INTENSITY-MODULATED RADIATION THERAPY

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INSTRUCTIONS FOR USE
This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit 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.

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COVERAGE RATIONALE
Breast Cancer
Intensity-modulated radiation therapy (IMRT) is proven preferentially* for treating breast cancer when homogeneity of dose is essential and the patient has at least one of the following conditions:

- Macromastia as defined by cup size of D or larger
- 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.

IMRT is proven non-preferentially* (offers no clinical advantage over standard therapy) for treating all other cases of breast cancer.
There is no difference in the criteria used for IMRT for male and female patients with breast cancer.

Intensity-Modulated Radiation Therapy: Medical Policy (Effective 07/01/2014)

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Primary Bone and Articular Cartilage Cancer
IMRT is proven preferentially* for treating primary bone and articular cartilage cancer of the skull and face, vertebral column, sacrum and coccyx when sparing the surrounding normal tissue from radiation therapy exposure is essential.

Other Cancers
IMRT is proven preferentially* for treating the following:
- Anal cancer
- Esophageal cancer
- Pancreatic cancer
- Prostate cancer
- Trachea cancer
- Head and neck cancers including the following sites: lip; eye; thyroid; salivary glands; hypopharynx; oropharynx; nasopharynx; other parts of the pharynx not explicitly identified here; oral cavity; tongue; nasal cavities; middle ear; accessory sinuses; larynx; lymph nodes of the head, face and neck; pituitary gland, pineal gland, carotid body; and skin of lip, eyelid, ear and external auditory canal
- Malignant (primary and secondary) and benign nervous system neoplasms of the following: brain including cranial nerves and cerebral meninges, spinal cord including spinal meninges

*See the Benefit Considerations section for more information.

The use of compensator based beam modulation treatment is proven when done in combination with an IMRT indication that is listed above as proven preferentially or non-preferentially.

IMRT is proven non-preferentially* for treating cervical cancer in individuals who have had a hysterectomy.

IMRT is unproven for treating all diagnoses not listed above as proven, including the following:
- Colon cancer
- Gastric cancer
- Gynecological cancer (except where noted above)
- Lung cancer
- Lymphoma
- Pelvic bone cancer
- Primary or secondary liver cancer
- Rectal cancer
- Secondary bone and articular cartilage cancer
- Soft tissue sarcoma and all other neoplasms not listed above as proven

Some studies have examined the use of IMRT for treating other cancers such as colon, rectum, uterus, stomach, liver, lung, lymphoma, and soft tissue neoplasms. However, because of limited studies, small sample sizes and weak study designs, there is insufficient data to conclude that IMRT is safe or effective for treating these neoplasms. There is also little evidence to indicate that IMRT increases survival in patients with these neoplasms.

Intensity-modulated radiation therapy (IMRT) may be covered for a diagnosis that is listed above as unproven for unusual cases when at least one of the following conditions is present:
- The target volume is in close proximity to critical structures that must be protected
• An immediately adjacent area has been previously irradiated and abutting portals must be established with high precision

Requests for these exceptions will be evaluated by an independent radiation oncologist. UnitedHealthcare will make a coverage decision based on this review.

**Intra-fraction localization and tracking systems such as the Calypso® 4D Localization System are unproven for use in guiding radiotherapy.**

Results of available studies suggest that the Calypso System can provide continuous information to guide prostate radiotherapy. However, although this technology has the potential to reduce complications of radiotherapy and improve local tumor control, none of the available studies reported clinical information related to the safety or efficacy of radiation therapy guided by the Calypso System. Further studies are needed to determine whether guidance of radiotherapy with the Calypso System benefits patients who have localized prostate cancer.

**Intensity-modulated radiation therapy used in conjunction with proton beam radiation therapy is unproven.**

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.

**Information Pertaining to Medical Necessity Review (When Applicable)**

**IMRT is medically necessary for treating breast cancer when homogeneity of dose is essential and the patient has at least one of the following conditions:**

- Macromastia as defined by cup size of D or larger
- 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.

**IMRT is medically necessary for the following preferential indications:**

- Primary bone and articular cartilage cancer of the skull and face, vertebral column, sacrum and coccyx when sparing the surrounding normal tissue from radiation therapy exposure is essential
- Anal cancer
- Esophageal cancer
- Pancreatic cancer
- Prostate cancer
- Trachea cancer
- Head and neck cancers including the following sites: lip; eye; thyroid; salivary glands; hypopharynx; oropharynx; nasopharynx; other parts of the pharynx not explicitly identified here; oral cavity; tongue; nasal cavities; middle ear; accessory sinuses; larynx; lymph nodes of the head, face and neck; pituitary gland, pineal gland, carotid body; and skin of lip, eyelid, ear and external auditory canal
- Malignant (primary and secondary) and benign nervous system neoplasms of the following: brain including cranial nerves and cerebral meninges, spinal cord including spinal meninges

**IMRT is medically necessary for indications other than those listed above when at least one of the following conditions is present:**

- The target volume is in close proximity to critical structures that must be protected
- An immediately adjacent area has been previously irradiated and abutting portals must be established with high precision
BENEFIT CONSIDERATIONS

This policy applies to persons 19 years of age and older. IMRT is covered without further review for persons 18 years and younger.

For purposes of benefit administration, when IMRT is considered to be proven non-preferentially, the following 2 conditions apply:

1. If an enrollee has benefits for out-of-network services, and external beam radiation therapy is available in-network, out-of-network intensity-modulated radiation therapy would be covered at the out-of-network benefit level. Travel costs would not be covered in this situation.

2. If an enrollee does not have benefits for out-of-network services ("Standard"), no out-of-network benefit would be available for out-of-network intensity-modulated radiation therapy as long as external beam radiation therapy is available within the network.

When IMRT is proven preferentially, out of network service could be covered at an in-network level of benefits if IMRT is not available as an in-network service. The enrollee-specific benefit document must be consulted to determine what form of coverage exists.

When deciding coverage for use of IMRT for a person who has a life-threatening health condition, refer to the member-specific benefit document language for further information. In some benefit documents, coverage exists for unproven services for persons with life-threatening conditions, under certain circumstances.

BACKGROUND

Intensity-modulated radiation therapy (IMRT) is a specialized form of external beam radiation treatment that allows clinicians to shape radiation doses to more closely match the contours of a tumor. By precisely targeting only the cancerous tissue, clinicians may be able to apply much higher radiation doses to tumors while minimizing unnecessary radiation of surrounding normal tissues. Larger, precisely targeted radiation doses may result in better local control with fewer side effects.

IMRT should be distinguished from conformal radiotherapy. Conformal radiotherapy uses computed tomography (CT)-based treatment planning to construct a precise target and more focused (conformal) delivery of radiation dose. Three-dimensional conformal radiation therapy (3D-CRT) systems are intended to permit higher radiation dosing of tumor tissue, limit dosing of normal tissue, and ultimately improve local control of radiation exposure. IMRT involves adjusting the beam-intensity to permit even more conformal dose distributions. In IMRT, the intensity of the radiation exposure in one portion of the field is modified depending on whether tumor or normal tissue is present in the beam pathway. To do this IMRT divides the beam into multiple beamlets. When the beamlet hits normal tissues, the intensity is lowered, and when the beamlet hits tumor, the intensity is higher. The changing of beam intensity is computer controlled. Conformal radiotherapy does not allow for this type of beam adjustment.

The Calypso 4D Localization System is a device for intra-fraction image guidance. It was developed to further improve targeting of prostate cancer during intensity-modulated radiation therapy by enabling continuous, real-time compensation for patient and organ motion. To use this system, patients must undergo permanent transrectal implantation of a set of Beacon Electromagnetic Transponders in the prostate. Before radiation treatment, a 4D Electromagnetic Array is positioned over the patient, and it collects information about the location of the prostate. This information is intended to provide the radiation oncologist with data on patient position and prostate movement so that radiation from a linear accelerator can be more accurately targeted to the cancerous tissue within the prostate.
CLINICAL EVIDENCE

Veldeman et al. (2008) conducted a systematic review of the evidence behind the use of IMRT for various disease sites. 49 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 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.

The National Cancer Institute (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, such as intra-thoracic treatments (NCI, 2006).

Breast Cancer

Rusthoven et al. (2008) compared dose distribution and normal tissue sparing in partial-breast treatment using 3D-CRT vs. intensity-modulated radiotherapy 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 quality of life compared with standard radiotherapy using wedges. A total of 331 patients were included in the analysis. The dose distribution within the breast was significantly improved with IMRT. Breast IMRT and smaller breast size were significantly associated with a decreased risk of moist desquamation. The investigators concluded that breast IMRT significantly reduced the occurrence of moist desquamation compared with a standard wedged technique (Pignol, 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 quality of life. The investigators concluded that the use of IMRT reduces late adverse effects.

McDonald et al. (2008) evaluated long-term outcomes of adjuvant breast IMRT with a comparison cohort receiving conventional radiation (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 Radiation Therapy Oncology Group 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 were 92% for IMRT and 81% for cRT. Comparing IMRT with cRT, there were no statistically significant differences in overall survival, disease-specific survival, 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. (2006) 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 conventional radiation therapy. The authors concluded that IMRT for breast cancer was associated with a decrease in acute desquamation compared with a matched control group treated with conventional radiation therapy. The authors also concluded that further study of patient symptoms, quality of life, 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, 2007; Bhatnagar, 2006; Bhatnagar, 2004). A study by Selvaraj et al. (2007) compared IMRT, standard radiotherapy, and brachytherapy and found that brachytherapy delivers substantially less radiation to the skin than IMRT.

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.

The National Comprehensive Cancer Network (NCCN) states that target definition in whole breast radiation is best done by both clinical assessment and CT-based treatment planning. A uniform dose distribution and minimal normal tissue toxicity are the goals and can be accomplished using compensators such as wedges, forward planning using segments, IMRT, respiratory gating or prone positioning (NCCN, Clinical Practice Guidelines in Oncology, Breast Cancer 2012).

Written communication from the American Society for Radiation Oncology (ASTRO) indicates that patients with small breast size may not benefit from IMRT. ASTRO recommends that patients whose separation is 25.5 cm or more at mid breast or whose cup size is D or larger may particularly benefit from the improved dose homogeneity with the use of IMRT. This recommendation is based on expert opinion. ASTRO has not published a guideline or policy regarding the use of IMRT for these indications (Written communication from ASTRO, January 21, 2009).

**Bone and Articular Cartilage Cancer**

The evidence for the use of IMRT for the treatment of bone and articular cartilage cancer is limited. Pai Panandiker et al. (2007) evaluated 12 patients who were treated with craniospinal irradiation (CSI) using posteroanterior IMRT. Sixteen children were treated with a conventional field arrangement. Evaluation of the spinal IMRT technique compared with a standard posteroanterior technique revealed a 7% reduction in the target volume receiving 110% or more of the prescribed dose and an 8% increase in the target volume receiving 95% or more of the prescribed dose. Although target homogeneity was improved, the maximum dose delivered in the paraspinous muscles was increased by approximately 8.5% with spinal IMRT compared to the posteroanterior technique.

The National Comprehensive Cancer Network (NCCN) does not mention IMRT for treating bone cancer (NCCN, Clinical Practice Guidelines in Oncology, Bone Cancer 2012).
Other Cancers

Anal Cancer
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 freedom from distant failure were 83.7%, 93.4%, 83.9%, and 92.9%, respectively. The investigators concluded that preliminary outcomes suggest that concurrent chemotherapy and IMRT for anal canal cancers is effective and tolerated favorably compared with historical standards.

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.

The National Comprehensive Cancer Network (NCCN) states that IMRT may be used in place of 3-D conformal radiation therapy in the treatment of anal carcinoma. Multiple pilot studies have demonstrated reduced toxicity while maintaining local control using IMRT for anal cancer. IMRT requires expertise and careful target design to avoid reduction in local control by “marginal miss.” Specific protocols are referenced in the guidelines (NCCN, Clinical Practice Guidelines in Oncology, Anal Cancer 2013).

Central Nervous System (CNS) Neoplasms
Wang et al. (2007) retrospectively reviewed the charts of 78 patients with brain metastases treated by tomotherapeutic intensity-modulated radiosurgery (IMRS) and concluded that IMRS was safe and effective for this group of patients. Narayana et al. (2007) evaluated 20 patients with one to two brain metastases who were treated with hypo-fractionated stereotactic radiotherapy using IMRT. The 1-year local control at the original disease site was 70%. The median overall survival was 8.5 months. The investigators concluded that the preliminary results are comparable to surgery and stereotactic radiosurgery data for solitary brain metastases in terms of local control and overall survival.

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), intensity-modulated radiotherapy (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 organs at risk, AMOA was slightly preferable (Cozzi, 2006).

The National Comprehensive Cancer Network (NCCN) states that every attempt should be made to decrease the radiation dose outside the target volume. This can be achieved with 3-dimensional planning or IMRT (NCCN, Clinical Practice Guidelines in Oncology, Central Nervous System Cancers 2012).

Colon and Rectal Cancer
Freedman et al. (2007) assessed the safety and efficacy of preoperative hypo-fractionated radiotherapy using IMRT and an incorporated boost with concurrent capecitabine in patients with locally advanced rectal cancer. Eight patients completed RT at the initial dose level of 55 Gy. The study was discontinued because of toxicity-six Grade 3 toxicities occurred in 3 (38%) of 8 patients. The investigators concluded that this regimen, using hypo-fractionated RT with an incorporated boost, had unacceptable toxicity despite using standard doses of capecitabine and IMRT. Additional research is needed to determine whether IMRT is able to reduce the side effects during and after pelvic RT with conventional dose fractionation.
The National Comprehensive Cancer Network (NCCN) states that IMRT for treating colon or rectal cancer should only be used in the context of a clinical trial and reserved for unique clinical situations including re-irradiation of recurrent disease after previous radiotherapy (NCCN, Clinical Practice Guidelines in Oncology, Colon Cancer 2013; NCCN, Clinical Practice Guidelines in Oncology, Rectal Cancer 2013).

The American College of Radiology’s (ACR) Appropriateness Criteria employ a rating scale ranging from 1 (least appropriate) to 9 (most appropriate). Under Resectable Rectal Cancer, IMRT received a rating of 1 (investigational use only) (ACR, Resectable Rectal Cancer, 2007).

Esophageal Cancer
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.

The National Comprehensive Cancer Network (NCCN) states that IMRT may be appropriate in selected cases to reduce dose to normal structures such as heart and lungs. Retrospective planning studies comparing 3D conformal versus IMRT for 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 2012).

Gastric Cancer
Good quality clinical trials with larger sample sizes evaluating IMRT for treating gastric cancer are lacking at the present time.

The National Comprehensive Cancer Network (NCCN) states that IMRT has a great potential to reduce radiation-related toxicity by delivering large doses of radiation to target tissues; however, the use of IMRT for gastric cancer remains investigational. IMRT may be appropriate in selected cases to reduce dose to normal structures such as heart, lungs, kidneys and liver (NCCN, Clinical Practice Guidelines in Oncology, Gastric Cancer 2012).

Gynecological Cancer
Jhingran et al. (2012) conducted a phase II feasibility study of pelvic intensity modulated radiation therapy (IMRT) for patients with endometrial cancer to determine whether the treatment is associated with fewer short-term bowel adverse events than standard radiation therapy. Fifty-eight patients were accrued by 25 institutions; 43 were eligible for analysis. Forty-two patients (98%) had an acceptable IMRT plan; 1 had an unacceptable variation from the prescribed dose to the nodal planning target volume. The proportions of cases in which doses to critical normal structures exceeded protocol criteria were as follows: bladder, 67%; rectum, 76%; bowel, 17%; and femoral heads, 33%. Twelve patients (28%) developed grade ≥2 short-term bowel adverse events. The authors concluded that pelvic IMRT for endometrial cancer is feasible across multiple institutions with use of a detailed protocol and centralized quality assurance. This study is limited by a small sample size and lack of randomization and control.

Du et al. (2012) evaluated the dosimetry, efficacy and toxicity of reduced field intensity-modulated radiation therapy (RF-IMRT) for patients with advanced cervical cancer. Sixty patients with stage IIB-IIIB cervical cancer underwent reduced field IMRT (RF-IMRT group) and 62 patients underwent conventional radiotherapy (c-RT group). Treatment response, toxicities and survival were assessed. The mean dose delivered to the planning target volume was significantly higher in the RF-IMRT group than in the c-RT group (61.5 vs. 50.8Gy). IMRT plans yielded better dose conformity to the target and better sparing of the rectal, bladder and small intestine. The RF-IMRT patients experienced significantly lower acute and chronic toxicities with comparable short-term effects than did those treated with conventional RT (CR: 87.7% vs. 88.3%; PR: 7.0% vs. 6.7%). No significant differences were found between treatment groups for 1-year, 3-year and 5-year survival.
overall survival (OS) levels, although the latter approached statistical significance in favor of IMRT, while a significantly higher progression-free survival was seen for IMRT. The authors concluded that RF-IMRT yields improved dose distributions, with lower toxicities, while providing comparable clinical outcomes.

Hasselle et al. (2011) evaluated disease outcomes and toxicity in cervical cancer patients treated with pelvic intensity-modulated radiation therapy (IMRT). Patients treated with extended field or conventional techniques were excluded. Intensity-modulated radiation therapy 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% (95% confidence interval [CI], 68-88%) and 69% (95% CI, 59-81%), respectively. The 3-year pelvic failure rate and the distant failure rate were 14% (95% CI, 6-22%) and 17% (95% CI, 8-25%), respectively. Estimates of acute and late Grade 3 toxicity or higher were 2% (95% CI, 0-7%) and 7% (95% CI, 2-13%), respectively. The authors concluded that intensity-modulated radiation therapy 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. (2011) investigated treatment outcomes and toxicity of intensity-modulated radiotherapy (IMRT) with concurrent chemotherapy for patients with locally advanced cervical cancer. 109 patients with stage IB2-IVA cervical carcinoma treated with IMRT and concurrent cisplatin-based chemotherapy were evaluated retrospectively. The endpoints were overall survival (OS), local failure-free survival (LFFS) and disease-free survival (DFS). The median follow up time for all surviving patients was 32.5 months, with a range from 5 to 75 months. The 3-year OS, LFFS and DFS were 78.2%, 78.1% and 67.6%, respectively. Three (2.7%) patients developed grade 3 or greater acute gastrointestinal (GI) toxicity and 26 (23.9%) patients developed grade 3 or greater hematological toxicity. Five (4.6%) patients developed grade 3 or greater chronic GI toxicity and 7 (6.4%) patients developed grade 3 or greater genitourinary system toxicity. The authors noted that a large, randomized, multi-institutional study is needed to verify the effectiveness of IMRT and concurrent chemotherapy for patients with locally advanced cervical cancer. This study is limited by its retrospective nature.

Varlotto et al. (2006) followed 23 women with gynecologic malignancies who underwent IMRT of the para-aortic (PA) area for a median of 10.9 months. Their preliminary results indicate that IMRT + cisplatin chemotherapy to the PA area of women is safe and is not associated with any clinical sequelae of renal toxicity despite a small decrement in creatinine clearance in most, but not all patients. The authors recommend limiting kidney dose above 15 to 16 Gy when using IMRT to the PA area.

Beriwal et al. (2006) evaluated the use of IMRT for adjuvant treatment of endometrial cancer. The authors stated that their results show excellent local control and low toxicity. However, the study was limited due to short follow-up (median follow-up of 20 months) and small number of patients (n=47). A larger number of patients and longer-term follow-up is needed to confirm these results.

Beriwal et al. (2007) assessed the early clinical outcomes with concurrent cisplatin and extended-field IMRT for carcinoma of the cervix in 36 patients. The investigators concluded that extended-field IMRT with concurrent chemotherapy was tolerated well, with acceptable acute and early late toxicities. The locoregional control rate was good, with distant metastases being the predominant mode of failure.

Beriwal et al. (2008) assessed the clinical outcome in 18 patients with locally-advanced vulvar cancers treated using preoperative chemotherapy with IMRT and concluded that preoperative...
chemotherapy and IMRT were well tolerated with good clinical response and early clinical outcome. Prospective clinical trials with sufficient patient numbers and follow-up are needed to determine the true impact of IMRT in these patients.

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 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.

Beriwal et al. (2006) assessed early clinical outcome of IMRT in the treatment of vulvar cancer and compared dosimetric parameters with 3D conformal radiotherapy (3D CRT) in 15 patients. Seven patients were treated with preoperative chemoradiation, and 8 patients were treated with adjuvant postoperative radiation therapy. Median follow-up was 12 months. In the preoperative group, 5 patients (71%) had clinical complete response and 3 patients (42.8%) had pathologic complete response. In the adjuvant group, 2 patients had recurrences in the treatment field. The 2-year actuarial disease-specific survival was 100%.

Bouchard et al. (2008) assessed disease control and acute and chronic toxicity with aperture-based intensity-modulated radiotherapy (AB-IMRT) for postoperative pelvic irradiation of endometrial cancer in 15 patients. The AB-IMRT plans were used for treatment and were dosimetrically compared with three other approaches: conventional four-field, enlarged four-field, and beamlet-based IMRT (BB-IMRT). Disease control and toxicity were prospectively recorded and compared with retrospective data from 30 patients treated with a conventional four-field technique. At a median follow-up of 27 months, no relapse was noted among the AB-IMRT group compared with five relapses in the control group. AB-IMRT plans significantly improved target coverage (93% vs. 76% of planning target volume receiving 45 Gy for AB-IMRT vs. conventional four-field technique, respectively). The sparing of organs at risk was similar to that of BB-IMRT. The investigators concluded that AB-IMRT provides excellent disease control with equivalent late toxicity compared with the conventional four-field technique.

Van de Bunt et al. (2006) investigated the impact of tumor regression on the dose within cervical tumors and surrounding organs, comparing conventional, conformal, and IMRT in 14 patients. After having delivered about 30 Gy external beam radiation therapy, the primary gross tumor volumes decreased on average by 46% (range, 6.1-100%). Second IMRT plans significantly diminished the treated bowel volume, if the primary gross tumor volumes decreased >30 cc. The investigators concluded that intensity-modulated radiation therapy is superior in sparing of critical organs compared with conventional and conformal treatment, with adequate coverage of the target volumes.

The National Comprehensive Cancer Network (NCCN) states 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 is required for proper delivery. The role of IMRT in cervical cancer continues to be actively evaluated in several prospective multicenter clinical trials. Issues regarding target definition, patient and target immobilization, tissue deformation and reproducibility remain to be validated (NCCN, Clinical Practice Guidelines in Oncology, Cervical Cancer 2012).

Intensity-Modulated Radiation Therapy: Medical Policy (Effective 07/01/2014)

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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, 2010).

Nutting et al. (2011) assessed whether parotid-sparing intensity-modulated radiotherapy (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 quality of life 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 quality of life.

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, 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, 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 quality of life (QOL) and survival outcomes for 203 newly diagnosed nasopharyngeal carcinoma (NPC) patients who were curatively treated by three-dimensional conformal radiotherapy (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

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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. (2007a) 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, 2007).

The National Comprehensive Cancer Network (NCCN) states that IMRT, 3D and 2D 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 2012).

Liver Cancer
Cheng et al. (2003) compared the difference in dose-volume data between three-dimensional conformal radiotherapy (3D-CRT) and IMRT for patients with hepatocellular carcinoma (HCC) and previously documented radiation-induced liver disease (RILD) after 3D-CRT. Sixty-eight patients with HCC who were treated with 3D-CRT were included in the study. The study results indicated that IMRT is capable of preserving acceptable target coverage and improving or at least maintaining the nonhepatic organ sparing for patients with HCC and previously diagnosed RILD after 3D-CRT. The true impact of this technique on the liver remains unsettled and may depend on the exact volume effect of this organ.

The National Comprehensive Cancer Network (NCCN) does not mention IMRT for treating hepatobiliary cancers (NCCN, Clinical Practice Guidelines in Oncology, Hepatobiliary Cancers 2012).

Lung Cancer
It remains to be seen whether the dosimetric improvements achievable with IMRT will lead to significant clinical outcome improvements.

IMRT has shown promise in dosimetry modeling studies for reducing normal tissue complication probability to allow for dose escalation in lung cancer patients. Early clinical reports of IMRT indicate favorable toxicity profiles and tumor control. Prospective trials are underway to further evaluate this technology in the clinical setting (ACR, Nonsurgical Treatment for Non-Small Cell Lung Cancer, 2010).
Liao et al. (2010) conducted a retrospective study comparing disease outcomes and toxicity in non-small-cell lung cancer (NSCLC) patients treated with concomitant chemotherapy and either four-dimensional computed tomography simulation plus intensity-modulated radiotherapy (4DCT/IMRT) or three-dimensional conformal radiotherapy (3DCRT). A total of 496 NSCLC patients at a single institution were treated with concomitant chemoradiotherapy. Among these, 318 were treated with CT/3DCRT and 91 with 4DCT/IMRT. Disease end points were locoregional progression (LRP), distant metastasis (DM) and overall survival (OS). Mean follow-up times in the 4DCT/IMRT and CT/3DCRT groups were 1.3 and 2.1 years, respectively. The authors concluded that treatment with 4DCT/IMRT was at least as good as that with 3DCRT in terms of the rates of freedom from LRP and DM. There was a significant reduction in toxicity and a significant improvement in OS.

Several studies report dosimetric benefits with IMRT for treating lung cancer (Murshen, 2004; Liu, 2004; Grills, 2003).

Chang et al. (2006) compared dose-volume histograms (DVH) in 25 patients with non-small cell lung cancer (NSCLC) treated by photon or proton radiotherapy. The authors found that in all cases, the doses to lung, spinal cord, heart, esophagus, and integral dose were lower with proton therapy compared with IMRT. They concluded that proton treatment appears to reduce dose to normal tissues significantly, even with dose escalation, compared with standard-dose photon therapy, 3D CRT, or IMRT.

Yom et al. (2007) investigated the rate of high-grade treatment-related pneumonitis (TRP) in 151 patients with advanced non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and IMRT. The investigators concluded that in advanced NSCLC patients treated with chemoradiation, IMRT resulted in significantly lower levels of treatment-related pneumonitis (TRP) compared with 3D-CRT.

The National Comprehensive Cancer Network (NCCN) guideline for non-small cell lung cancer states that use of more advanced technologies, such as IMRT, is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints. In nonrandomized retrospective comparisons in patients with locally advanced non-small cell lung cancer treated with concurrent chemotherapy, 4D computed tomography planned IMRT significantly reduced rates of high grade pneumonitis and higher overall survival compared to 3D conformal radiation therapy. When IMRT is used, the National Cancer Institute (NCI) IMRT guideline should be followed and daily image guidance at delivery is recommended for quality assurance. Whenever feasible, respiratory motion should be managed (NCCN, Clinical Practice Guidelines in Oncology, Non-small Cell Lung Cancer 2012).

The National Comprehensive Cancer Network (NCCN) guideline for small cell lung cancer states that use of more advanced technologies, such as IMRT and motion management, is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints. (NCCN, Clinical Practice Guidelines in Oncology, Small Cell Lung Cancer 2013).

Mediastinal, Thoracic and Abdominal Neoplasms
Nieder et al. (2007) compared different radiotherapy techniques in a challenging population (i.e., females with different classes of para-clavicular and mediastinal post-chemotherapy target volumes). These scenarios can be found in stage II Hodgkin's and non-Hodgkin's lymphoma. The authors reported that target volume coverage did not improve significantly with 4-field or IMRT techniques. However, IMRT resulted in better dose reduction to the heart than the other techniques. The median maximum dose to the breasts was lowest with IMRT. The breast volume receiving low doses (15% or less), however, was highest with IMRT. There was also a disadvantage in mean lung dose. The authors stated that the best technique for a given patient depends on age, comorbidity, and the individual risk estimates for breast cancer and cardiac morbidity, respectively.

Girinsky et al. (2006) compared 5 different IMRT treatment plans with conventional treatment and Intensity-Modulated Radiation Therapy: Medical Policy (Effective 07/01/2014)
3D-CRT in 12 patients with mediastinal masses in Hodgkin's disease and found that IMRT plan with dose constraints assigned to the planning target volume and virtual volumes allows better dose conformation than conventional treatment and 3D-CRT, notably with better protection of the heart and coronary arteries. They noted that the "spreading out" of low doses to the rest of the patient's body is of concern.

The National Comprehensive Cancer Network (NCCN) guidelines for lymphoma do not mention IMRT as a radiation therapy option (NCCN, Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas (2012) and Hodgkin Lymphoma (2012)).

**Pancreatic Cancer**

Yovino et al. (2011) evaluated whether improved dose distributions from using intensity-modulated radiation therapy (IMRT) resulted in decreased toxicity when compared to patients who received a similar 5-fluorouracil-based protocol with 3-D 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 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 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 intensity-modulated radiotherapy (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.

The National Comprehensive Cancer Network (NCCN) states that IMRT with breathhold/gating techniques can result in improved planning target volume (PTV) coverage with decreased dose to organs at risk (OARs). IMRT is increasingly being applied for therapy of pancreatic adenocarcinoma in the adjuvant setting with the aim of increasing radiation dose to the gross tumor/tumor bed while minimizing toxicity to surrounding tissues. There is no clear consensus on appropriate maximum dose of radiation when IMRT technique is used (NCCN, Clinical Practice Guidelines in Oncology, Pancreatic Adenocarcinoma 2012).

**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.
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 intensity-modulated radiotherapy (IMRT) for the radical treatment of prostate cancer. IMRT was compared to three-dimensional conformal radiotherapy (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.

Results of a nonrandomized comparison of 3D-CRT and IMRT suggested that high-dose IMRT was feasible and safe, improved dose conformity relative to tumor coverage and exposure to normal tissue, and had a lower risk of late moderate rectal bleeding (Zelefsky 2000). One of the largest prospective studies (n=1100) conducted by the same group of investigators assessed long-term therapeutic outcome and tolerance of 3D-CRT or IMRT, reporting that higher radiation doses were associated with improved local tumor control, biochemical outcomes, and biopsy findings. In this study, IMRT was associated with minimal rectal and bladder toxicity, and the authors concluded that IMRT may have the more favorable risk-to-benefit ratio than standard 3D-CRT (Zelefsky 2001). In 2002, the same investigators conducted a larger prospective study (n=772), reporting that IMRT for high dose radiotherapy resulted in a 81% to 92% three-year actuarial rate of prostate specific antigen (PSA) relapse-free survival, depending on patient disease progression. Patients were treated with a minimum of 81 Gy. Late rates of gastrointestinal toxicity, grades 1 to 3, ranged from 0.5% to 9% and 0.5% to 16% for genitourinary toxicity, grade 1-3. Overall, 28% of patients developed acute grade 2 rectal toxicity (Zelefsky, 2002).

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.

The National Comprehensive Cancer Network (NCCN) recommends that 3D conformal or IMRT techniques should be employed for treating prostate cancer. Daily prostate localization using image-guided radiation therapy (IGRT) is essential for target margin reduction and treatment accuracy. Imaging techniques, including ultrasound, implanted fiducials (an object placed in the field of view of an imaging system for use as a point of reference), electromagnetic targeting and tracking or endorectal balloon can be helpful in improving cure rates and minimizing
complications. The guidelines do not mention intra-fraction localization (NCCN, Clinical Practice Guidelines in Oncology, Prostate Cancer 2012).

In a 2007 guideline for prostate cancer, the American Urological Association (AUA) stated that the advent of IMRT and image guidance radiotherapy either with trans-abdominal ultrasound or the intra-prostatic 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).

The American College of Radiology (ACR) Appropriateness Criteria employ a rating scale ranging from 1 (least appropriate) to 9 (most appropriate). Under locally advanced prostate cancer and clinically localized prostate cancer, IMRT received a rating of 8 (ACR, Prostate cancer, 2011).

**Soft Tissue Sarcoma**
The National Comprehensive Cancer Network (NCCN) states that sophisticated treatment planning with IMRT can be used for soft tissue sarcomas to improve therapeutic effect. Postoperative IMRT following limb-sparing surgery is associated with excellent local control in selected patients (NCCN, Clinical Practice Guidelines in Oncology, Soft Tissue Sarcoma 2012).

**Trachea Cancer**
Clinical trials that include larger patient populations treated with IMRT for trachea cancer are lacking at the present time.

**Calypso Localization System**
Noel et al. (2009) evaluated whether pre- and post-treatment imaging (immediately before and after a radiation therapy treatment fraction) and intermittent imaging (at intervals during a treatment fraction) are accurate predictors of prostate motion during the delivery of radiation. The Calypso 4D Localization System was used to continuously track the prostate during radiation delivery in 35 prostate cancer patients, for a total of 1,157 fractions (28-45 per patient). The results of the study suggested that pre- and post-treatment imaging is not a sensitive method of assessing intra-fraction prostate motion, and that intermittent imaging is sufficiently sensitive only at a high sampling rate. According to the investigators, these findings support the value of continuous, real-time tracking in prostate cancer radiation therapy.

Quigley et al. (2009) evaluated the accuracy and usefulness of the Calypso 4D Localization System and Beacon transponders to continuously monitor tumor location and movement during external beam radiation therapy of the prostate. This clinical trial studied 43 patients at 5 sites. According to the study investigators, the Calypso System permits clinicians to intervene when the prostate moves outside the radiation isocenter, which should decrease adverse events and improve patient outcomes.

**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 Society for Radiation Oncology (ASTRO)/American College of Radiology (ACR)
According to the 2010 ASTRO/ACR Guide to Radiation Oncology Coding, IMRT planning may be clinically indicated when one or more of the following conditions are present:

- The target volume is in close proximity to critical structures that must be protected.
- The volume of interest must be covered with narrow margins to adequately protect immediately adjacent structures.
- An immediately adjacent area has been previously irradiated and abutting portals must be established with high precision.
• The target volume is concave or convex, and the critical normal tissues are within or around that convexity or concavity.
• Dose escalation is planned to deliver radiation doses in excess of those commonly utilized for similar tumors with conventional treatment.

According to the 2010 ASTRO/ACR Guide to Radiation Oncology Coding, the most common sites that support the use of IMRT include the following:

• Primary, metastatic or benign tumors of the central nervous system, including the brain, brain stem and spinal cord,
• Primary or metastatic tumors of the spine where spinal cord tolerance may be exceeded by conventional treatment,
• Primary, metastatic or benign lesions to the head and neck area, including:
  o Orbits
  o Sinuses
  o Skull base
  o Aerodigestive tract
  o Salivary glands
• Carcinoma of the prostate,
• Selected cases of thoracic and abdominal malignancies,
• Selected cases (i.e., not routine) of breast cancers with close proximity to critical structures,
• Anal cancer, gynecological cancer and other pelvic and retroperitoneal tumors that meet the clinical indications listed above,
• Reirradiation that meets the clinical indications listed above.

As stated by ASTRO, other sites that meet the criteria for dose constraints described above should be considered appropriate for IMRT.

Proper IMRT treatment documentation is necessary for accurate reconstruction of prior treatments when a patient presents with a marginal recurrence. This is especially important when the follow-up care is managed at a second treatment facility not involved in the initial IMRT treatment. To address the lack of adequate guidelines in this area, ASTRO developed a set of recommendations and sample forms for documenting IMRT treatments, as well as image-guidance procedures (ASTRO, 2009).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

The FDA has approved a number of devices for use in intensity-modulated radiation therapy (IMRT), including several linear accelerators and multileaf collimators. See the following Web site for more information (use product codes MUJ and IYE): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/PMN.cfm. Accessed October 4, 2013.

The Calypso 4D Localization System is regulated by the FDA as a component of a medical linear accelerator. This device received FDA 510(k) approval on July 28, 2006 as an adjunct to radiation therapy in patients who have undergone permanent implantation of at least two Beacon transponders. See the following Web site for more information: http://www.accessdata.fda.gov/cdrh_docs/pdf6/K060906.pdf. Accessed October 4, 2013.

Additional products
Examples of approved devices and systems are the NOMOS Slit Collimator (BEAK™) (NOMOS Corp.), the Peacock™ System (NOMOS Corp.), the Varian Multileaf Collimator with dynamic arc therapy feature (Varian Oncology Systems), the Saturne Multileaf Collimator (GE Medical Systems), the Mitsubishi 120 Leaf Multileaf Collimator (Mitsubishi Electronics America Inc.), the Stryker Leibinger Motorized Micro Multileaf Collimator (Stryker Leibinger), the Mini Multileaf Collimator, model KMI (MRC Systems GMBH), and the Preference® IMRT Treatment Planning
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Module (Northwest Medical Physics Equipment Inc.). The RayPilot® system (Micropos Medical, Sweden) is not FDA approved for marketing in the U.S.

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 Category III Codes, Intensity Modulated Radiation Therapy (IMRT), Proton Beam Radiotherapy, Proton Beam Therapy, Radiation Oncology Including Intensity Modulated Radiation Therapy (IMRT), Radiation Oncology: External Beam /Teletherapy, Radiation Therapy Services, Radiology: Proton Beam Therapy.

(Accessed October 9, 2013)

APPLICABLE CODES

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

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<td>Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator convergent beam modulated fields, per treatment session</td>
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<tr>
<td>0197T</td>
<td>Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment</td>
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increase late rectal toxicity over conformal prostate-only radiotherapy to 76 Gy? Strahlenther Onkol. 2006;182(9):543-549.


to 76 Gy? Strahlenther Onkol. 2006;182(9):543-549.


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**POLICY HISTORY/REVISION INFORMATION**

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