Intensity-Modulated Radiation Therapy (for Louisiana Only)

Policy Number: CS064LA.~~K~~**L**
Effective Date: ~~June 1, 2020~~**TBD**

➲ Instructions for Use

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Application

This Medical Policy only applies to the state of Louisiana.

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** ~~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**; or**
    - Partial breast irradiation **of up to 5 fractions** ~~when dose is at least 3Gy/fraction~~
  - 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 **(stage III or IV glottic cancer),** ~~,~~ salivary glands, oral cavity (includes the tongue), nasal cavity, paranasal sinuses

- Mediastinal tumors (e.g., lymphomas, thymomas), including tracheal cancer
- **Non-small cell lung cancer, stage III, undergoing chemoradiation therapy**
- Pancreatic cancer
- Prostate cancer

- Compensator based beam modulation treatment when done in combination with an IMRT indication that is listed above as proven.
- **Hippocampal-avoidance whole brain radiation therapy (HA-WBRT) of up to 10 fractions and all the following:**
  - **Brain metastasis**
  - **Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 or Karnofsky performance status (KPS) status of ≥ 70**
  - **Prognosis of 4 months or greater**
  - **Absence of leptomeningeal disease**
- 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:
  - **Use of clinically appropriate radiation dose and a** ~~A~~ non-IMRT technique would increase the probability of clinically meaningful normal tissue **toxicity,** (e.g., as specified by the Radiation Therapy Oncology Group (RTOG) or ~~QUANTEC guidelines~~ **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 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

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

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

Codes labeled with an asterisk (*) are not on the Louisiana Medicaid Fee Schedule and therefore may not be covered by the state of Louisiana Medicaid Program.

For additional coding guidance, refer to the related Reimbursement Policies titled Intensity Modulated Radiation Therapy and Replacement Codes.

Description of Services

External beam radiation therapy (EBRT) delivers high-energy x-ray, electron, or proton beams that are generated using 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 **radiation therapy (RT)** ~~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, **2021b** ~~2019b~~).

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], **2019b** ~~2019c~~).

Clinical Evidence

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, **2021a** ~~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** ~~substancial~~ benefits compared to CRT for patients with anal cancer undergoing concurrent chemoradiation therapy.

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 conformal radiation therapy (CRT) is associated with improved survival when compared with non-IMRT based 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 5FU and mitomycin C. The median follow-up time was 34 months. The authors reported that IMRT reduced acute grade 3+ hematologic and 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.

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.

~~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).~~

~~NCCN guidelines for the treatment of anal carcinoma state that IMRT is preferred over~~ Clinical Practice Guidelines

~~3-D CRT, citing benefits of reduced toxicity while maintaining local control in multiple studies (NCCN 2019).~~

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 CRT~~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).

European Society for Medical Oncology (ESMO)

ESMO guidelines for anal cancer state that for management of local/locoregional disease, IMRT spares OARs, reduces toxicity, and may allow full or even escalated doses to be delivered within a shorter overall treatment time. IMRT or volumetric modulated arc therapy (VMAT) is currently recommended for the treatment of anal cancer, setting strict radiation therapy (RT) dose constraints to normal organs. Additionally, IMRT and VMAT allow for treatment with simultaneous integrated boost (Rao et al., 2021).

~~European Society for Medical Oncology (ESMO); European Society of Surgical Oncology (ESSO); European Society of Radiotherapy and Oncology (ESTRO)~~

~~Glynne-Jones et al. (2014) developed guidelines by the ESMO, ESSO and ESTRO who recommend more conformal treatment, such as IMRT, for anal cancer. The guideline notes several studies of IMRT in anal canal carcinoma have reported significant reduction in the doses delivered to the bowel, bladder and genitalia/perineal skin. The guideline states that IMRT spares OAR, reduces toxicity, and may allow full or escalated doses to be achieved within a shorter overall treatment time.~~

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for the treatment of anal carcinoma state that IMRT is preferred over 3D-CRT, citing benefits of reduced toxicity while maintaining local control (LC) in multiple studies (NCCN, 2022~~1~~).

Breast Cancer

Meattini et al. (2020) conducted phase III, single-center randomized trial (NCT02104895) to assess whether accelerated partial-breast irradiation (APBI) is a safe and effective alternative treatment as compared to whole-breast irradiation (WBI) for selected patients with early breast cancer (BC). A total of 520 patients, more than 90% of whom had characteristics associated with low recurrence risk, participated in the study. Women randomized to the APBI-IMRT arm (n=260) received a dose of 30 Gy in 5 non-consecutive daily fractions at 6 Gy/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. The median follow-up was 10.7 years. The 10-year cumulative incidence of IBTR was 2.5% (n=6) in the WBI arm and 3.7% (n=9) in the APBI arm (HR, 1.56; 95% CI, 0.55 to 4.37; p=0.40). OS at 10 years was 91.9% in both arms (HR, 0.95; 95% CI, 0.50 to 1.79; p=0.86). Breast cancer-specific survival at 10 years was 96.7% in the WBI arm and 97.8% in the APBI arm (HR, 0.65; 95% CI, 0.21 to 1.99; p=0.45). The APBI arm showed significantly less acute toxicity (p=0.0001) and late toxicity (p=0.0001), and improved cosmetic outcome as evaluated by both physician (p=0.0001) and patient (p=0.0001). The authors concluded that the 10-year cumulative IBTR incidence in early breast cancer treated with external APBI using IMRT technique in 5 once-daily fractions is low and does not differ from that after WBI. They

also stated that acute and late treatment-related toxicity and cosmesis outcomes were significantly in favor of APBI.

Jagsi et al. (2018) conducted an **randomized controlled trial (**RCT**)** comparing IMRT and deep inspiration breath hold (DIBH) versus standard, free-breathing, forward-planned, **three-dimensional conformal radiation therapy (**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 **RCT** ~~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 **LC**~~local control~~, survival, cosmetic results and toxicity profile, and warrants further investigation.

Donovan et al. (2007) conducted a prospective, multicenter, phase III **randomized** ~~ramdomized~~ 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 By 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** ~~assesed~~ 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 s in patient reported breast discomfort, hardness or QOL between the arms. The authors concluded that use of 3D-IMRT reduces late radiation AEs.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN) ~~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).~~

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 **including deep inspiration breath-hold** and prone positioning may be used to try to further reduce dose to adjacent normal tissues, particularly the heart and lungs (**NCCN, 2022** ~~1~~2019).

Central Nervous System (CNS) Tumors

Chen et al. (2022) conducted a RCT to analyze the effects of three-dimensional IMRT on QOL in patients with low-grade gliomas. One hundred patients with low-grade gliomas, from February 2015 to December 2019, were randomized into two groups, 3D-CRT control group (n = 50) and three-dimensional IMRT research group (n = 50). The cognitive function of the two groups were analyzed by the Mini-Cog Assessment (Mini-Cog) and the Montreal Cognitive Assessment (MoCA). The self-care ability score (BI), and the effect of symptom improvement and the QOL SF-36 score were also compared between the two groups. After RT, the self-care ability of patients in the two groups was significantly improved, and the improvement of three-dimensional IMRT group was better than that of the control group. The Mini-Cog and MOCA scores in the three-dimensional IMRT group were significantly higher than those in the control group. Additionally, the symptom improvement effect and QOL of the patients in the three-dimensional IMRT group were also significantly better than those in the control group. The scores of Self-Rating Depression Scale (SDS) and Self-Rating Anxiety Scale (SAS) of patients who underwent three-dimensional conformal IMRT were significantly lower than those of the control group. Mortality was not significantly different between the two groups. The authors concluded three-dimensional conformal IMRT can delineate the target volume more accurately, regulate the intensity of radiation, and improve the symptoms and QOL of patients with low-grade gliomas. Limitations include single institution study design and small study size.

A Cochrane evidence review sought to compare the efficacy of advanced forms of RT (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 RT is better than delayed RT. 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 **progression-free survival (**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 **a case series study** ~~an analysis~~ of a single institution's long-~~-~~term experience with IMRT in patients with complex-shaped meningioma of the skull base. Over a 7-year period, 94 patients 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, overall **LC**~~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 **LC**~~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 **RCT**~~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 **CRT**~~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.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

In a 2022 ASTRO guideline, Halasz et al. strongly recommend IMRT/VMAT to reduce acute and late toxicity, especially for tumors located near critical OARs for patients with IDH-mutant WHO grade 2 and grade 3 diffuse glioma. When IMRT/VMAT is unavailable, 3-D CRT is strongly recommended as a treatment option for patients.

National Comprehensive Cancer Network (NCCN)

In its CNS Cancers guideline, NCCN states that lower doses of targeted conformal RT (including **3D-CRTand** ~~3-D CRT and~~ IMRT) are recommended 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 (**NCCN, 2022** ~~1~~2019).

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 ≥2 (P=0.026) and GU ≥G2 (P=0.038). The authors concluded that their results show that IRMT could reduce the incidence of late severe GI obstruction and that additional studies are warranted.

Lin et al. (2018) conducted a meta-analysis to compare the efficacies and toxicities of IMRT with 3D-CRT or 2D-RT for definitive treatment of cervical cancer. A search for relevant studies was conducted using PubMed, the Cochrane Library, Web of Science, and Elsevier. Outcomes of interest included OS, DFS, and acute and chronic toxicities. The literature review yielded 2,808 publications and after screening and review, a total of six articles, with 1,008 participants (350 IMRT and 658 CRT) were included in the final analysis. Three-year OS and 3-year DFS revealed no significant differences between IMRT and 3D-CRT or 2D-RT (3-year OS: OR, 2.41, CI, 0.62 to 9.39, p=0.21; 3-year DFS: OR, 1.44, 95% CI, 0.69 to 3.01, p=0.33). The incidence of acute GI toxicity and GU toxicity in patients who received IMRT was significantly lower than that in the control group (GI: Grade 2: OR, 0.5, 95% CI, 0.28 to 0.89, p=0.02; Grade 3 or higher: OR, 0.55, 95% CI, 0.32 to 0.95, p=0.03; GU: Grade 2: OR, 0.41, 95% CI, 0.2 to 0.84, p=0.01; Grade 3 or higher: OR, 0.31, 95% CI, 0.14 to 0.67, p=0.003). Furthermore, patients who received IMRT experienced fewer incidences of chronic GU toxicity than patients in the control group (Grade 3: OR, 0.09, 95% CI, 0.01 to 0.67, p=0.02). The authors concluded that IMRT and conventional radiotherapy demonstrated equivalent efficacy in terms of 3-year OS and DFS, and that IMRT significantly reduced acute GI and GU toxicities as well as chronic GU toxicity in patients with cervical cancer.

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. 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 **study** 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 **(PTV)** 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** ~~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** ~~Grade~~ 3 toxicity or higher were 2% and 7%, respectively. The authors concluded that **IMRT** ~~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.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

In a 2020 ASTRO Cervical Cancer Guideline, Chino et al. recommend IMRT for women with cervical cancer treated with postoperative RT with or without chemotherapy to decrease acute and chronic toxicity (strength of recommendation: strong). For women with cervical cancer treated with definitive RT with or without chemotherapy, IMRT is conditionally recommended to decrease acute and chronic toxicity.

European Society of Gynaecological Oncology (ESGO)/European Society for Radiotherapy and Oncology (ESTRO)/European Society of Pathology (ESP)

Cibula et al. (2018) developed clinically relevant and evidence-based guidelines in order to improve the quality of care for women with cervical cancer. The guideline recommends a minimum of 3D-CRT for definitive chemoradiotherapy for cervical cancer. IMRT is the preferred treatment because of the more conformal dose distribution that maximizes sparing of OAR. Image-guided radiotherapy (IGRT) is recommended for IMRT to ensure safe dose application in the tumor-related targets, to account for motion uncertainties, to reduce margins, and to achieve reduced doses to OAR.

National Comprehensive Cancer Network (NCCN)

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 (**NCCN, 2022** ~~12019~~).

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 **GU**~~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 ≥ 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.

Clinical Practice Guidelines

American College of Radiology (ACR)

Wahl et al. (2016) developed consensus guidelines on adjuvant radiotherapy for early-stage endometrial cancer from a multidisciplinary expert panel convened by the ACR. Per the ACR appropriateness criteria, IMRT has been shown to reduce dose to critical structures in dosimetric studies, and retrospective reviews of IMRT for early-stage endometrial cancer have shown excellent LC rates, with low GI toxicity rates. The ACR appropriateness criteria for advanced stage endometrial cancer states IMRT may further improve treatment of areas at risk for tumor recurrence while sparing adjacent normal tissues. The authors note that several studies of IMRT for gynecologic malignancies showed that, compared with external beam pelvic RT, IMRT improved target coverage, reduced the volume of normal tissues receiving the prescription dose, and that the reduction in dose resulted in a decrease in both acute and chronic GI side effects compared with historic controls (Elshaikh et al., 2014).

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 ≥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.

Kole et al. (2011) conducted a retrospective review to compare heart and coronary artery radiation exposure using IMRT vs 3D-CRT for patients with distal esophageal cancer undergoing chemoradiation. Nineteen patients who underwent treatment with IMRT from March 2007 to May 2008 were included in the review. Theoretical 3D-CRT plans with four-field beam arrangements were generated. Dose-volume histograms of the planning target volume, heart, right coronary artery, left coronary artery, and other critical normal tissues were compared between the IMRT and 3D-CRT plans. IMRT treatment planning showed significant reduction ($p < 0.05$) in heart dose over 3D-CRT and there was significant sparing of the right coronary artery. However, the left coronary artery showed no

significant improvement. There was no significant difference in percentage of total lung volume receiving at least 10, 15, or 20 Gy or in the mean lung dose between the planning methods. There were also no significant differences observed for the kidneys, liver, stomach, or spinal cord. IMRT attained a significant improvement in target conformity as measured by the conformality index with the mean conformality index reduced from 1.56 to 1.30 using IMRT. The authors concluded IMRT significantly reduced heart dose, spared more of right coronary artery and improved target conformity when compared with 3D-CRT. Limitations include small study size and the retrospective nature of the study.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for esophageal and esophagogastric junction cancers state that IMRT is appropriate in clinical settings where reduction in dose to OAR (e.g., heart and lungs) is required that cannot be achieved by 3D techniques (**NCCN, 2022** ~~1~~2019).

Head and Neck Cancer (HNC)

Gupta et al. (2020) compared long-term disease-related outcomes and late radiation morbidity between IMRT and 3D-CRT in head and neck squamous cell carcinoma (HNSCC) in a prospective RCT. The primary endpoint was the incidence of physician-rated acute salivary gland toxicity (≥grade 2). Secondary endpoints included other acute toxicity (mucositis, dermatitis, dysphagia), late radiation morbidity, patterns of failure, loco-regional disease status, and OS. Patients (n=60) who were previously untreated and had early to moderately advanced non-metastatic squamous carcinoma of the oropharynx, larynx, or hypopharynx planned for comprehensive irradiation of primary site and bilateral neck nodes were randomly assigned to either IMRT or 3D-CRT. Treatment consisted of 6MV photons to a total dose of 70Gy/35 fractions over 7 weeks (3D-CRT) or 66Gy/30 fractions over 6 weeks (IMRT). At a median follow-up of 140 months for surviving patients, 10-year Kaplan-Meier estimates of locoregional control (LRC), PFS, and OS with 95% confidence interval were 73.6%, 45.2%, and 50.3% respectively. There were no significant differences in 10-year disease-related outcomes between 3D-CRT and IMRT for LRC 79.2% vs 68.7%; PFS 41.3% vs 48.6%; or OS 44.9% vs 55.0%. Significantly lesser proportion of patients in the IMRT arm experienced ≥grade 2 late xerostomia and subcutaneous fibrosis at all time-points. At longer follow-up, fewer patients remained evaluable for late radiation toxicity reducing statistical power and precision. The authors concluded IMRT provides sustained clinically meaningful benefit compared to 3D-CRT in reducing the late morbidity of radiation without compromising disease-related outcomes in long-term survivors of non-nasopharyngeal HNSCC. Limitations include lack of blinding to treatment arm and small study size with even much lesser numbers on long-term follow-up (between 5 and 10 years).

Oertel and colleagues (2019) conducted a single-center retrospective analysis investigating the impact of different radiation dose regimens on **LC**~~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, **CRT** ~~conventional RT~~ n=19). The median RT dose was 45 Gy (range: 12-55.8), the **LC**~~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 (≤ 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 **LC**~~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 ≤ 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 × 25 fractions to low-risk **PTV**~~planning target volume (PTV)~~ followed by a sequential boost (2 Gy × 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 **LC**~~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 modalities in 1,237~~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.

Lim et al. (2015) conducted a single-center case series study to evaluate the long-term results of definitive RT for early glottic cancer. The investigators retrospectively reviewed 222 patients with T1-2N0 squamous cell carcinoma of the glottic larynx treated with definitive RT. None of the patients received elective nodal RT or combined chemotherapy. The median total RT dose was 66 Gy. The daily fraction size was < 2.5 Gy in 69% and 2.5 Gy in 31% of patients. The RT field extended from the hyoid bone to the cricoid cartilage. The median age was 60 years, and 155 patients (70%) had T1 disease. The 5-year rates of local recurrence-free survival (LRFS) and ultimate LRFS with voice preservation were 87.8% and 90.3%, respectively. T2 HR, 2.30; 95% CI, 1.08 to 4.94) and anterior commissural involvement (HR, 3.37; 95% CI, 1.62 to 7.02) were significant prognostic factors for LRFS. In 34 patients with local recurrence, tumors recurred in the ipsilateral vocal cord in 28 patients. There were no contralateral vocal cord recurrences. Most acute complications included grade 1-2 dysphagia and/or hoarseness. There was no grade 3 or greater chronic toxicity. The authors concluded that definitive RT achieved a high cure rate, voice preservation, and tolerable toxicity in early glottic cancer, and T2 stage and anterior commissural involvement were prognostic factors for LC. However, the authors also state that further optimization of the RT method is needed to reduce the risk of ipsilateral tumor recurrence.

Trotti et al. (2014) conducted a multi-center randomized trial (RTOG 9512) to compare hyperfractionation (HFX) to standard fractionation (SFX) for T2N0 vocal cord carcinoma. The primary endpoint was LC at 5 years. Secondary endpoints were disease-free survival, OS and toxicity associated with each schedule. SFX consisted of 2 Gy per fraction, once a day to a total dose of 70 Gy in 35 fractions in 7 weeks. Two-dimensional RT using 2 or 3 co-planar portals was used. Field reduction at 50 Gy was permitted to reduce arytenoid dose. HFX consisted of 1.2 Gy per fraction, twice a day with a minimum interval of 6 hours, to a total dose of 79.2 Gy in 66 fractions in 6.5 weeks. A total of 250 patients with T2 (stratified by substage T2a vs T2b) glottic cancer enrolled and were randomly assigned to SFX or HFX. Of 239 patients (SFX, n=119; HFX, n=120) with analyzable outcomes, 94% were male, 83% had KPS 90-100, and 62% had T2a tumor. The median follow-up for all surviving patients was 7.9 years (range, 0.6 to 13.1). The 5-year LC rate was 8 points higher (but not statistically significant: p=0.14) for HFX (78%) vs SFX (70%), corresponding to a 30% HR reduction. Five-year DFS was 49% vs 40% (p=0.13) and OS 72% vs 63% (p=0.29). HFX had higher rates of acute skin, mucosal, and laryngeal toxicity. Grade 3-4 late effects were similar with 5-year cumulative incidence of 8.5% (3.4-13.6%) after SFX and 8.5% (3.4-13.5%) after HFX. In the subcategory analysis (T2b versus T2a) outcomes

were significantly worse in T2b disease for loco-regional control (5-year: T2b 63.3% vs. T2a 74.1%) (HR 1.65 (1.05-2.59); p=0.03), disease-free survival (5-year: T2b 31.4% vs. T2a 52.4%) (HR 1.62 (1.19-2.22); p=0.002) and OS (5-year: T2b 50.0% vs. T2a 77.5%) (2.06 (1.43-2.97); p=0.0001). The authors concluded that 5-year LC was modestly higher with HFX compared to SFX for T2 glottic carcinoma, but the difference was not statistically significant, and sub staging by T2a vs. T2b carries prognostic value for DFS and OS. They also state that their results were achieved with 2-D radiotherapy techniques and that current IMRT techniques might enhance outcomes further however, data have not been reported in early glottic cancers.

~~An Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review of RT for HNC found that while IMRT is more successful than traditional RT 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 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 2~~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, LRC~~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 (2019). 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~~An Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review of RT for HNC found that while IMRT is more successful than traditional RT 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).

~~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 evaluated 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 (V_{20}, V_{40}, and V_{60}; 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 clairify whether differences in long-term survival exist between treatment with IMRT and 3D-CRT.~~

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 3D-CRT 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).

Yamazaki et al. (2006) conducted a single-center, randomized trial to determine the effect of radiation fraction size and overall treatment time on the LC of early glottic carcinoma. A total of 180 patients with early glottic carcinoma (T1N0M0) participated in the study. Patients were randomly allocated to either treatment arm A (radiation fraction size 2 Gy, n=89) or B (2.25 Gy, n=91). The total radiation dose administered was 60 Gy in 30 fractions within 6 weeks for minimal tumors (two-thirds of the vocal cord or less) or 66 Gy in 33 fractions in 6.6 weeks for larger than minimal tumors (more than two-thirds

of the vocal cord) in Arm A and 56.25 Gy in 25 fractions within 5 weeks for minimal tumor or 63 Gy in 28 fractions within 5.6 weeks for larger than minimal tumors in Arm B. The 5-year LC rate was 77% for Arm A and 92% for Arm B (p=0.004). The corresponding 5-year cause-specific survival rates were 97% and 100% (no significant difference). No significant differences were found between these two arms in terms of rates of acute mucosal reaction, skin reactions, or chronic adverse reactions. The authors concluded that use of 2.25-Gy fractions with a shorter overall treatment time for Arm B showed superior LC compared with conventional use of 2-Gy fractions for Arm A without adverse reactions from the greater fraction.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for head and neck cancers state that IMRT is appropriate and may offer clinically relevant advantages to spare important OARs, such as brain, brain stem, cochlea, semicircular canals, optic chiasm, cranial nerves, retina, lacrimal glands, cornea, spinal cord, brachial plexus, mucosa, salivary glands, bone, pharyngeal constrictors, larynx, esophagus, and decrease the risk for late, normal tissue damage and toxicity while still achieving the primary goal of local tumor control (NCCN, 2022).

Hippocampal-Avoidance Whole Brain Radiation Therapy (HA-WBRT)

Brown et al. (2020) conducted a phase III trial to determine if hippocampal avoidance using IMRT during whole-brain radiotherapy (WBRT) preserves cognition. Between July 2015 and March 2018, 518 patients were randomly assigned to two groups, one group with brain metastases to HA-WBRT plus memantine, and one group with WBRT plus memantine. Time to cognitive function failure, defined as decline using the reliable change index on at least one of the cognitive tests was the primary endpoint. Overall survival, intracranial PFS, toxicity, and patient-reported symptom burden, were secondary endpoints. Median follow-up for alive patients was 7.9 months. Risk of cognitive failure was significantly lower after HA-WBRT plus memantine versus WBRT plus memantine (adjusted hazard ratio, 0.74; 95% CI, 0.58 to 0.95; P = .02). This difference was attributable to less deterioration in executive function at 4 months, and learning and memory at 6 months. Treatment arms did not differ significantly in OS, intracranial PFS, or toxicity. At 6 months, using all data, patients who received HA-WBRT plus memantine reported less fatigue (P = .04), less difficulty with remembering things (P = .01), and less difficulty with speaking (P = .049) and using imputed data, less interference of neurologic symptoms in daily activities (P = .008) and fewer cognitive symptoms (P = .01). The authors concluded HA-WBRT plus memantine effectively spares the hippocampal neuroregenerative niche to better preserve cognitive function and patient-reported symptoms and should be considered a standard of care for patients with good performance status who plan to receive WBRT for brain metastases with no metastases in the HA region. Additionally, no differences were observed in intracranial PFS, toxicity, or OS. Limitations include lack of blinding.

Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO) - Society for Neuro-Oncology (SNO) - American Society for Radiation Oncology (ASTRO)

The ASCO/SNO/ASTRO guideline for patients with brain metastases from solid tumors recommends memantine and hippocampal avoidance should be offered to patients who receive WBRT, and have no hippocampal lesions, and four months or more expected survival. Patients with asymptomatic brain metastases with either KPS ≤ 50 or KPS < 70 with

systemic therapy options do not derive benefit from radiation therapy (Vogelbaum et al., 2021).

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for central nervous system cancers state that HA-WBRT (plus memantine) 30Gy in 10 fractions is preferred for patients with a better prognosis (≥4) and no metastases within 5mm of the hippocampi (NCCN, 2022~~1~~).

Mediastinal Tumors

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

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

~~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 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 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 (NCCN, 2022 ~~2019~~).

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

esophagus, ~~and~~ spinal cord). **The guideline states that since these patients are younger and mostly long-term survivors, the mean total dose to the heart should be as low as reasonably achievable to potentially maximize survival. IMRT is preferred over 3D-CRT and** ~~IMRT~~ may further improve the dose distribution and decrease the dose to the normal tissue as indicated **(NCCN, 2022**~~. If IMRT is applied, the ASTRO/ACR guidelines for its use should be strictly followed (2019~~).

Non-Small Cell Lung Cancer (NSCLC), Stage III

A secondary analysis of the NRG Oncology RTOG 0617 RCT (Chun et al. 2017) was conducted to evaluate OS, PFS, LF distal metastasis and adverse events 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). 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 (V_{20}, V_{40}, and V_{60}; 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 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.

Speirs et al. (2017) analyzed clinical and dosimetric parameters affecting OS in individuals (n=416) with locally advanced NSCLC, with a focus on heart dose. Treatment plans recontoured using normal tissue guidelines from Radiation Therapy Oncology Group 0617, toxicity and dosimetry data were analyzed on 322 patients with a multivariate analysis performed on 251 patients. Primary endpoints were OS, disease-free survival, and toxicity. Patients were treated with radiation therapy to prescribed doses of 50.0 to 84.9 Gy (median 66.0 Gy). Median follow-up was 14.5 months. Median OS was 16.8 months. The 1- and 2-year OS rates were 61.4% and 38.8%, respectively. On multivariate analysis, factors independently associated with worse OS were increasing heart V50, heart volume, lung V5, bilateral mediastinal lymph node involvement, and lack of concurrent chemotherapy. When stratified by heart V50 less than 25% versus 25% or greater, the 1-year OS rates were 70.2% versus 46.8% and the 2-year OS rates were 45.9% versus 26.7% (p < 0.0001). Median heart V50 was significantly higher for patients with cardiac toxicity with a Common Terminology Criteria for Adverse Events grade of 1 or higher. Based on the authors conclusion, for patients with locally advanced NSCLC treated with chemoradiotherapy, heart dose is associated with OS and cardiac toxicity. Limitations include retrospective, single-institution study design and short-term follow-up.

Movsas et al. (2016) performed a secondary analysis of the RTOG 0617 RCT to determine QOL via the Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS) in the high-dose RT arm at 3 months. Of 424 eligible stage III NSCLC patients, 360 (85%) consented to QOL with 313 completing the baseline QOL assessments. Quality of life was collected prospectively, and data were presented at baseline, three, and twelve months. Two-hundred and nineteen patients (70%) completed the 3-month QOL assessments, and 137 of the living patients (57%) completed the 12-month assessment. Patient demographics and

baseline QOL scores were comparable between the 74-Gy and 60-Gy arms. Significantly more patients in the 74-Gy arm than in the 60-Gy arm had clinically meaningful decline in FACT-LCS at 3 months (45% vs 30%; P = .02). At 12 months, fewer patients who received IMRT (vs 3D-CRT) had clinically meaningful decline in FACT-LCS (21% vs 46%; P = .003). Baseline Fact-Trial Outcome Index was associated with OS in multivariate analysis. The authors concluded the QOL analysis demonstrated a clinically meaningful decline in QOL in the 74-Gy arm at 3 months, despite few differences in clinician-reported toxic effects between treatment arms.

Wang et al. (2016) retrospectively compared the clinical outcomes and radiation-related toxicities between patients with locally advanced NSCLC receiving 3D-CRT and IMRT between 2002 and 2010, from a single academic center. Overall survival, local-regional progression-free survival (LRPFS), distant metastasis-free survival (DMFS), and PFS were compared among patients (IMRT, n=446, and 3D-CRT, n=206) irradiated with different techniques. The median OS of the 3DCRT and IMRT groups were 19.4 and 23.3 months, with the 5-year rate of 13% and 19%, respectively (p 5 .043). Multivariate analysis identified IMRT as an independent favorable factor associated with LRPFS and DMFS. PSM analysis further verified the beneficial effect of IMRT on LRPFS. No difference in OS or PFS was observed between the two techniques. Subgroup analysis revealed that IMRT might be differentially more effective in both OS and LRPFS among patients who were female, nonsmokers, with adenocarcinoma, or without weight loss. There was a significant reduction of lung toxicity and similar esophagus toxicity in the IMRT group when compared with the 3D-CRT group. The authors concluded pulmonary toxicity was reduced with IMRT. Additionally, IMRT may provide superior LRPFS and similar OS than 3D-CRT. Limitations include the retrospective study design.

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 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) RT. 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.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for non-small cell lung cancer state that In a prospective trial of definitive/consolidative chemo/RT for patients with stage III NSCLC (RTOG 0617), IMRT was 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 (NCCN, 2022).

Pancreatic Cancer

Bittner et al. (2015) conducted a systematic review to determine whether toxicities can be reduced by using IMRT rather than 3D-CRT in patients with pancreatic cancer, and to compare OS and PFS between the two techniques. A search for relevant studies was conducted using PubMed/Medline. Outcomes of interest included details regarding the therapy given, acute and late toxicities, and patient survival (OS and PFS). A total of 13 IMRT and 7 3D-CRT studies were included in the final analysis. For acute toxicities, nausea and vomiting ≥ grade 3 were 13.4% (109/747 patients) vs. 7.8% (35/446 patients) for 3D-CRT and IMRT, respectively (p<0.001). Diarrhea ≥ grade 3 was 11.6% (87/747) vs. 2.0% (9/446) for 3D-CRT and IMRT, respectively (p<0.001). Late toxicities were predominantly gastrointestinal: toxicities ≥ grade 3 were 10.6% (22/207) and 5.0% (19/381), for 3D-CRT and IMRT, respectively (p=0.017). However, those were mainly attributed to the group of patients with GI bleeding/duodenal ulcer. There were no differences in hematological toxicity, OS and PFS between the two techniques. The authors concluded that when comparing 3D-CRT and IMRT in the treatment of pancreatic cancer, there is no significant differences in OS and PFS however, treatment-related toxicities i.e., nausea, vomiting, diarrhea and late GI toxicity are significantly reduced with IMRT.

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 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~~ Clinical Practice Guidelines

~~breathhold/gating techniques can result in improved planning target volume coverage with decreased dose to OAR. 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 (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.).

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for pancreatic adenocarcinoma state that IMRT with breath hold/gating techniques can result in improved planning target volume (PTV) coverage with decreased dose to OAR. 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 (NCCN, 2022~~1~~).

Prostate Cancer

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/mLnadir). 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 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.

Alicikus 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.

~~***NCCN guidelines state that highly CRT, such as IMRT, should be used to treat prostate cancer. IMRT significantly reduces the risk of GI toxicities and rates of salvage therapy compared to***~~ ***Clinical Practice Guidelines***

~~3-D 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. (2019)~~

~~***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. 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., 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).~~

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

The AUA, in collaboration with ASTRO, developed guidelines for treating clinically localized prostate cancer. The guideline notes that various RT options, including IMRT, can be considered an appropriate option for patients with low, intermediate, and high-risk disease. The guideline strongly recommends that dose escalation should be utilized when external beam radiation therapy (EBRT) is the primary treatment for prostate cancer and IMRT is noted as the current standard technique of EBRT. When treating the pelvic lymph nodes with radiation, the guideline strongly recommends that clinicians should utilize IMRT with doses between 45 Gy to 52 Gy. The ~~)/~~Society of Urologic Oncology (SUO) endorsed this guideline (Eastham et al., 2022).

~~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, developed guidelines for treating clinically localized prostate cancer. They state that various RT options, including IMRT, can be considered as an appropriate option for patients with low, intermediate, and high-risk disease (Sanda et al., 2017).~~

National Comprehensive Cancer Network (NCCN)

NCCN guidelines state that highly CRT, such as IMRT, should be used to treat prostate cancer. 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 with similar efficacy and toxicity to conventionally fractionated IMRT in some studies, and they can be considered as an alternative to conventionally fractionated regimens when clinically indicated (NCCN, 2023~~2~~).

~~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 in a single treatment plan.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The FDA has approved a number of devices for use in IMRT. **Refer to** ~~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 19,** 2022 ~~12, 2019~~)

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Policy History/Revision Information

Date	Summary of Changes
TBD	**Coverage Rationale** • Added language to indicate intensity-modulated radiation therapy (IMRT) is proven and medically necessary for: ○ Definitive Therapy of the primary site for non-small cell lung cancer, stage III, undergoing chemoradiation therapy ○ Hippocampal-avoidance whole brain radiation therapy (HA-WBRT) of up to 10 fractions and all the following: ▪ Brain metastasis ▪ Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 or Karnofsky performance status (KPS) status of ≥ 70 ▪ Prognosis of 4 months or greater ▪ Absence of leptomeningeal disease • Replaced language indicating: ○ "Intensity-modulated radiation therapy (IMRT) for Definitive Therapy of the primary site of breast cancer is proven and medically necessary for partial breast irradiation *when dose is at least 3Gy/fraction*" with "IMRT for Definitive Therapy of the primary site of breast cancer is proven and medically necessary for partial breast irradiation *of up to 5 fractions*" ○ "Intensity-modulated radiation therapy (IMRT) for Definitive Therapy of the primary site of larynx cancer is proven and medically necessary" with "IMRT for Definitive Therapy of the primary site of larynx cancer *(stage III or IV glottic cancer)* is proven and medically necessary" • Revised criteria for requests for exceptions to cover conditions not listed in the policy as proven; replaced criterion requiring "a non-IMRT technique would increase the probability of clinically meaningful normal tissue toxicity and demonstrated on a comparison of treatment plans for the IMRT and non-IMRT technique" with "*use of clinically appropriate radiation dose and* a non-IMRT technique would increase the probability of clinically meaningful normal tissue toxicity and demonstrated on a comparison of treatment plans for the IMRT and non-IMRT technique" **Applicable Codes** • Added notation to indicate: ○ HCPCS codes G6015, G6016, and G6017 are not on the State of Louisiana Fee Schedule and therefore are not covered by the State of Louisiana Medicaid Program

	○ **For additional coding guidance, refer to the related Reimbursement Policies titled *Intensity Modulated Radiation Therapy* and *Replacement Codes*** **Supporting Information** • **Updated *Clinical Evidence* and *References* sections to reflect the most current information** • **Archived previous policy version CS064LA.K**

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.

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