



INTENSITY-MODULATED RADIATION THERAPY

Policy Number: CS064.~~JK~~

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[Instructions for Use](#) ⓘ

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Related Community Plan Policy

- [Proton Beam Radiation Therapy](#)

Commercial Policy

- [Intensity-Modulated Radiation Therapy](#)

Medicare Advantage Coverage Summary

- [Radiologic Therapeutic Procedures](#)

APPLICATION

This policy does not apply to the states of New Jersey, and Tennessee.

- **For the state of New Jersey, refer to the Medical Policy titled Intensity-Modulated Radiation Therapy (for New Jersey Only)**
- **For the state of Tennessee, refer to the Medical Policy titled Intensity-Modulated Radiation Therapy (for Tennessee Only)**

COVERAGE RATIONALE

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 **in the following circumstances:**
 - **When the left-sided internal mammary nodes are being treated**
 - **Partial breast irradiation when dose is at least 3Gy/fraction** ~~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
 - **Cervical cancer**
 - **Endometrial cancer**
 - Esophageal cancer
 - Head and neck cancers including **lymphoma and solitary plasmacytomas, when treatment includes** the following areas: pharynx (nasopharynx, oropharynx and hypopharynx), larynx, salivary glands, oral cavity (includes the tongue), nasal cavity, ~~and~~ paranasal sinuses
 - Mediastinal tumors **(e.g., lymphomas, thymomas), including tracheal cancer**
 - 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 (e.g., as specified by ~~the~~ **the Radiation Therapy Oncology Group (RTOG)** or 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 policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

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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HCCPS 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

For additional coding guidance, please refer to the Reimbursement Policy titled [Intensity Modulated Radiation Therapy Policy](#).

DESCRIPTION OF SERVICES

External beam radiation therapy (EBRT) delivers **high-energy x-rays, electron, or proton beams** that are generated using ~~a machine called~~ a linear accelerator. **Beams are targeted to destroy cancer cells while sparing surrounding normal tissues. EBRT is used to treat many types of cancer, and also may be used to relieve symptoms in individuals with advanced cancer or cancer that has metastasized (American College of Radiology (ACR), 2019a).**

Intensity-modulated radiation therapy (IMRT) is an advanced mode of high-precision RT that uses computer-controlled linear accelerators to deliver precise radiation doses to a malignant tumor or specific areas within the tumor. IMRT allows for the radiation dose to conform more precisely to the three-dimensional (3D) shape of the tumor by modulating—or controlling—the intensity of the radiation beam in multiple small volumes. IMRT also allows higher radiation doses to be focused on the tumor while minimizing the dose to surrounding normal critical structures (ACR, 2019b).

~~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 CRT 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) **employs imaging to maximize accuracy and precision throughout the entire process of treatment delivery. This process can include target and normal tissue delineation, radiation delivery, and adaptation of therapy to anatomic and biological and positional changes over time in individual patients. It is often used in conjunction with IMRT and other advanced forms of RT (ACR/American Society for Radiation Oncology [ASTRO], 2019c).** 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 boney or soft-tissue anatomy. Other methods use markers placed on the surface of the body or implanted in the body (e.g., optical surface imaging or electromagnetic localization) (ACR website, 2018; ACR/American Society for Radiation Oncology [ASTRO], 2014).

CLINICAL EVIDENCE

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

IMRT has become widely used for a variety of clinical indications, such as tumors of the CNS, head and neck, breast, prostate, gastrointestinal (GI) tract, lung, and gynecologic system, as well as sites previously irradiated. In general, the ability of IMRT to deliver dose preferentially to target structures in close proximity to organs at risk (OAR) and other nontarget tissues makes it a valuable tool enabling the radiation oncologist to deliver dose to target volumes while minimizing dose to adjacent normal tissues (ACR, 2016).

Anal Cancer

Jhaveri et al. (2018) conducted a retrospective cohort analysis using the National Cancer Data Base to identify patients with non-metastatic anal cancer. Patients were required to have histologic confirmed malignancy and concurrent chemoradiation, and were stratified into two groups based on radiation type: IMRT and non-IMRT. A 1:1 propensity score (PS) match was implemented to balance differences in demographics, tumor characteristics and treatment details. The primary endpoint was overall survival (OS). A total of 8,108 patients were identified with a median follow-up time of 54.4 months. After PS matching, 2,334 IMRT patients were matched to 2,334 non-IMRT patients with no imbalances in demographics, tumor characteristics or treatment variables. The multivariable cox proportional hazard model for OS showed that the IMRT group had superior survival compared with the non-IMRT group (HR 0.83, 95% CI: 0.74 – 0.94; P=0.002). The adjusted Kaplan Meier survival analysis showed that IMRT was associated with improved OS at 5 years (74.6% vs. 70.5%; P=0.0022). The authors concluded that for treatment of non-metastatic anal cancer, concurrent IMRT-based CRT is associated with improved survival when compared with non-IMRT based therapy.

Bryant et al. (2018) conducted a retrospective cohort analysis using the Veterans Affairs database to identify patients diagnosed with nonmetastatic, stage I or II, anal squamous cell carcinoma and treated with concurrent chemoradiation therapy between 2000 and 2015. Patients were stratified into two groups based on radiation type: IMRT and conventional RT (CRT). Short-term outcomes included: receipt of 2 cycles of chemotherapy, radiation treatment breaks, grade 3 or 4 hematologic toxicity and hospital admissions for GI toxicity and long-term outcomes included: survival and ostomy placement. Multivariable logistic regression models were used to assess the impact of IMRT on short term and long term outcomes. The overall sample include a total of 779 patients (403 received CRT and 376 received IMRT) with a median follow-up period of 5.9 years. Results showed that treatment with IMRT is associated with decreased treatment breaks for 5 or more days (HR 0.58; 95% CI 0.37–0.91; P=0.02), increased rates of receiving 2 cycles of mitomycin C chemotherapy (OR 2.04; 95% CI 1.22–3.45; P<0.007) and a decreased risk of ostomy due to progression or recurrence (HR 0.60; 95% CI 0.37–0.99; P=0.045). IMRT was not associated with a decreased risk of grade 3 or 4 hematologic toxicity, hospital admission for GI toxicity or cancer-specific survival. The authors concluded that in the real-world setting, use of IMRT offers substantial benefits compared to CRT for patients with anal cancer undergoing concurrent chemoradiation therapy.

Han et al. (2014) conducted a prospective cohort study to evaluate toxicity, **quality of life (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 and 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, RTOG 0529, assessing dose-painted IMRT (DP-IMRT) for anal cancer. The primary outcome was reducing grade 2+ combined acute GI and genitourinary (GU) adverse events (AEs) of 5-fluorouracil (5FU) and mitomycin-C (MMC) chemoradiation for anal cancer by at least 15% compared with the conformal RT (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.

~~Kachnic et al. (2013) conducted a prospective, multi-institutional phase II, Radiation Therapy Oncology Group trial (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 genitourinary (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.~~

Hayes reports titled "Intensity Modulated Radiation Therapy (IMRT) for Anal or Rectal Cancer" evaluated 10 studies specific to anal cancer and 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 (2015/2018). 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 3--D CRT, citing benefits of reduced toxicity **while maintaining** ~~and~~ local control in multiple studies (NCCN 2018⁹).

Professional Societies

American College of Radiology (ACR)

ACR Appropriateness Criteria states that in terms of the dosage of ionizing radiation, IMRT can reduce the dose to normal structures and is associated with decreased acute toxicity when compared to conventional RT for anal carcinoma. They recommend IMRT use as "usually appropriate" if given outside of a protocol setting and note that further evaluations are underway (Hong et al., 2014).

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).

Jagsi et al. (2018) conducted an RCT comparing IMRT and deep inspiration breath hold (DIBH) versus standard, free-breathing, forward-planned, 3D-CRT in individuals with left-sided, node-positive breast cancer in whom the internal mammary nodal region was targeted. The purpose of the study was to determine whether using these technologies reduces cardiac or pulmonary toxicity during breast RT. Endpoints included dosimetric parameters and changes in pulmonary and cardiac perfusion and function, measured by single photon emission computed tomography (SPECT) scans and pulmonary function testing performed at baseline and 1 year post treatment. Of 62 patients randomized, 54 who completed all follow-up procedures were analyzed. Mean doses to the ipsilateral lung, left ventricle, whole heart, and left anterior descending coronary artery were lower with IMRT-DIBH; the percent of left ventricle receiving ≥ 5 Gy averaged 15.8% with standard RT and 5.6% with IMRT-DIBH. SPECT revealed no differences in perfusion defects in the left anterior descending coronary artery territory, the study's primary endpoint, but did reveal statistically significant differences ($P = .02$) in left ventricular ejection fraction (LVEF), a secondary endpoint. No differences were found for lung perfusion or function. The authors concluded that this study suggests a potential benefit in terms of preservation of cardiac ejection fraction among patients with left-sided disease in whom the internal mammary region was targeted. Future studies are essential, including comparative evaluation of outcomes and the impact of advances in radiation treatment planning and delivery, in order to inform and shape clinical practice and policy.

Meattini et al. (2017) used data from the Accelerated Partial Breast Irradiation Intensity Modulated Radiation Therapy (APBI-IMRT)-Florence phase 3 randomized clinical trial (NCT02104895) to compare health-related (HR)QOL in women with breast cancer (BC) and who were treated with either APBI or standard whole breast irradiation (WBI). Assessments were completed at the beginning and end of RT, and at the 2-year follow-up visit. A total of 205 women completed the HRQOL protocol of which 105 received APBI-IMRT and 100 received standard WBI. After adjusting for difference between the cohorts, at the end of treatment and 2 years later, women treated with APBI-IMRT reported better QOL related to physical, role, emotional and social functioning, as well as symptoms including fatigue, pain, dyspnea, insomnia and appetite loss compared with woman treated with standard WBI ($p < 0.01$). The authors concluded that early BC treated with APBI-IMRT showed improved short-term and 2 year HRQOL and should be strongly considered for patients of low risk.

Livi et al. (2015) conducted a phase III randomized controlled trial (NCT02104895) comparing local recurrence and survival in woman with early stage breast cancer (maximum diameter 2.5 cm) and treated with either APBI-IMRT or conventional WBI. Women randomized to the APBI-IMRT arm ($n=260$) received a dose of 30 Gy in 5 non-consecutive daily fractions at 6Gy/fraction (2 weeks of treatment) and those randomized to the WBI arm ($n=260$) received a total of 50 Gy in 25 fractions, followed by a boost on a

surgical bed of 10 Gy in 5 fractions, delivered by direct external electron beam. The primary endpoint was the ipsilateral breast tumor recurrence (IBTR) rate and secondary outcomes included OS, acute and late side effects and cosmetic results. At a median follow-up of 5 years, there was no difference in OS rates between the two arms. The APBI-IMRT cohort had significantly better results as it relates to acute toxicity ($p=0.0001$), late toxicity ($p=0.004$) and cosmetic results ($p=0.045$). The authors concluded that their results may aid clinicians in selecting candidates for APBI-IMRT, which is an effective technique and offers a significantly better toxicity profile.

Lei et al. (2013) used data from a multicenter phase II non-randomized clinical trial (NCT 01185145, still ongoing) to provide a four-year clinical update. This study's final study protocol included patients age 40 and older with stage 0/I ductal carcinoma in situ (DCIS) breast cancer and negative margins ≥ 0.2 cm. Patients were treated with APBI using IMRT. Outcomes of interest included treatment efficacy, pain, cosmesis and treatment-related toxicity and were evaluated at 4–6 weeks after treatment and every 3–4 months up to 4 years. The final analysis included 136 patients with a median follow-up period of 53.1 months (range 8.9–83.2). At 4 years, the Kaplan-Meier estimates were 0.7% for ipsilateral breast tumor recurrences, 0% for contralateral breast failure, 0.9% for distal failure, 96.8% for OS and 100% for cancer-specific survival. At last follow-up, 97.0% of patients rated breast pain as none/mild and 88.2% rated cosmesis as excellent/good. Toxicities were mild (1.4%) edema, and mild (2.2%) or moderate (1.4%) telangiectasia. The authors concluded that 4-year results of APBI-IMRT demonstrate excellent local control, survival, cosmetic results and toxicity profile, and warrants further investigation.

Donovan et al. (2007) conducted a prospective, multicenter, phase III randomized clinical trial to compare 3D-IMRT and standard two dimensional 2D radiotherapy with wedge compensators to evaluate late AEs and QOL among patients with early breast cancer (T1 – 3a N0-1 M0) and judged to be at higher than average risk of radiation-induced normal tissue changes by virtue of breast size and/or breast shape. All enrolled patients ($n=306$, 156 received Standard 2D and 150 received 3D-IMRT) received whole breast RT as 50 Gy in 25 fractions over 5 weeks and a boost of 10 Gy in 5 fractions to the 90% isodose (11.1 Gy to 100%) in 5 fractions. The primary endpoint was change in breast appearance (scored from serial photographs), secondary endpoints included self-assessed breast discomfort and hardness, and QOL. At 5 years, 240 patients (122 received Standard 2D and 118 received 3D-IMRT) completed photograph compliance. Patients treated with standard 2D RT were more likely to have a breast appearance change than patients treated with IMRT (OR 1.7; 95% CI 1.2–2.5; $P=0.008$). Significantly fewer patients who received 3D-IMRT developed clinician assessed palpable induration in the center of the breast ($P=0.02$), pectoral fold ($P=0.006$), inflammatory fold ($P=0.009$) and at the boost site ($P<0.001$). There was no significant difference in patient reported breast discomfort, hardness or QOL between the arms. The authors concluded that use of 3D-IMRT reduces late radiation AEs.

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.

Hayes Reports titled "Accelerated Partial Breast Irradiation for Breast Cancer Using Conformal and Intensity-Modulated Radiation Therapy" reviewed whether APBI is an acceptable treatment alternative to standard WBI following breast-conserving surgery in patients with early-stage breast cancer. Evidence from 12 available studies suggests that APBI delivered by 3D-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 (2016/2018).

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 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 QOL 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 (2018⁹).

Central Nervous System (CNS) Tumors

A Cochrane evidence review sought to compare the efficacy of advanced forms of **RTradiotherapy** (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 (**Karim et al., 2002**). 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 **RTradiotherapy** is better than delayed **RTradiotherapy**. 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).

Rieken et al. (2011) conducted a retrospective study to investigate treatment outcome and prognostic factors after postoperative craniospinal irradiation (CSI) RT in patients with medulloblastomas (MB). Sixty-six patients (24 > 18 years of age) were treated at a single institution between 1985 and 2009. All patients underwent initial neurosurgical tumor resection (47% complete resection), and all underwent postoperative CSI with additional boosts to the posterior fossa in all but 2 patients. RT was delivered with Cobalt before 1991 and with linear accelerators afterward according to standard protocols. Three patients were treated with helical IMRT via tomotherapy. Boosts to the posterior fossa were applied with conventional photon RT with two lateral opposing fields in 48 patients; and in 15 patients, 3-D cross-sectional image-based plans were employed with 3 using a stereotactic setting. Regarding chemotherapy, 47 of the 66 patients received chemotherapy prior to CSI, with adults representing less than half of that number. Median follow-up was 93 months. Overall survival (OS), and local and distant PFS were 73%, 62%, and 77% at 60 months. Macroscopic complete tumor resection, desmoplastic histology and early initiation of postoperative RT within 28 days were associated with improved outcome. The addition of chemotherapy was associated with slightly enhanced acute side effects, causing treatment delay or interruptions due to hematological toxicity in 15% of patients opposed to 6% in RT alone. However, chemotherapy did not improve OS. Study limitations include study design and small sample size. The authors concluded that complete resection of MB followed by CSI resulted in longer survival rates in both children and adults. Delayed initiation of CSI is associated with poor outcome. The role of chemotherapy, especially in the adult population, must be further investigated in clinical studies.

Milker-Zabel et al. (2007) conducted an analysis of a single institution's long term experience with IMRT in patients with complex-shaped meningioma of the skull base. Milker-Zabel et al. (2007) evaluated Over a 7-year period, 94 patients with meningiomas of the skull base who were treated with IMRT. Twenty-six patients received RT as primary treatment, 14 patients received postoperative IMRT for residual disease, and 54 patients were treated after local recurrence. Median total dose was 57.6 Gy given in 32 fractions. During a median follow-up period of 4.4 years, and overall local control was 93.6%. %. Sixty-nine patients had stable disease based on computed tomography (CT)/magnetic resonance imaging (MRI), 19 had tumor volume reduction after IMRT, and 6 patients showed local tumor progression a median of 22.3 months after RT. In 39.8% of the patients, preexisting neurologic deficits improved. The authors concluded that IMRT is an effective and safe treatment modality for long-term local control of especially complex-shaped and otherwise difficult to treat meningioma of the skull base with lower risk for AEs. Furthermore, IMRT offers the possibility of highly conformal irradiation, while sparing adjacent critical radiosensitive structures with the potential of dose escalation for malignant meningiomas.

Karim et al. (2002) conducted a multicenter randomized trial to assess the efficacy of early postoperative RT for adult patients with cerebral low-grade glioma (LGG). Post-surgical patients (n=311) were accrued and randomized from March 1986 through September 1997, with 290 patients identified as eligible and

assessable. One treatment group was allocated for early conventional RT (54 Gy in 6 weeks) within 8 weeks of the day of surgery (the treated arm). The control arm received no postoperative RT until the tumor showed progression. Both groups were followed every 4 months during the first 2 years after randomization, and annually thereafter. The median follow up period was 5 years. Of the 290 patients, the treatment arm showed a significant (log-rank $p = 0.02$) improvement in time to progression but not in OS, with a median follow-up of 5 years. The 5-year estimates were 63% vs. 66% (OS) and 44% vs. 37% (time to progression) for the treated and control arms, respectively. The authors concluded that the significantly longer time to progression of the patients in the early RT group treated with conventional techniques such as were used in this study indicates that, at present, routine postoperative and early RT may be advisable for adult patients with cerebral LGG.

In its CNS Cancers guideline, NCCN states that lower doses of targeted conformal RT radiotherapy (including 3D CRT and planning or IMRT) are recommended as effective as higher doses for treatment of low grade anaplastic gliomas, infiltrative astrocytomas, oligodendrogliomas, glioblastomas and meningiomas. Higher doses of RT are found to be no more effective than lower doses. For medulloblastomas, the guidelines state that for patients at average risk, a regimen of IMRT or proton CSI alone or with chemotherapy are both viable treatment options (2019). 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

Tsuchida et al. (2019) conducted a retrospective cohort analysis to compare clinical outcomes and toxicity incidence among patients diagnosed with cervical cancer that underwent radical hysterectomy and were treated with either 3D-CRT or IMRT. Concurrent chemotherapy was not given during the study. Outcomes of interest included GI, GU and hematologic (HT) toxicities, and OS, disease-free survival (DFS) and loco-regional control (LRC). A total of 73 patients (33 received 3D-CRT and 40 received IMRT) were included in the final analysis. The median follow-up period differed between the group with 82 months in the 3D-CRT group and 50 months in the IMRT group ($P < 0.001$). After four years, there was no difference OS or DFS between the groups. Loco-regional recurrence was more frequent in patients with vaginal invasion reported in the post-operative pathological report (17% vs. 2.3%; $P = 0.033$). GI obstruction was more frequent in the group that received 3D-CRT vs. IMRT (27% vs. 7.5%; $P = 0.026$) and surgical intervention for the obstruction was higher in the 3D-CRT group as well (18% vs. 0%; $P = 0.005$). There was no significant difference in acute GI, GU or HT toxicities however, in the IMRT group, there were fewer late toxicities, $GI \geq 2$ ($P = 0.026$) and $GU \geq 2$ ($P = 0.038$). The authors concluded that their results show that IMRT could reduce the incidence of late severe GI obstruction and that additional studies are warranted.

Mell et al. (2017) conducted an international, multicenter, single-arm phase II clinical trial ((NCT01554397, still ongoing) to evaluate the incidence of hematologic and GI toxicities in patients with stage IB-IVA, biopsy-proven invasive carcinoma of the cervix among patients who were treated with IMRT. 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) **conducted a case series that** 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 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. (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~~9~~).

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, 2012).

Endometrial Cancer

Klopp et al. (2018) conducted a multicenter, phase III randomized clinical trial (NCT01672892, still ongoing) to evaluate patient-reported acute toxicity and QOL in patients with invasive cervical or endometrial cancer and treated with standard 4 field pelvic RT or pelvic IMRT. The primary end point, change in acute GI toxicity, was measured at baseline and end of RT (5 weeks) using the bowel domain of the Expanded Prostate Cancer Index Composite (EPIC). The secondary endpoints, measured at the same points in time, were change in GU toxicity and the extent to which it interfered with daily activities. To measure GU toxicity, the urinary domain of the EPIC was used and to determine the extent to which genitourinary toxicity impacted daily activities, the Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE), FACT-Cx, FACT-G and Trial Outcome Index were used. A total of 278 patients were included in the final analysis, 149 received standard RT and 129 received IMRT. Compared to baseline, the standard RT arm had larger mean EPIC bowel and urinary score declines compared with the IMRT arm (-26.3 vs. -18.6; P=0.05 and -10.4 vs. -5.3, P=0.03, respectively). The FACT-Cx mean scores showed a decline of 4.9 points in the standard RT group vs. 2.7 points in the IMRT group (P=0.015). There was no difference between the arms in the FACT-G subscale or Trial Outcome Index scores. In addition, the PRO-CTCAE results showed that at the end of therapy, more patients in the standard RT arm experienced diarrhea frequently or almost constantly compared with the IMRT arm (51.9% vs. 33.7%, respectively; P=0.01) and were taking antidiarrheal medications four or more times

daily (20.4% vs. 7.8%, respectively; P=0.04). The authors concluded based on the patient's perspective, pelvic IMRT was associated with significantly less acute GI and urinary toxicity.

Shih et al. (2016) conducted a retrospective cohort analysis to evaluate the rate of bowel obstruction (BO) in patients with endometrial and cervical cancer and underwent post-operative pelvic RT with either 3D-CRT or IMRT. Patients who received definitive or palliative RT, were diagnosed with BO due to disease progression or had stage IV disease were excluded. The primary outcome was to determine whether IMRT was associated with a lower incidence of BO and secondary objective was to identify other potential risk factors for BO. A total of 224 patients were identified (152 were diagnosed with endometrial cancer and 72 were diagnosed with cervical cancer) and the median follow-up time was 67 months. The IMRT group (n=120) consisted of 80 patients with endometrial cancer and 40 patients with cervical cancer and the 3D-CRT group (n=104) consisted of 72 patients with endometrial cancer and 32 patients with cervical cancer). At 5 years, the BO rate was lower in the IMRT group compared with the 3D-CRT group (0.9% vs. 9.3%, P=0.006, respectively). Patient characteristics such as age, prior abdominal surgeries and cancer type did not impact the rate of BO however, patients with a BMI \geq 30 were less likely to develop a BO (2.6% vs. 8.3%, P=0.03). The authors concluded that use of post-operative IMRT for endometrial and cervical cancers is associated with a significant reduction in BO and that if other researchers confirm these findings it will further solidify the benefit of IMRT in these types of cancers.

Barillot et al. (2014) conducted a multicenter, single arm phase II clinical trial to test their hypothesis that patients with stage I or II endometrial cancer and treated IMRT would have an acute grade 2 GI toxicity incidence rate of less than 30%. All patients underwent a total hysterectomy with bilateral oophorectomy, and those with chronic inflammatory bowel disease, inadequate surgery, previous pelvic radiation, another progressive cancer or contraindication to contrast were excluded. The primary endpoint was acute GI toxicity, grade 2 or higher and secondary endpoints were GU toxicity and any other type of toxicity during radiation and through the following 10 weeks. A total of 49 patients were enrolled, at the end of IMRT, a total of 47 patients were available for analysis and at week 15, 46 patients remained. At the completion of IMRT, 13 patients (27.1%, 95% CI 14.5-39.7%) developed at least one grade 2 GI toxicity and no patients experienced grade 3 GI toxicity. Among the 36 patients who received brachytherapy, 8 patients had experienced grade 2 GI toxicity at the time of insertion and also experienced grade 2 diarrhea during the previous weeks therefore, the investigators concluded that brachytherapy did not increase the severity of diarrhea induced by IMRT. Nineteen percent (95% CI 8.9-32.6) experienced grade 2 cystitis or urinary frequency however, these resolved by week 15. The investigators concluded that post-operative IMRT resulted in an acute, grade 2 GI toxicity incidence rate of less than 30% in patients with stage I or II endometrial cancer, and that additional research examining late toxicity and survival in this population is needed.

Esophageal Cancer

Xu et al. (2017) performed a systematic review and meta-analysis to compare IMRT and 3D-CRT in the treatment of esophageal 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 \geq 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 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 time, interval to local failure and interval to distant metastasis. Compared with IMRT, 3D-CRT patients had a significantly greater risk of dying (72.6% vs. 52.9%) and of locoregional recurrence. No difference was seen in cancer-specific mortality or distant metastasis. An increased cumulative incidence of cardiac death was seen in the 3D-CRT group, but most deaths were undocumented.

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

NCCN guidelines for **esophageal and esophagogastric junction cancers** EC state that IMRT is appropriate in clinical settings where reduction in dose to **OAR**organs-at-risk (e.g., heart and lungs) is required that cannot be achieved by 3D techniques (2018⁹⁹).

Head and Neck Cancer (HNC)

Oertel and colleagues (2019) conducted a single-center retrospective analysis investigating the impact of different radiation dose regimens on local control and OS in individuals with extramedullary head and neck plasmacytoma (EMP). A total of 33 radiation courses were administered to 27 patients between January 2005 and January 2017 (IMRT n=14, conventional RT n=19). The median RT dose was 45 Gy (range: 12-55.8), the local control rate was 76% (93% for primary vs. 61% for secondary EMP lesions). A complete response (CR) rate to local RT was achieved for 42% of lesions (67% for primary vs. 22% for secondary EMP lesions). The overall response rate (ORR) for lesions treated with high-dose regimens (> 45 Gy) versus low-dose regimens (\leq 45 Gy) was 87% versus 67%, respectively. The median survival for the high-dose RT group was significantly longer. In subgroups analysis, primary EMP patients treated with high-dose RT had a non-significant higher ORR (100% vs. 80%, respectively) with longer duration of local control and longer survival than patients in the low-dose group. There were no significant differences detected in secondary EMP patients treated with high-dose RT regarding ORR and survival (60% vs. 62%, respectively). RT was well tolerated without significant AEs. The authors concluded that compared with secondary EMP, patients with primary tumor manifestations are associated with better outcomes with a dose \leq 45 Gy, resulting in a CR rate that is comparable to high-dose regimens. Lower-dose RT also appears to be an effective treatment for controlling tumor progression. Further studies with a larger sample size are needed to confirm the results of this analysis.

Lertbutsayanukul et al. (2018) conducted a randomized phase III study to compare acute and late toxicities as well as survival outcomes between sequential (SEQ)-IMRT and SIB-IMRT in nasopharyngeal carcinoma (NPC). Patients with stage I-IVB disease were randomized to receive SEQ-IMRT (2 Gy \times 25 fractions to low-risk planning target volume (PTV) followed by a sequential boost (2 Gy \times 10 fractions) to high-risk PTV) or SIB-IMRT (treating low- and high-risk PTVs with doses of 56 and 70 Gy in 33 fractions). Between October 2010 and September 2015, 209 patients completed treatment (SEQ n=102, SIB n=107) and were included in the analysis. The majority had undifferentiated squamous cell carcinoma (82%). Mucositis and dysphagia were the most common grade 3-5 acute toxicities. There were no statistically significant differences in the cumulative incidence of grade 3-4 acute toxicities between the two arms (59.8% in SEQ vs. 58.9% in SIB). Common grade 3-4 late toxicities for SEQ and SIB included hearing loss (2.9 vs. 8.4%), temporal lobe injury (2.9 vs. 0.9%), cranial nerve injury (0 vs. 2.8%), and xerostomia (2 vs. 0.9%). With the median follow-up of 41 months, 3 year PFS and OS rates in the SEQ and SIB arms were 72.7 vs. 73.4% and 86.3 vs. 83.6%, respectively. The authors concluded that while both techniques

provide excellent survival outcomes with few late toxicities, SIB-IMRT with a satisfactory dose-volume constraint to nearby critical organs is the technique of choice for NPC treatment due to its convenience.

Tandon et al. (2018) conducted a prospective, single-institution, non-blinded randomized study comparing two fractionation schedules, simultaneous integrated boost (SIB)-IMRT and simultaneous modulated accelerated RT (SMART) boost in individuals with Stage III or non-metastatic Stage IV locally advanced head and neck cancer. Sixty patients met inclusion criteria and were randomized into the control arm using the standardized technique (SIB-IMRT) or the study arm who received RT using the SMART boost technique. All patients received weekly cisplatin-based concurrent chemotherapy at 40 mg/m². In the control arm, patients received 70, 63 and 56 Gy in 35 fractions to clinical target volumes (CTV) 1, 2 and 3, respectively. In the study arm, patients received 60 and 50 Gy to CTV 1 and CTV 3, respectively. Toxicities, PFS, and OS were compared between both arms. Baseline patient-related characteristics were comparable between the arms except for primary site of tumor. No significant differences were noted in acute toxicities except for fatigue which was statistically higher for control arm. No significant differences in 2-year late toxicities were observed. The median follow-up duration was 25.5 months (range 1.8 - 39.9 months). The 2-year PFS was 53.3% and 80%, and the 2-year OS was 60% and 86.7% for the control and study arms, respectively. The authors concluded that the SMART boost technique can be a feasible alternative fractionation schedule that reduces the overall treatment time, maintaining comparable toxicity and survival compared with SIB-IMRT. However, given the lack of phase III trials and longer survival studies, such a fractionation schedule should only be used in a clinical trial.

In 2018, the International Lymphoma Radiation Oncology Group conducted a literature review and developed guidelines covering staging, work-up, and RT management of patients with plasma cell neoplasms. With a localized plasmacytoma in the bone or in extramedullary (extraosseous) soft tissues, definitive RT is the standard treatment. It provides long-term local control in solitary bone plasmacytomas and is potentially curative in the extramedullary cases. On the basis of comparative treatment planning (comparison dose-volume histogram) and determination of the priority of the OARs to protect, the radiation oncology team should make a clinical judgment as to which treatment technique to use. In some situations, more conformal techniques such as IMRT, helical-IMRT, or volumetric arc therapy (VMAT) approaches may offer significantly better sparing of critical normal structures, usually at the cost of a larger total volume of normal tissue irradiated, but with a lower dose (Tsang, et al.)

In a retrospective analysis, Moon et al. (2016) compared treatment outcomes of different **RT** 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 **RT** radiotherapy for HNC found that while IMRT is more successful than traditional **RT** 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 **RT** 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; 7 patients from the CRT 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 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 CRT. 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 (20189). **RT is also the intervention of choice for solitary plasmacytoma. While the optimal radiation dose is not known, the dose used in most published papers ranges from 30-60 Gy (2020).**

Mediastinal Tumors

Bradley et al. (2015) conducted a multi-institution, open-label randomized, two-by-two factorial, phase III clinical trial where patients, who were diagnosed with unresectable stage III non-small-cell lung cancer (NSCLC), were randomized to receive concurrent chemotherapy of carboplatin and paclitaxel with or without cetuximab, and either 60-Gy (standard-dose) or 74-Gy (high-dose) radiation therapy. The primary outcome was OS and secondary outcomes included PFS, local regional tumor control and toxicity. In this study, 166 patients received standard-dose chemoradiotherapy, 121 patients received high-dose chemoradiotherapy, 147 patients received standard-dose chemoradiotherapy and cetuximab, and 110 patients received high-dose chemoradiotherapy and cetuximab. Patients who received standard-dose radiotherapy had a longer median OS compared with patients who received high-dose radiotherapy (28.7 vs. 20.3 months; hazard ratio [HR] 1.38, 95% CI 1.09–1.76; p=0.004). In addition, use of cetuximab was associated with a higher rate of grade 3 or worse toxicity, 86% (205/237) vs. 70% (160/228); p<0.0001. The authors concluded that 74-Gy radiation, given in 2-Gy fractions with concurrent chemotherapy, was not better than 60-Gy plus concurrent chemotherapy, and may be potentially harmful. In addition, cetuximab added to concurrent chemoradiation and consolidation treatment did not benefit OS. A secondary analysis of the NRG Oncology RTOG 0617 RCT (Chun et al. 2016) was conducted to evaluate OS, PFS, LF distal metastasis and adverse event between those who received IMRT vs. 3D-CRT. A total of 482 patients who were diagnosed with stage III NSCLC were treated. Of those, 53% (n=254) received 3D-CRT (57.1% received standard dose and 42.9% received high dose RT) and 47% (n=228) received IMRT (59.2% received standard dose and 52.6% received high dose RT). At baseline, slightly more patients in the IMRT group had stage IIIB/N3 disease than patients in the 3D-CRT group (38.6% vs. 30.3%; p=0.056), more patients in the IMRT group had staging by positron emission tomography than patients in the 3D-CRT group (94.3% vs. 88.2%, p=0.019) and patients treated with IMRT were less likely to have completed high school or post-secondary education compared with patients in the 3D-CRT group (p=0.01). After treatment, there were no differences in 2-year rates of OS, PFS, local failure, and distal metastasis-free survival between the IMRT and 3D-CRT groups. IMRT was associated with less grade ≥ 3 pneumonitis (7.9% vs. 3.5%, p=0.039) and lower doses of radiation to the heart (V20, V40, and V60; p<0.5). Furthermore, after adjusting for differences between the groups, the volume of the heart receiving 40-Gy was significantly associated with OS (p<0.05). The authors concluded that in this early analysis of outcomes, IMRT was associated with lower rates of severe pneumonitis, lower doses of radiation to the heart, and by reducing those, IMRT may be associated with improved OS in the long term. They also stated that continued follow-up of this population is essential to further clarify whether differences in long-term survival exist between treatment with IMRT and 3D-CRT.

Besson et al. (2016) evaluated toxicities secondary to different **RT** 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 ~~RT~~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).~~

2019 NCCN guidelines for NSCLC state that advanced technologies such as 4D-CT simulation, IMRT/VMAT, IGRT, motion management strategies, and PBRT have been shown to reduce toxicity and increase survival in nonrandomized trials. IMRT is associated with a nearly 60% decrease in high-grade radiation pneumonitis as well as similar survival and tumor control outcomes despite a higher proportion of stage IIIB and larger treatment volumes compared to 3D-CRT; as such IMRT is preferred over 3D-CRT in this setting. IGRT is recommended when using SABR, 3D-CRT/IMRT, and proton therapy with steep dose gradients around the target, when OARs are in close proximity to high dose regions, and when using complex motion management techniques. When higher doses (>30 Gy) are warranted in patients with advanced lung cancer (i.e., stage IV), technologies to reduce normal tissue irradiation may be used (including IMRT or PBRT as appropriate).

NCCN guidelines for lymphomas state that advanced ~~RT~~radiation therapy technologies, such as IMRT, **breath hold or respiratory gating, and/or IGRT or PBT**, may offer significant and clinically relevant advantages in specific instances to spare ~~OAR~~organs at risk and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. **Randomized studies to test these concepts are unlikely to be done since these techniques are designed to decrease late effects which take 10+ years to evolve. Therefore, the guidelines recommend that RT delivery techniques that are found to best reduce the doses to the OAR in a clinically meaningful way without compromising target coverage should be considered in these patients, who are likely to enjoy long life expectancies following treatment** (20189).

NCCN guidelines for thymomas and thymic carcinomas state that ~~RT~~radiation therapy should be given by 3D conformal technique to reduce surrounding normal tissue damage (e.g., heart, lungs, esophagus, and 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 (20189).

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 ≥ 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 ≤ 2 were 44% in both groups, while ≥ 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 OARorgans-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~~2019).

Professional Societies

American Society for Radiation Oncology (ASTRO)

ASTRO's 2019 clinical practice guideline states that modulated treatment techniques such as IMRT and VMAT for planning and delivery of both conventionally fractionated and hypofractionated RT are recommended for treatment of localized pancreatic cancer (Strength of recommendation: Strong) (Palta et al.)

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 5-year rate of freedom from biochemical failure was 95.4% in the IMRT arm and 94.3% in the 3DCRT arm (P = .678).~~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.

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=1,368), 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.

Alicik 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 compared to 3D-CRT in some but not all older studies. Moderately hypofractionated image-guided IMRT regimens have been tested in randomized trials reporting similar efficacy and toxicity to conventionally fractionated IMRT in some studies. 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 (20189).~~

Professional Societies

American College of Radiology (ACR)

ACR Appropriateness Criteria states that external beam radiation is a key component of the curative management of T1 and T2 prostate cancer. ~~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 (Zaorsky et al., 20167).

American Urological Association (AUA))/American Society for Radiation Oncology (ASTRO)/Society of Urologic Oncology (SUO)

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

American Society of Clinical Oncology (ASCO)

In 2018, ASCO endorsed the AUA/ASTRO/SUO guidelines in all but two of their collaborative recommendations. The 2 exceptions were related to cryosurgery (Bekelman, et al).

Combined Therapies

No evidence was identified in the clinical literature supporting the combined use of IMRT and proton beam RT 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 website for more information (use product codes MUJ and IYE): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>. (Accessed October 2, 2019 ~~November 8, 2018~~)

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) exist; see the LCDs for Intensity Modulated Radiation Therapy (IMRT) and Proton Beam Radiotherapy. (Accessed October 17, 2019)

~~Medicare does not have a National Coverage Determination (NCD) for intensity-modulated radiation therapy (IMRT). Local Coverage Determinations (LCDs) exist; see the LCDs for Intensity Modulated Radiation Therapy (IMRT), Proton Beam Radiotherapy and Proton Beam Therapy. (Accessed November 7, 2018)~~

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
<u>TBD</u>	<p><u>Application</u></p> <ul style="list-style-type: none"> <u>Added language to indicate this policy does not apply to the states of New Jersey, and Tennessee:</u> <ul style="list-style-type: none"> <u>For the state of New Jersey, refer to the Medical Policy titled Intensity-Modulated Radiation Therapy (for New Jersey Only)</u> <u>For the state of Tennessee, refer to the Medical Policy titled Intensity-Modulated Radiation Therapy (for Tennessee Only)</u> <p><u>Coverage Rationale</u></p> <ul style="list-style-type: none"> <u>Replaced "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" with "Breast cancer in the following circumstances:</u> <ul style="list-style-type: none"> <u>When the internal mammary nodes are being treated</u> <u>Partial breast irradiation when dose is at least 3Gy/fraction"</u> <u>Replaced "Cervical cancer in individuals who are post hysterectomy" with "Cervical cancer"</u> <u>Added "lymphoma and solitary plasmacytomas when treatment includes" to Head and Neck Cancers</u> <u>Added "e.g., lymphomas, thymomas" to Mediastinal tumors</u> <u>Added the following condition as "proven": Endometrial cancer</u> <u>Moved Tracheal cancer to Mediastinal tumors</u> <u>Added reference to the Radiation Therapy Oncology Group (RTOG) to the guideline for when IMRT may be considered proven on a case by case basis</u> <p><u>Supporting Information</u></p> <ul style="list-style-type: none"> <u>Updated Clinical Evidence, CMS, and References sections to reflect the most current information</u> <u>Archived previous policy version CS064.J</u>

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The UnitedHealthcare Medical Policies 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.