CT for locally advanced oropharyngeal carcinoma, IMRT results in lower toxicity and similar treatment outcomes when compared with CBRT.

Fang et al. (2008) investigated the changes of QOL and survival outcomes for 203 newly diagnosed nasopharyngeal carcinoma (NPC) patients who were curatively treated by 3D-CRT (n = 93) or IMRT (n = 110). The 3-year locoregional control, metastasis-free survival and overall survival rates were 84.8%, 76.7% and 81.7% for the 3D-CRT group, respectively, compared with 84.2%, 82.6%, and 85.4% for the IMRT group. A general trend of maximal deterioration in most QOL scales was observed during radiotherapy, followed by a gradual recovery thereafter. There was no significant difference in most QOL scales between the 2 groups at each time point. The exception was that patients treated by IMRT had a both statistically and clinically significant improvement in global QOL, fatigue, taste/smell, dry mouth and feeling ill at 3 months after radiotherapy. The investigators concluded that the potential advantage of IMRT over 3D-CRT in treating NPC patients might occur in QOL outcome during the recovery period from the treatment.

Chen et al. (2007b) evaluated 127 patients with sinonasal carcinoma who underwent radiotherapy. Fifty-nine patients were treated by conventional radiotherapy; 45 patients by three-dimensional conformal radiotherapy; and 23 patients by IMRT. No differences in survival at 5 years follow-up were noted, but 3D-CRT had fewer side effects than conventional radiotherapy, and IMRT had even fewer side effects than 3D-CRT.

Rades et al. (2007) evaluated 148 head-and-neck cancer patients treated with surgery plus RT, IMRT, 3D-conformal RT, and conventional RT. The 3 radiation techniques had similar disease control and had similar toxicity profiles. IMRT was associated with less xerostomia than conformal RT and conventional RT (17% versus 63% and 73%).

A retrospective chart review was completed for 34 patients with pituitary adenomas who were treated with IMRT. With a median follow-up of 42.5 months, the treatment was well tolerated, with performance status remaining stable in 90% of patients. Radiographic local control was 89%, and among patients with secretory tumors, 100% had a biochemical response. One patient required salvage surgery for progressive disease, giving a clinical progression free survival of 97% (Mackley et al., 2007).

NCCN guidelines for head and neck cancers state that IMRT or other conformal techniques may be used to treat head and neck cancers as appropriate depending on the stage, tumor location, physician training/experience and available physics support. IMRT has been shown to be useful in reducing long-term toxicity in oropharyngeal, paranasal sinus and nasopharyngeal cancers by reducing the dose to salivary glands, temporal lobes, auditory structures (including cochlea) and optic structures. The application of IMRT to other head and neck cancers is evolving and may be used at the discretion of the treating physicians (NCCN, Clinical Practice Guidelines in Oncology, Head and Neck Cancer, 2016).

Mediastinal Tumors
In selected patients with Hodgkin's lymphoma and non-Hodgkin's lymphoma involving the mediastinum, IMRT has been shown to improve planning target volume coverage, reduce pulmonary toxicity and provide better cardiac protection when compared to conventional treatments or 3D conformal radiation therapy (Fiandra et al., 2012; Lu et al., 2012; Girinsky et al., 2006; Goodman et al., 2005).

NCCN guidelines for lymphomas state that advanced radiation therapy technologies, such as IMRT, may offer significant and clinically relevant advantages in specific instances to spare OARs (e.g., heart, lungs, esophagus, spinal cord) and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. Achieving highly conformal dose distributions is especially important for patients who are being treated with curative intent or who have long life expectancies following therapy (NCCN, Clinical Practice Guidelines in Oncology, Hodgkin Lymphoma, 2016; NCCN, Clinical Practice Guidelines in Oncology, Non-Hodgkin’s Lymphomas, 2016).

NCCN guidelines for thymomas and thymic carcinomas state that radiation therapy should be given by 3D conformal technique to reduce surrounding normal tissue damage (e.g., heart, lungs, esophagus, spinal cord). IMRT may further improve the dose distribution and decrease the dose to the normal tissue as indicated. If IMRT is applied, the ASTRO/ACR guidelines should be strictly followed (NCCN, Clinical Practice Guidelines in Oncology, Thymomas and Thymic Carcinomas, 2016).

Pancreatic Cancer
Yovino et al. (2011) evaluated whether improved dose distributions from using IMRT resulted in decreased toxicity when compared to patients who received a similar 5-fluorouracil-based protocol with 3D conformal radiation in the RTOG 97-04 trial. Forty-six patients with pancreatic/ampullary cancer were treated with concurrent chemoradiation (CRT) using IMRT. Rates of acute gastrointestinal (GI) toxicity for the IMRT-treated patients were compared with those from RTOG 97-04, where all patients were treated with 3D conformal techniques. The overall incidence of Grade 3-4 acute GI toxicity was low in patients receiving IMRT-based CRT. When compared with patients who had 3D treatment planning (RTOG 97-04), IMRT significantly reduced the incidence of Grade 3-4 nausea and vomiting (0% vs.
11%) and diarrhea (3% vs. 18%). The authors concluded that IMRT is associated with a statistically significant decrease in acute upper and lower GI toxicity among patients treated with CRT for pancreatic/ampullary cancers. Future clinical trials plan to incorporate the use of IMRT, given that it remains a subject of active investigation.

Milano et al. (2004) assessed the efficacy and toxicity of IMRT in 25 patients with pancreatic and bile duct (cholangiocarcinoma) malignancies. Twenty-three received concurrent 5-fluorouracil. One patient with a pancreatic primitive neuroectodermal tumor received concurrent etoposide and ifosfamide. Eight patients had resected tumors, and 17 had unresectable primary (n = 14) or recurrent (n = 3) tumors. Six patients underwent treatment planning with conventional three-dimensional four-field techniques for dosimetric comparison with IMRT. Compared with conventional radiotherapy, IMRT reduced the mean dose to the liver, kidneys, stomach, and small bowel. IMRT was well tolerated, with 80% experiencing Grade 2 or less acute upper GI toxicity. At a median follow-up of 10.2 months, no resected patients had local failure, and only 1 of 10 assessable patients with unresectable cancer had local progression. The median survival and distant metastasis-free survival of the 24 patients with adenocarcinoma was 13.4 and 7.3 months, respectively. Grade 4 late liver toxicity occurred in 1 patient surviving >5 years. The remainder of the assessable patients experienced no (n = 9) or Grade 1 (n = 4) late toxicity. Local control was not compromised, despite efforts to increase conformity and avoid doses to normal structures.

NCCN guidelines for pancreatic adenocarcinoma state that IMRT with breathhold/gating techniques can result in improved planning target volume (PTV) coverage with decreased dose to OAR. IMRT is increasingly being applied for therapy of locally advanced pancreatic adenocarcinoma and in the adjuvant setting with the aim of increasing radiation dose to the gross tumor while minimizing toxicity to surrounding tissues. There is no clear consensus on appropriate maximum dose of radiation when IMRT is used (NCCN, Clinical Practice Guidelines in Oncology, Pancreatic Adenocarcinoma, 2016).

**Prostate Cancer**

Bauman et al. (2012) conducted a systematic review of 11 studies evaluating IMRT in the treatment of prostate cancer. The findings were in favor of recommending IMRT over 3D-CRT in the radical treatment of localized prostate cancer where doses greater than 70 Gy are required. There was insufficient data to recommend IMRT over 3D-CRT in the postoperative setting.

Alicikius et al. (2011) investigated long-term tumor control and toxicity outcomes after IMRT in 170 patients with clinically localized prostate cancer. Primary outcomes were freedom from biochemical relapse, distant metastases and cause-specific survival. The median follow-up was 99 months. The 10-year 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 10-year distant metastases-free rates were 100%, 94% and 90%, respectively. The 10-year cause-specific mortality rates were 0%, 3% and 14%, respectively. The 10-year likelihood of developing grade 2 and 3 late genitourinary toxicity was 11% and 5%, respectively, and the 10-year likelihood of developing grade 2 and 3 late gastrointestinal toxicity was 2% and 1%, respectively. No grade 4 toxicities were observed. The authors concluded that high-dose IMRT is well tolerated and is associated with excellent long-term tumor-control outcomes in patients with localized prostate cancer.

Sheets et al. (2012) evaluated the comparative morbidity and disease control of IMRT, proton therapy and conformal radiation therapy for primary prostate cancer treatment. The authors conducted a population-based study using Surveillance, Epidemiology, and End Results-Medicare-linked data. Main outcomes were rates of gastrointestinal and urinary morbidity, erectile dysfunction, hip fractures and additional cancer therapy. In a comparison between IMRT and conformal radiation therapy (n=12,976), men who received IMRT were less likely to experience gastrointestinal morbidity and fewer hip fractures but more likely to experience erectile dysfunction. IMRT patients were also less likely to receive additional cancer therapy. In a comparison between IMRT and proton therapy (n=1368), IMRT patients had a lower rate of gastrointestinal morbidity. There were no significant differences in rates of other morbidities or additional therapies between IMRT and proton therapy.

Hummel et al. (2010) conducted a systematic review evaluating the clinical effectiveness of IMRT for the radical treatment of prostate cancer. IMRT was compared to 3DCRT or radical prostatectomy. No randomized controlled trials (RCTs) of IMRT versus 3DCRT in prostate cancer were available, but 13 non-randomized studies were found, of which five were available only as abstracts. The comparative data seem to support the theory that higher doses, up to 81 Gy, can improve biochemical survival for patients with localized prostate cancer. The data also suggest that toxicity can be reduced by increasing conformality of treatment, particularly with regard to GI toxicity, which can be more easily achieved with IMRT than 3DCRT. The authors note that the strength of the conclusions of this review are limited by the lack of RCTs, and any comparative studies for some patient groups.

Al-Mamgani et al. (2009) compared the acute and late gastrointestinal (GI) and genitourinary (GU) toxicity in 78 prostate cancer patients treated with either a three-conformal radiotherapy technique with a sequential boost (SEQ) or a simultaneous integrated boost using intensity-modulated radiotherapy (SIB-IMRT). All patients were treated to a total dose of 78 Gy. A significantly lower incidence of acute Grade 2 or greater GI toxicity occurred in patients treated
with SIB-IMRT compared with SEQ. For acute GU toxicity and late GI and GU toxicity, the incidence was lower after SIB-IMRT, but these differences were not statistically significant. The authors found that SIB-IMRT reduced the toxicity without compromising the outcome in patients with localized prostate cancer treated to 78 Gy radiation.

Several prospective studies by the same group of investigators reported excellent clinical outcomes with acceptable toxicity when using IMRT to treat prostate cancer (Zelefsky et al., 2001, 2002, 2006; Spratt et al., 2013).

Jani et al. (2007) compared acute genitourinary (GU) and gastrointestinal (GI) toxicity results of radiotherapy using IMRT versus conventional radiotherapy. The records of 481 consecutive prostate cancer patients receiving radiotherapy to localized fields at a single institution were reviewed; 108 received IMRT and 373 received conventional radiotherapy. The investigators found that IMRT was not associated with reduction of acute GU toxicity but was associated with a reduction of acute GI toxicity over conventional radiotherapy in the treatment of prostate cancer to localized fields.

ACR Appropriateness Criteria recommend that IMRT is usually appropriate for treating prostate cancer (ACR, 2011).

NCCN states that highly conformal radiation therapy, such as IMRT, should be used to treat prostate cancer. IMRT significantly reduces the risk of gastrointestinal toxicities and rates of salvage therapy. Moderately hypofractionated image-guided IMRT regimens have been tested in randomized trials reporting similar efficacy and toxicity to conventionally fractionated IMRT. They can be considered as an alternative to conventionally fractionated regimens when clinically indicated. Extremely hypofractionated image-guided IMRT regimens are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated IMRT. They can be considered as a cautious alternative to conventionally fractionated regimens at clinics with appropriate technology, physics and clinical expertise. Daily prostate localization using IGRT is essential for target margin reduction and treatment accuracy. Imaging techniques, such as ultrasound, implanted fiducials, electromagnetic targeting and tracking or endorectal balloon, can improve cure rates and decrease complications (NCCN, Clinical Practice Guidelines in Oncology, Prostate Cancer, 2016).

In a 2007 guideline for prostate cancer, the American Urological Association (AUA) stated that the advent of IMRT and image guidance radiotherapy either with transabdominal ultrasound or the intraprostatic placement of fiducial markers further refined radiation treatment delivery. The resulting dose accuracy and escalation provide proven improvements in local tumor elimination and reduction in late radiation-related complications (AUA, 2007; validity confirmed 2011).

**Combined Therapies**

No evidence was identified in the clinical literature supporting the combined use of IMRT and proton beam radiation therapy in a single treatment plan.

**Professional Societies**

**American College of Radiology (ACR)**

An ACR practice parameter states that IMRT is a widely used clinical modality that enables radiation oncologists to deliver higher doses of radiation to target structures while reducing doses to adjacent normal critical tissues, thereby improving therapeutic outcomes in many clinical areas. Successful IMRT programs involve integration of many processes: patient selection, patient positioning/immobilization, target definition, treatment plan development and accurate treatment delivery. Appropriate quality assurance (QA) procedures, including patient specific QA measures, are essential for maintaining the quality of an IMRT program and assuring patient safety (ACR, 2016).

**American Society for Radiation Oncology (ASTRO)**

ASTRO’s model policy considers IMRT reasonable in instances where sparing the surrounding normal tissue is of added clinical benefit to the patient. The final determination of the appropriateness and medical necessity for IMRT resides with the treating radiation oncologist who should document the justification for IMRT for each patient (ASTRO, 2015).

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

The FDA has approved a number of devices for use in IMRT. See the following website for more information (use product codes MUJ and IYE): [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm).

(Accessed October 21, 2016)

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

Medicare does not have a National Coverage Determination (NCD) for intensity-modulated radiation therapy (IMRT). Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for [Intensity Modulated Radiation Therapy (IMRT)], [Radiology: Intensity Modulated Radiation Therapy (IMRT)], [Proton Beam Radiotherapy], [Proton Beam Therapy].
REFERENCES


### POLICY HISTORY/REVISION INFORMATION

<table>
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<tr>
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<th>Action/Description</th>
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<tr>
<td>09/01/2017</td>
<td>Revised coverage rationale; replaced language indicating:</td>
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<td>○ &quot;Intensity-modulated radiation therapy (IMRT) is proven and medically necessary for <strong>treating</strong> the primary site of the [listed] diagnoses&quot; with &quot;IMRT is proven and medically necessary for <strong>definitive therapy of</strong> the primary site of the [listed] diagnoses&quot;</td>
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<td>○ &quot;IMRT may be covered for a diagnosis that is not listed above as proven when at least one of the [listed] conditions is present&quot; with &quot;IMRT may be covered for a diagnosis that is not listed above as proven, <strong>including recurrences or metastases in selected cases</strong>, when at least one of the [listed] conditions is present&quot;</td>
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