

INTENSITY-MODULATED RADIATION THERAPY

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[Instructions for Use](#) ⓘ

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Related Medical Management Guideline
• Proton Beam Radiation Therapy

COVERAGE RATIONALE

See [Benefit Considerations](#) ⓘ

Note: 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.

The following are proven and medically necessary:

- IMRT for [Definitive Therapy](#) of the primary site of the following conditions:
 - Anal cancer
 - Breast cancer where the individual 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 individuals who are post-hysterectomy
 - Central nervous system (CNS) tumors (primary or benign) including the brain, brainstem and spinal cord
 - 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
 - Prostate cancer
 - Tracheal cancer
- Compensator based beam modulation treatment when done in combination with an IMRT indication that is listed above as proven.
- IMRT may be covered for a condition that is not listed above as proven, including recurrences or metastases in selected cases. Requests for exceptions will be evaluated on a case-by-case basis, when at least one of the following conditions is present:
 - A non-IMRT technique would increase the probability of clinically meaningful normal tissue toxicity (e.g., as specified by the [QUANTEC guidelines](#)) and demonstrated on a comparison of treatment plans for the IMRT and non-IMRT technique (e.g., three-dimensional conformal treatment plan).
 - The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the individual must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

The following is unproven and not medically necessary due to insufficient evidence of efficacy:

- IMRT used in conjunction with proton beam radiation 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 guideline 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 Guidelines may apply.

CPT Code	Description
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
77385	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
77386	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex
77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

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HCPCS Code	Description
G6015	Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session
G6016	Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session
G6017	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

DESCRIPTION OF SERVICES

External beam radiation therapy (EBRT) 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 EBRT 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 CRT 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, 2017a; ACR website, 2017b).

Image-guided radiation therapy (IGRT) is 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 bony 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, 2018; ACR/ American Society for Radiation Oncology [ASTRO], 2014).

BENEFIT CONSIDERATIONS

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.

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 (OS), disease-specific survival (DFS) 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) the planning target volume.

NCI published guidelines and protocol requirements were updated in 2006 to include explicit language regarding IMRT when utilized in anatomical regions where target motion can have a significant effect, such as intra-thoracic treatments (2006).

Anal Cancer

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 (5FU) and mitomycin C. The median follow-up time was 34 months. The authors reported that IMRT reduced acute grade 3 + hematologic and gastrointestinal (GI) 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 5FU cisplatin (75%), capecitabine and oxaliplatin (11%) and 5FU 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 OS and DFS rates were 96% and 86%, respectively.

Kachnic et al. (2013) conducted a prospective, multi-institutional phase II trial, Radiation Therapy Oncology Group (RTOG) 0529, assessing dose-painted intensity modulated radiation therapy (DP-IMRT) for anal cancer. The primary outcome was reducing grade 2+ combined acute GI and GU adverse events (AEs) of 5FU and mitomycin-C (MMC) chemoradiation for anal cancer by at least 15% compared with the CRT/5FU/MMC arm from RTOG 9811. Of 52 evaluable patients, the grade 2+ combined acute AE rate was 77%. However, significant reductions were seen in acute grade 2+ hematologic events (73% vs. 85%), grade 3+ GI 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 GI 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 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 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 CRT. 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.

Through evaluation of 6 studies, a Hayes report stated that clinical outcomes following IMRT are similar to those seen with standard CRT for treating anal cancer, although IMRT resulted in fewer high-grade toxicities (2018).

NCCN guidelines for the treatment of anal carcinoma state that IMRT is preferred over 3D CRT, citing benefits of reduced toxicity and local control in multiple studies. (2018).

Professional Societies

American College of Radiology (ACR)

ACR Appropriateness Criteria recommend that while the use of IMRT in the treatment of anal cancer is usually appropriate, studies are still ongoing (2013).

Breast Cancer

Rusthoven et al. (2008) compared dose distribution and normal tissue sparing in partial-breast treatment using 3D-CRT vs. IMRT in 63 patients with breast cancer. The investigators concluded that in T1N0 patients treated with external beam partial-breast radiotherapy, IMRT improves normal tissue sparing in the ipsilateral breast compared with 3D-CRT, without compromising dose delivery to the lumpectomy cavity and clinical target volume.

A multicenter, double-blind, randomized controlled trial was performed to determine whether breast IMRT would reduce the rate of acute skin reaction, decrease pain, and improve QOL compared with standard radiotherapy using wedges. A total of 331 patients were included in the analysis. The authors reported that IMRT improved the homogeneity of the radiation dose distribution and decreased acute toxicity. (Pignol et al, 2008)

Donovan et al. (2007) evaluated 306 women who underwent whole breast radiotherapy after tumor excision for early stage cancer and were randomized to 3D IMRT (test arm) or 2D radiotherapy delivered using standard wedge compensators (control arm). Eligibility criteria included patients judged to be at higher than average risk of radiation-induced normal tissue changes by virtue of breast size and/or breast shape. The greatest dose variation appears to occur in large-breasted women. Patients were evaluated yearly for 5 years after treatment. A total of 240 (79%) patients with 5-year photographs were available for analysis. Change in breast appearance was identified in 71/122 (58%) allocated to standard treatment compared to only 47/118 (40%) patients allocated to 3D IMRT. No significant differences between treatment groups were found in patient reported breast discomfort, breast hardness or QOL. The investigators concluded that the use of IMRT reduces late AEs.

McDonald et al. (2008) evaluated long-term outcomes of adjuvant breast IMRT with a comparison cohort receiving CRT during the same period. A total of 245 breasts were treated in 240 patients: 121 with IMRT and 124 with CRT. Median follow-ups were 6.3 years for patients treated with IMRT and 7.5 years for those treated with CRT. Treatment with IMRT decreased acute skin toxicity of RTOG Grade 2 or 3 compared with CRT (39% vs. 52%). For patients with Stages I-III (n = 199), 7-year Kaplan-Meier freedom from ipsilateral breast tumor recurrence (IBTR) rates were 95% for IMRT and 90% for CRT. For patients with Stage 0 (ductal carcinoma in situ, n = 46), 7-year freedom from IBTR rates with IMRT vs CRT were 92% and 81% respectively. Comparing IMRT with CRT, there were no statistically significant differences in OS, DFS, or freedom from IBTR, contralateral breast tumor recurrence, distant metastasis, late toxicity, or second malignancies. The investigators concluded that patients treated with IMRT had decreased acute skin toxicity, and long-term follow-up shows excellent local control similar to a contemporaneous cohort treated with CRT.

Bhatnagar et al. (2006a) studied 83 breast cancer patients and found that primary breast irradiation with tangential IMRT technique significantly reduces the dose to the contralateral breast 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 CRT. The authors concluded that IMRT for breast cancer was associated with a decrease in acute desquamation compared with a matched control group treated with CRT. 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.

IMRT is one approach that is being evaluated for treating accelerated partial breast irradiation (APBI). A Hayes report reviewed whether APBI is an acceptable treatment alternative to standard whole-breast irradiation (WBI) following breast-conserving surgery in patients with early-stage breast cancer. Evidence from the 11 available studies suggests that APBI delivered by 3-D CRT or IMRT is relatively safe with acceptable toxicity compared to WBI. APBI is as effective as WBI over the short and intermediate term (≤ 5 years). However, conclusions on outcomes exceeding 5 years cannot yet be determined (2017).

Results of the APBI-IMRT-Florence phase 3 randomized trial (NCT02104895) were analyzed and reported by Meattini et al. (2017). Of the 520 women enrolled, 205 fully participated in treatment and all follow up activities (200 receiving APBI-IMRT, 100 receiving standard WBI). Results showed that individuals receiving APBI had an improved health-related quality of life outcome in both the short-term and at 2 years as compared with WBI. The authors concluded that APBI with IMRT represents a valid treatment option and should be strongly considered for selected early breast cancer patients of low risk. For more information on this clinical trial, please go to www.clinicaltrials.gov (Accessed November 20, 2018)

The meta-analysis by Vaidya et al. (2016) examined 5-year data from 9 published randomized trials of PBI (including but not limited to IMRT, alone or as part of a risk-adapted approach) versus WBI for invasive breast cancer treated with breast conserving therapy. There was no difference in breast cancer mortality between participants receiving PBI versus WBI (n=4489). However, a 25% relative risk reduction was identified in non-breast cancer mortality (n=4231) and total mortality, resulting in the authors' conclusion that PBI was superior to WBI for this patient demographic.

A prospective phase II single-arm study by Lei et al. (2013) gathered data on patients seeking breast-sparing therapy via IMRT as the mode of delivery for APBI. Outcome measures included cosmesis, efficacy, and toxicity in 136 patients. At four years, patients and physicians rated cosmesis as excellent/good in 88.2% and 90.5 %, respectively. OS was 96.8%, and cancer-specific survival 100 %. Toxicities were minimal. The authors concluded that APBI-IMRT is a promising treatment option in early stage breast cancer and that further studies are underway.

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 (2018).

Central Nervous System (CNS) Tumors

A Cochrane evidence review sought to compare the efficacy of advanced forms of radiotherapy (including IMRT) delivered in the immediate postoperative period (early) versus at the point of disease recurrence in patients with low grade gliomas. The search identified 1 multi-institution RCT with 311 participants. While individuals from the group treated early experienced a longer period of disease-free progression and had better seizure control than the delayed treatment group, OS for early and delayed treatment was about the same at 7.4 years and 7.2 years, respectively. Reported toxicities were minimal, and QOL was not evaluated for either group. The authors were unable to make a determination whether or not early radiotherapy is better than delayed radiotherapy. Limitations to this study include the lack of QOL and follow up cognitive function data as well as a documented risk of bias (Sarmiento et al., 2015).

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%.

In its CNS cancers guideline, NCCN states that lower doses of targeted radiotherapy (via 3D planning or IMRT) are as effective as higher doses for treatment of low grade gliomas. Additionally, IMRT should be considered when treating meningiomas. IMRT is not the radiotherapy delivery method of choice for glioblastoma, mixed anaplastic oligoastrocytoma, anaplastic astrocytoma, anaplastic oligodendrocytoma and other rare anaplastic gliomas (2018).

Cervical Cancer

Mell et al. (2017) studied IMRT and the incidence of hematologic and GI toxicities in patients with stage IB-IVA, biopsy-proven invasive carcinoma of the cervix through a single-arm, randomized, phase II, multi-institution, international trial (NCT01554397). All 83 patients received daily IMRT concurrently with weekly cisplatin for 6 weeks, with an intracavitary brachytherapy boost given at completion of the chemoradiation regimen. Additionally, the researchers conducted a subgroup analysis on whether the use of positron emission tomography (PET)-based image-guided IMRT (IG-IMRT) had an influence on the development of neutropenia compared to standard IMRT. Post-simple hysterectomy patients were included, initiating the regimen within 8 weeks of surgery. Individuals who underwent

radical hysterectomy with extensive nodal involvement were excluded. Primary outcome measures were either acute grade ≥ 3 neutropenia or clinically significant GI toxicity occurring within 30 days of regimen completion. The median follow-up was 26 months. The incidence of any primary event was 26.5%, significantly less than the 40% hypothesized in historical data. The incidence of grade ≥ 3 neutropenia and clinically significant GI toxicity was 19.3% and 12.0%, respectively. In the analysis on neutropenia, those treated with IG-IMRT (n=35) had a significantly lower incidence (8.6%) compared with the 48 patients who received standard IMRT (27.1%). The differences in the incidence of grade ≥ 3 leukopenia and any grade ≥ 3 hematologic toxicity were considered insignificant between the 2 types of IMRT delivery. The authors concluded that IMRT, compared with standard therapy, reduces both acute hematologic events and GI toxicity and that PET-based IG-IMRT reduces the incidence of acute neutropenia compared with historical data.

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 RTOG 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 OS rate and the DFS 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. (2007) 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 locoregional control for patients in the IMRT and Box-RT groups was 93% and 94%, respectively. IMRT was well tolerated, with significant reduction in acute GI and 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.

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, in treating the para-aortic nodes when necessary, and when high doses are required to treat gross regional lymph nodes disease. 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 is required for proper delivery (2017).

Professional Societies

American College of Radiology (ACR)

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, 2012b).

Esophageal Cancer

Xu et al. (2017) performed a systematic review and meta-analysis to compare IMRT and 3D-CRT in the treatment of esophagus cancer (EC) in terms of dose-volume histograms and outcomes including survival and toxicity. A total of 7 studies were included. Of them, 5 studies (80 patients) were included in the dosimetric comparison, 3 studies (871 patients) were included in the OS analysis, and 2 studies (205 patients) were included in the irradiation toxicity analysis. For the lung in patients receiving doses ≥ 20 Gy and the heart in patients receiving dose = 50 Gy, the average irradiated volumes of IMRT were less than those from 3D-CRT. IMRT resulted in a higher OS than 3D-CRT. However, no significant difference was observed in the incidence of radiation pneumonitis and radiation esophagitis between the 2 radiotherapy techniques. The authors concluded that high-dose delivery of IMRT produces significantly less average percent volumes of irradiated lung and heart than 3D-CRT. IMRT is superior to 3D-CRT in the OS of EC, but showed no benefit on radiation toxicity.

Xi & Lin (2017) reviewed radiotherapy advances for the treatment of EC in a retrospective comparative study. While 3D-CRT is today's standard of care in this diagnosis, the authors conclude that that the dosimetric advantage of IMRT over 3D-CRT can lead to better clinical outcomes. Prospective clinical data are needed.

Deng et al. (2016) performed a retrospective analysis of toxicity and long-term survival of patients with esophageal squamous cell cancer treated with 3D-CRT or IMRT versus conventional two-dimensional radiotherapy (2DRT). The data used for this analysis was gathered from 4 prospective clinical trials conducted at a single institution between 1996-2004 and included 308 participants. Of that number, 254 patients were included in the analysis with 96 being treated with 3D-CRT/IMRT and 158 receiving 2DRT. The rates of \geq Grade 3 acute toxicities of the esophagus and lungs were 11.5% vs 28.5% and 5.2% vs 10.8% in the 3D-CRT/IMRT and 2DRT groups, respectively. The incidences of \geq Grade 3 late toxicity of the esophagus was 3.1% vs 10.7% and lung toxicities were 3.1% vs 5.7% in the 3D-CRT/IMRT and 2DRT groups, respectively. For the 3D-CRT/IMRT group, the 1-year, 3-year and 5-year estimated OS rates were 81%, 38% and 34%, respectively. In the 2DRT group, survivals were 79%, 44% and 31% at 1, 3, and 5 years, respectively. The local control rates at 1, 3, and 5 years were 88% vs 84%, 71% vs 66%, and 66% vs 60% in the 3D-CRT/IMRT and 2DRT groups, respectively. The authors concluded that while there were fewer incidences of acute and late toxicities in patients with EC treated with 3D-CRT/IMRT compared with 2DRT, there was no significant survival benefit with either radiotherapy delivery technique

Lin et al. (2012) performed an analysis of long-term clinical outcomes comparing 3D-CRT (n=413) vs. IMRT (n=263) for EC. Primary outcomes were OS, 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 EC using IMRT significantly decreased the exposure of the heart and right coronary artery when compared with 3D-CRT.

NCCN guidelines for EC 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. (2018).

Head and Neck Cancer (HNC)

In a retrospective analysis, Moon et al. (2016) compared treatment outcomes of different radiotherapy modalities in 1237 individuals with nasopharyngeal carcinoma (NPC). Modalities studied included 2D-RT (n=350), 3D-CRT (n=390), and IMRT (n=497). At 5 years, OS rates for 2D-RT, 3D-CRT, and IMRT were 59.7%, 73.6%, and 76.7%, respectively. In individuals with advanced primary tumors, 5-yr OS was 50.4%, 57.8%, and 70.7% with 2D-RT, 3D-CRT, and IMRT, respectively. The authors concluded that outcomes demonstrated IMRT was superior to 2D-RT or 3D-CRT in cases of advanced primary disease, and that IMRT and 3D-CRT were associated with better outcomes than 2D-RT.

An Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review of radiotherapy for HNC 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 3D-CRT. 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 OS 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 CRT (n=47). The primary endpoint was the proportion of patients with grade 2 or worse xerostomia at 12 months. Median follow-up was 44 months. Six patients from each group died before 12 months and 7 patients from the CRT and 2 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 CRT group (74%). The only recorded acute AE 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 CRT, 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 OS. 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.

To minimize doses to critical structures, NCCN guidelines for HNC state that either IMRT (preferred) or 3D-CRT is recommended for the following conditions: tumors of the maxillary sinus, paranasal/ethmoid sinus, and salivary gland; cancers of the oropharynx, hypopharynx, nasopharynx, glottic/supraglottic larynx and mucosal melanoma (2018).

Mediastinal Tumors

Besson et al. (2016) evaluated toxicities secondary to different radiotherapy modalities and the evolution of those modalities in the treatment of mediastinal tumors associated with Hodgkin's (HL) and non-Hodgkin's lymphoma (NHL). Between 2003 and 2015, 173 individuals with Stage I-III nodal lymphoma were treated at a single institution with either 3D-CRT or IMRT as part of a chemoradiotherapy protocol (HL=64, NHL=5). Of interest, between 2003 and 2006, 16 patients were treated by 3D-CRT vs zero patients treated by IMRT. Between 2007-2009, 16 patients were treated by 3D-CRT vs 1 patient receiving IMRT. Between 2010-2015, 19 patients were treated by IMRT, and zero received 3D-CRT. All patients were followed for 5 years alternately by a radiation oncologist or a hematologist. Results demonstrated local control at 100% in both groups and acute (grade 1 or 2) toxicities of 55% and 71.4% with IMRT vs 3D-CRT, respectively. Authors concluded that the use of IMRT as an improved radiotherapy technique over 3D-CRT has promoted the evolution of improved acute and late outcomes for HL and NHL patients. Longer follow-up is necessary to evaluate very late toxicities, as this study only evaluated acute (grade 1 and 2) toxicities.

In selected patients with HL and NHL 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-CRT (Fiandra et al., 2012; Lu et al., 2012).

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 organs at risk and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. (2018).

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 for its use should be strictly followed (2018).

Pancreatic Cancer

Nagakawa et al. (2017) conducted a phase II clinical trial to evaluate efficacy of neoadjuvant chemoradiotherapy (NACRT) in patients with borderline-resectable pancreatic cancer with arterial involvement. NACRT included IMRT, gemcitabine and S-1 administered to 27 patients between February 2012 and September 2015. Nineteen patients (70.3%) underwent resection. Only 1 patient experienced a local recurrence, and 13 patients (68.4%) developed distant metastasis post-resection. One patient experienced \geq grade 3 GI toxicity. Median OS and 1-year survival rates were 22.4 months and 81.3%, respectively. The researchers concluded that IMRT is effective for borderline-resectable pancreatic cancer, has low GI toxicity, and can be used as a standard radiotherapy.

Wang et al. (2015) conducted a single institution retrospective analysis evaluating efficacy and pain control when IMRT is used for locally advanced pancreatic cancer (LAPC) and metastatic pancreatic cancer (MPC). Participants were identified from the medical record database, selecting 63 patients who were treated between May 2006 and April 2013. All participants received IMRT. Among the 63, 36 received radiotherapy (RT) alone, and 27 received concurrent chemoradiotherapy (CCRT). Non-hematological toxicities of Grades \leq 2 were 44% in both groups, while \geq grade 3 hematologic toxicities in both groups were approximately 14%. Moderate to severe abdominal and/or back pain was reported by 44 patients prior to therapy. Pain elimination or reduction was achieved in 100% of those reporting symptoms prior to RT or CCRT. The median OS for LAPC and MPC patients were 15.7 months and 8 months, respectively. The authors concluded that while both RT and CCRT provided marked pain relief, the use of CCRT resulted in better OS with acceptable toxicities for both LAPC and MPC.

Yovino et al. (2011) evaluated whether improved dose distributions from using IMRT resulted in decreased toxicity when compared to patients who received a similar 5FU based protocol with 3D-CRT in the RTOG 97-04 trial. Forty-six patients with pancreatic/ampullary cancer were treated with CCRT using IMRT. Rates of acute GI toxicity for the IMRT-treated patients were compared with those from RTOG 97-04, where all patients were treated with 3-D 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 3-D 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 CCRT for pancreatic/ampullary cancers. Future clinical trials plan to incorporate the use of IMRT, given that it remains a subject of active investigation.

NCCN guidelines for pancreatic adenocarcinoma state that IMRT with breathhold/gating techniques can result in improved planning target volume coverage with decreased dose to organs at risk. IMRT is increasingly being applied in treatment 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 (2018).

Prostate Cancer

Macchia et al. (2017) conducted a phase I/II clinical trial evaluating adjuvant and salvage simultaneous integrated boost-IMRT (SIB-IMRT) in 124 patients after radical prostatectomy (NCT03233672). Primary outcome measurements were early and late toxicities as well as biochemical relapse-free survival. Median follow up was 30 months. The most notable toxicities were Grade 2 acute GI and GU events, which were documented in 24.2% and 17.7% of patients, respectively. Five-year biochemical relapse-free survival was 86.5%. Conclusions by the authors were that postoperative SIB-IMRT in treatment of prostate cancer was both favorable and encouraging.

Viani et al. (2016) compared IMRT with 3D-CRT for the treatment of prostate cancer through a randomized, phase III clinical trial (NCT02257827). In total, 215 patients were enrolled in the study, randomly selected into the IMRT group (n=109) or the 3D-CRT group (n=106). Primary outcome measures included early and late GU and GI toxicities as well as freedom from biochemical failure, determined through use of Phoenix criteria (PSA + 2 ng/mL nadir). The median follow up period was 3 years. The 3D-CRT arm reported incidences of grade ≥ 2 acute GU and GI toxicities at 27% and 24%, respectively, compared with 9% and 7%, respectively, in the IMRT group. In assessing the rate of grade ≥ 2 late GU and GI toxicities spanning the entire follow-up period, the 3D-CRT group reported 12.3% and 21%, respectively, compared to the IMRT arm which reported 3.7% and 6.4%, respectively. The differences in the 5 year rate of freedom from biochemical failure was statistically insignificant for both groups, at approximately 95%. The authors concluded that the use of IMRT resulted in significantly less acute and late toxicities than 3D-CRT when used in the treatment of prostate cancer.

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 GU toxicity was 11% and 5%, respectively, and the 10-year likelihood of developing grade 2 and 3 late GI 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 CRT 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 GI and urinary morbidity, erectile dysfunction, hip fractures and additional cancer therapy. In a comparison between IMRT and CRT (n=12,976), men who received IMRT were less likely to experience GI 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 GI morbidity. There were no significant differences in rates of other morbidities or additional therapies between IMRT and proton therapy.

NCCN guidelines state that highly CRT, such as IMRT, should be used to treat prostate cancer as IMRT significantly reduces the risk of GI 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. (2018)

Professional Societies

American College of Radiology (ACR)

ACR Appropriateness Criteria states that relative to static fields, IMRT is widely used for prostate cancer treatment, achieving highly conformal dose distributions and a high level of precision in treatment delivery. Photon energy of at least 6 MV is recommended for prostate IMRT, and 5–9 fields are typically used for a plan encompassing the prostate gland (2016).

American Urological Association (AUA)

In collaboration with the Society of Urologic Oncology (SUO) and ASTRO, the AUA guidelines for treating clinically localized prostate cancer state that various radiotherapy options, including IMRT, can be considered as an appropriate option for patients with low, intermediate, and high-risk disease (Sanda et al., 2017)

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.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

The FDA has approved a number of devices for use in IMRT. See the following web site for more information (use product codes MUJ and IYE): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmnm.cfm>. (Accessed November 8, 2018)

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GUIDELINE HISTORY/REVISION INFORMATION

Date	Action/Description
01/01/2019	<ul style="list-style-type: none"> • Reorganized policy template; simplified and relocated <i>Instructions for Use</i> and <i>Benefit Considerations</i> section • Updated and reformatted coverage rationale: <ul style="list-style-type: none"> ○ Simplified content ○ Modified language to clarify the listed services are: <ul style="list-style-type: none"> ▪ Proven and medically necessary (as described) ▪ Unproven and not medically necessary (as described) ○ Replaced references to: <ul style="list-style-type: none"> ▪ “Diagnoses” with “conditions” ▪ “Patient(s)” with “individual(s)” ○ Replaced language indicating “intensity-modulated radiation therapy (IMRT) may be covered for a condition that is not listed as proven, including recurrences or metastases in selected cases, when a non-IMRT technique would <i>substantially</i> increase the probability of clinically meaningful normal tissue toxicity, as demonstrated on a comparison of treatment plans for the IMRT and non-IMRT technique (e.g., three-dimensional conformal treatment plan)” with “IMRT may be covered for a condition that is not listed as proven, including recurrences or metastases in selected cases, when a non-IMRT technique would increase the probability of clinically meaningful normal tissue toxicity (e.g., as specified by the <i>QUANTEC guidelines</i>) and demonstrated on a comparison of treatment plans for the IMRT and non-IMRT technique (e.g., three-dimensional conformal treatment plan)” • Updated list of applicable CPT codes to reflect annual code edits; revised description for 77387 • Updated supporting information to reflect the most current clinical evidence and references • Archived previous policy version MMG068.I

INSTRUCTIONS FOR USE

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Management Guideline 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. UnitedHealthcare West Medical Management 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.

Member benefit coverage and limitations may vary based on the member’s benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.