Intensity-Modulated Radiation Therapy

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➲ Instructions for Use

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Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans in all states.

Coverage Rationale

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

The following are proven and medically necessary:

- IMRT for Definitive Therapy for the primary site of the following conditions:
  - Anus/anal canal cancer
  - Breast cancer in the following circumstances:
    - When the left-sided internal mammary nodes are being treated; or
    - Accelerated partial breast irradiation of up to 5 fractions
  - 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
  - Vulvar cancer

- Compensator based beam modulation treatment when done in combination with an IMRT indication 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) 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 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] 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

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the protocol titled Medical Records Documentation Used for Reviews.

Definitions

Definitive Therapy: Radiation treatments for cancer with a curative intent (Landsteiner et al., 2023).

Applicable Codes

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

CPT Code	Description
77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
77385	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
77386	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex
77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

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 three or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session
G6017	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

For additional coding guidance, 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), 2024].

Intensity-modulated radiation therapy (IMRT) is an advanced mode of high-precision radiation therapy (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, 2023).

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 individuals. It is often used in conjunction with IMRT and other advanced forms of RT [ACR/American Radium Society (ARS), 2024].

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, 2021).

Anal Cancer

Manfrida et al. (2024) conducted a retrospective, single-center cohort study to assess the results of a personalized approach that included dose stratification by stage and boost dose adjustments according to tumor early response. The study included 110 individuals (72.7% female, median age 64.3 years) diagnosed with squamous cell anal cancer (SCAC) (60.9% were staged cT3-4, 70.9% node-positive) who were treated with long-course IMRT and concurrent chemotherapy. The authors reported that 68.2% of the individuals received a sequential boost (administered by IMRT or interventional radiotherapy to obtain a total equivalent dose in 2 Gy [Gray] of 54-60 Gy) and that acute ≥ G3 toxicity rate was 36.4% with a median follow-up of 35.4 months. The authors also reported that a total of 83% of individuals achieved a clinical complete response while locoregional recurrence occurred in 20.9% of individuals and distant metastases occurred in 6.4% of cases. Salvage surgery was reported by the authors to have occurred in 12.7% of the individuals, while a total of 25.5% (N = 28) of the individuals reported ≥ G2 and, of these individuals, 4.5% (N = five) had G3 late toxicity. The authors reported that the estimated three-year overall survival (OS) rate was 92%, the disease-free survival (DFS) rate was 72% and the colostomy-free survival (CFS) rate was 84% with a three-year locoregional recurrence was 22%. Limitations of the study included the single-center, retrospective design, and the lack of data related to individuals' risk factors, such as smoking history and human papilloma virus status. The authors concluded that IMRT was confirmed to be effective in individuals with locally advanced SCAC with favorable acute and late toxicity rates and excellent long-term rates of tumor control and CFS compared to the outcomes of individuals who received historical three dimensional-conformal radiation therapy (3D-CRT) series.

Joseph et al. (2023) evaluated the effect of IMRT on long-term quality of life (QOL) in their prospective, phase II, single-center clinical trial with individuals with anal squamous cell carcinoma (ASCC) who were treated with IMRT and concurrent 5-fluorouracil/mitomycin-C. The study included 54 adults (34% male, median age 58) who underwent QOL evaluation with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) scales and the Colorectal Cancer-Specific Quality Of Life Questionnaire (QLQ-CR29) scales. The overall response rates for completing both QLQ-C30 and QLQ-C29 questionnaires were 100%, 88%, 83%, 74%, 74%, and 74% at the baseline, 12, 24, 36, 48, and 60 months, respectively. The authors reported that the mean scores of global health status, all functional scales and all symptoms except diarrhea had improved based on the QLQ-C30 scores at 60 months and that clinically and statistically significant improvements in the global health status, role functioning, emotional functioning, and social functioning were observed. The authors also reported that the QLQ-CR29 showed that rectal pain, mucous or blood discharge per rectum, and perianal soreness were improved both clinically and statistically. Clinically significant fecal leakage was reported by 16% of participants according to the authors, while clinically and statistically significant urinary incontinence occurred in 21% of participants. Limitations of the study include the single-center design, the lack of a comparator, the heterogeneity of concurrent treatments (such as surgery), the use of non-specific questionnaires, and the small sample size. The authors concluded that, when compared with historical data, IMRT was associated with reduced long-term effects on QOL and that the majority of participants treated with IMRT experienced clinically significant recovery of function and improvement in QOL over five years after completion of treatment, although chronic diarrhea, fecal incontinence, and urinary and sexual dysfunction were primarily responsible for deterioration of the long-term QOL. The authors recommended future research to reduce such toxicities to further improve long-term QOL in anal cancer.

Vendrely et al. (2023) performed a prospective, multicentric, observational, cohort study consisting of participants with non-metastatic squamous cell carcinoma of the anus (SCCA) using chemoradiotherapy or RT as first-line treatment to evaluate treatment characteristics, CFS, DFS, OS, and prognostic factors. Among 1015 participants (male: 24.4 %; female: 75.6 %; median age: 65 years), 43.3 %presented with early-stage (T1-2, N0) and 56.7 % with locally advanced stage (T3-4 or N +) tumors. IMRT was used for 815 participants (80.3 %) and a concurrent chemotherapy was administered in 781 participants, consisting of a mitomycin based chemotherapy for 80 %. The median follow-up was 35.5 months. Disease-free survival, CFS, and OS at three years were 84.3 %, 85.6 %, and 91.7 % respectively in the early-stage group compared to 64.4 %, 66.9 %, and 78.2 % in the locally advanced group ($P < 0.001$). In multivariate analyses, male gender, locally advanced stage, and Eastern Co-operative Oncology Group Scale (ECOG) Performance Status (PS) greater than or equal to one were associated with poorer DFS, CFS, and OS. IMRT was significantly associated with a better CFS in the whole cohort and nearly reached significance in the locally advanced group. The authors stated that treatment of individuals with SCCA showed good respect for the current regimen of IMRT combined with mitomycin-based chemotherapy.

Bryant et al. (2018) conducted a retrospective cohort analysis using the Veterans Affairs database to identify individuals diagnosed with nonmetastatic, stage I or II, ASCC and treated with concurrent chemoradiation therapy between 2000 and 2015. Individuals were stratified into two groups based on radiation type: IMRT and conventional RT (CRT). Short-term outcomes included: receipt of two 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 individuals (403 received chemoradiotherapy 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 five or more days (HR 0.58; 95% CI 0.37–0.91; $P = 0.02$), increased rates of receiving two cycles of mitomycin C chemotherapy (OR 2.04; 95% CI 1.22–3.45; $P < 0.007$) and a decreased risk of ostomy due to progression or recurrence (HR 0.60; 95% CI 0.37–0.99; $P = 0.045$). IMRT was not associated with a decreased risk of grade 3 or 4 hematologic toxicity, hospital admission for GI toxicity or cancer-specific survival. The authors concluded that in the real-world setting, use of IMRT offers substantial benefits compared to CRT for individuals with anal cancer undergoing concurrent chemoradiation therapy.

Jhaveri et al. (2018) conducted a retrospective cohort analysis using the National Cancer Data Base to identify individuals with non-metastatic anal cancer. Individuals 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 match was implemented to balance differences in demographics, tumor characteristics and treatment details. The primary endpoint was OS. A total of 8,108 individuals were identified with a median follow-up time of 54.4 months. After propensity score matching, 2,334 IMRT individuals were matched to 2,334 non-IMRT individuals 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 five 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, QOL and clinical outcomes in 58 participants 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 participants, 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 three 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 CRT/5FU/MMC arm from RTOG 9811. Participants with T2-4N0-3M0 anal cancer received 5FU and MMC on days one and 29 of DP-IMRT, prescribed per stage: T2N0, 42 Gy elective nodal and 50.4 Gy anal tumor planning target volumes (PTVs) in 28 fractions; T3-4N0-3, 45 Gy elective nodal, 50.4 Gy ≤ 3 cm or 54 Gy > 3 cm metastatic nodal and 54 Gy anal tumor PTVs in 30 fractions. Of 52 evaluable participants, the grade 2 + combined acute AE rate was 77%. However, significant reductions were seen in acute grade 2 + hematologic events (73% vs. 85%), grade 3 + GI events (21% vs. 36%) and grade 3 + dermatologic events (23% vs. 49%) with DP-IMRT. Although the trial did not meet its primary endpoint, the authors reported that DP-IMRT was associated with significant sparing of acute grade 2 + hematologic and grade 3 + dermatologic and GI toxicity. The authors also emphasized the importance of real-time radiation quality assurance for IMRT trials. Kachnic et al.(2022) performed a long-term outcome evaluation of RTOG 0529. Of fifty-two participants, 54% were stage II, 25% IIIA and 21% IIIB. Median follow-up was 7.9 years (0.02–9.2). Local-regional failures, colostomy failures, distant metastases, OS, disease-free, and CFS at five years were 16% (95% CI: [7%, 27%], 10% [4%, 20%], 16% [7%, 27%], 76% [61%, 86%], 70% [56%, 81%] and 74% [59%, 84%], and at eight years are 16% (95% CI: [7%, 27%]), 12% [5%, 23%], 22% [12%, 34%], 68% [53%, 79%], 62% [47%, 74%] and 66% [51%, 77%], respectively. Eight participants experienced local-regional failure; five having persistent disease at twelve weeks. No isolated nodal failures occurred in the microscopic elective nodal volumes. Six participants required colostomy, five for local-regional salvage and one a temporary ostomy for anorectal dysfunction. Rates of late AEs included: fourteen participants (27%) with grade 2, eight (16%) grade 3, zero grade 4, and two (4%) with grade 5 (sinus bradycardia and myelodysplasia, possibly due to chemotherapy). Only eleven participants reported grade 0–3 sexual dysfunction. The authors concluded the treatment of anal cancer with DP-IMRT and 5FU/MMC has similar long-term efficacy as conventional radiation. Additionally, rates of grade 3 and higher late effects without pelvic tumor control compromise were decreased with enhanced normal tissue protection. The authors noted that clinical trials to optimize the radiation response in locally advanced disease are warranted. Limitations included small study size.

Clinical Practice Guidelines

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 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).

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, 2024).

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 for

selected participants with early breast cancer. A total of 520 participants, 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 five non-consecutive daily fractions at 6 Gy/fraction (two weeks of treatment) and those randomized to the whole breast irradiation I arm (N = 260) received a total of 50 Gy in 25 fractions, followed by a boost on a surgical bed of 10 Gy in five 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 whole breast irradiation 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 whole breast irradiation 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 participant (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 whole breast irradiation. They also stated that acute and late treatment-related toxicity and cosmesis outcomes were significantly in favor of APBI.

Jagsi et al. (2018) conducted a RCT comparing IMRT and deep inspiration breath hold (DIBH) versus standard, free-breathing, forward-planned, 3D-CRT in individuals with left-sided, node-positive breast cancer in whom the internal mammary nodal region was targeted. The purpose of the study was to determine whether using these technologies reduces cardiac or pulmonary toxicity during breast RT. Endpoints included dosimetric parameters and changes in pulmonary and cardiac perfusion and function, measured by single photon emission computed tomography (SPECT) scans and pulmonary function testing performed at baseline and one year post treatment. Of 62 participants 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 individuals 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 (NCT02104895) to compare health-related (HR)QOL in women with breast cancer 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 two-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 two 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 whole breast irradiation (P < 0.01). The authors concluded that early breast cancer treated with APBI-IMRT showed improved short-term and two-year HRQOL and should be strongly considered for individuals of low risk.

Lei et al. (2013) used data from a multicenter phase II non-randomized clinical trial (NCT01185145) to provide a four-year clinical update. This study’s final study protocol included participants aged 40 and older with stage 0/I ductal carcinoma in situ (DCIS) breast cancer and negative margins ≥ 0.2 cm. Participants were treated with APBI using IMRT. Outcomes of interest included treatment efficacy, pain, cosmesis and treatment-related toxicity and were evaluated at four to six weeks after treatment and every three to four months up to four years. The final analysis included 136 participants with a median follow-up period of 53.1 months (range 8.9–83.2). At four 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 participants 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 four-year results of APBI-IMRT demonstrate excellent LC, survival, cosmetic results, and toxicity profile, and warrants further investigation.

Donovan et al. (2007) conducted a prospective, multicenter, phase III randomized clinical trial to compare 3D-IMRT and standard two-dimensional (2D) RT with wedge compensators to evaluate late AEs and QOL among individuals 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 participants (N = 306, 156 received standard 2D and 150 received 3D-IMRT) received whole breast RT as 50 Gy in 25 fractions over five weeks and a boost of 10 Gy in five

fractions to the 90% isodose (11.1 By to 100%) in five 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 five years, 240 participants (122 received Standard 2D and 118 received 3D-IMRT) completed photograph compliance. Participants treated with standard 2D RT were more likely to have a breast appearance change than participants treated with IMRT (OR 1.7; 95% CI 1.2–2.5; P 0.008). Significantly fewer participants who received 3D-IMRT developed clinician assessed palpable induration in the center of the breast (P = 0.02), pectoral fold (P = 0.006), inflammatory fold (P = 0.009) and at the boost site (P < 0.001). There was no significant differences in participant 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)

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 DIBH and prone positioning may be used to try to further reduce dose to adjacent normal tissues, particularly the heart and lungs (NCCN, 2024).

Central Nervous System (CNS) Tumors

Mills et al (2024) evaluated volumetric response, survival, and functional outcomes in a subgroup of individuals with isocitrate dehydrogenase (IDH)-mutant grade 3 gliomas. The authors divided a prospective database of 187 individuals with IDH-mutant grade 3 gliomas managed with IMRT into quartiles and performed a subgroup analysis on the top quartile (N = 44), referred to as the large volume quartile (LVC). Each individual received IMRT with FET-FDG guided integrated boost. At the time of data analysis, the median follow-up for survivors was 71.5 months, 61 individuals had relapsed with a median progression free survival (PFS) of 105.1 months and a projected 10-year PFS of 50%. Of the original 187 individuals, 47 individuals were deceased, and median OS had not been reached with a projected 10-year OS of 62%. The authors reported that the LVC had a median PTV of 320cm^3 compared to 186.2cm^3 for the total group and that the projected 10-year relapse-free survival was 40% for the LVC group and 53% for the overall cohort, while the OS was 62% for both the LVC group and the whole cohort; however, the impact of PTV volume reached significance when analyzed as a continuous variable. The authors also reported that, for individuals assessable at year four post-IMRT, there were no late Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 toxicity events and that 92% of individuals were ECOG PS of zero to one, while 45% were employed at prior capacity and 28% were working with impairment. Limitations of the study included the single center design, the heterogeneity of treatment that occurred at multiple locations prior to referral to the authors' institution for radiotherapy, and the lack of a control group. The authors concluded that individuals with large volume IDH-mutant Grade 3 glioma demonstrated significant tumor reduction post-IMRT and had good long-term outcomes with respect to survival and functional status.

Chen et al. (2022) conducted a RCT to analyze the effects of three-dimensional IMRT on QOL in individuals with low-grade gliomas. One hundred participants 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 participants 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 participants 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 participants 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 individuals with low-grade gliomas. Limitations included 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 individuals with low grade gliomas. The search identified one 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, updated 2020).

Rieken et al. (2011) conducted a retrospective study to investigate treatment outcome and prognostic factors after postoperative craniospinal irradiation (CSI) RT in individuals with medulloblastomas. Sixty-six individuals (24 > 18 years of age) were treated at a single institution between 1985 and 2009. All individuals underwent initial neurosurgical tumor resection (47% complete resection), and all underwent postoperative CSI with additional boosts to the posterior fossa in all but two individuals. RT was delivered with Cobalt before 1991 and with linear accelerators afterward according to standard protocols. Three individuals 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 individuals; and in 15 individuals, 3-D cross-sectional image-based plans were employed with three using a stereotactic setting. Regarding chemotherapy, 47 of the 66 individuals received chemotherapy prior to CSI, with adults representing less than half of that number. Median follow-up was 93 months. OS, and local and distant PFS were 73%, 62%, and 77% at 60 months. Macroscopic complete tumor resection, desmoplastic histology, and early initiation of postoperative RT within 28 days were associated with improved outcome. The addition of chemotherapy was associated with slightly enhanced acute side effects, causing treatment delay or interruptions due to hematological toxicity in 15% of individuals 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 medulloblastomas 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 of a single institution's long-term experience with IMRT in individuals with complex-shaped meningioma of the skull base. Over a seven-year period, 94 individuals were treated with IMRT. Twenty-six individuals received RT as primary treatment, 14 individuals received postoperative IMRT for residual disease, and 54 individuals 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 was 93.6%. Sixty-nine individuals had stable disease based on computed tomography (CT)/magnetic resonance imaging (MRI), 19 had tumor volume reduction after IMRT, and six individuals showed local tumor progression a median of 22.3 months after RT. In 39.8% of the individuals, preexisting neurologic deficits improved. The authors concluded that IMRT is an effective and safe treatment modality for long-term LC 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.

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 individuals with IDH-mutant World Health Organization (WHO) grade 2 and grade 3 diffuse glioma. When IMRT/VMAT is unavailable, 3-D CRT is strongly recommended as a treatment option.

National Comprehensive Cancer Network (NCCN)

In its CNS Cancer guideline, NCCN states that lower doses of targeted conformal RT (including 3D-CRTand IMRT) are recommended for treatment of low-grade 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 individuals at average risk, a regimen of IMRT or proton CSI alone or with chemotherapy are both viable treatment options (NCCN, 2024).

Cervical Cancer

In their single-center, prospective, randomized study, Padhi et al. (2023) analyzed dosimetry and the incidence of acute GI toxicity in individuals treated with IMRT and 3D-CRT for cervical cancer. The study included 24 adult women who were randomized into two groups of 12 participants who received either IMRT or 3D-CRT. The authors reported that 50% of the participants in the IMRT arm developed grade 1 acute GI toxicity, 50% developed grade 2 acute GI toxicity and none of the participants developed grade 3 toxicities. In the 3D-CRT arm, the authors reported that one participant experienced grade 1 acute GI toxicity, 67% developed grade 2 acute GI toxicities and 25% developed grade 3 acute GI toxicities. The authors also reported that, in both the univariate and multivariate analyses, only the treatment technique was the statistically significant factor. Limitations of the study include the small sample size, the single-center design, the subjectivity of the GI toxicity assessment tool used, and the heterogeneity of the concurrent chemotherapy the participants received. The authors concluded that IMRT was superior to 3D-CRT regarding the dose received by bowel bag, which translated into reduced acute GI toxicity.

Tsuchida et al. (2019) conducted a retrospective cohort analysis to compare clinical outcomes and toxicity incidence among individuals 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 toxicities, and OS, DFS and LRC. A total of 73 individuals (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 individuals 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 hematologic 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 three-year DFS revealed no significant differences between IMRT and 3D-CRT or 2D-RT (three-year OS: OR, 2.41, CI, 0.62 to 9.39, P = 0.21; three-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 participants 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, participants who received IMRT experienced fewer incidences of chronic GU toxicity than participants 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 three-year OS and DFS, and that IMRT significantly reduced acute GI and GU toxicities as well as chronic GU toxicity in participants with cervical cancer.

Mell et al. (2017) conducted an international, multicenter, single-arm phase II clinical trial (NCT01554397) to evaluate the incidence of hematologic and GI toxicities in individuals with stage IB-IVA, biopsy-proven invasive carcinoma of the cervix among participants who were treated with IMRT. All 83 participants received daily IMRT concurrently with weekly cisplatin for six 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 participants were included, initiating the regimen within eight 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 participants 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 two 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 individuals with cervical cancer treated with pelvic IMRT. Participants 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 PTV while minimizing dose to the bowel, bladder, and rectum. Toxicity was graded according to the RTOG system. The study included 111 participants with Stage I-IVA cervical carcinoma. Of these, 22 were treated with postoperative IMRT, eight with IMRT followed by intracavitary brachytherapy and adjuvant hysterectomy, and 81 with IMRT followed by planned intracavitary brachytherapy. Of the participants, 63 had Stage I-IIA disease and 48 had Stage IIB-IVA disease. The median follow-up time was 27 months. The three-year OS rate and the DFS rate were 78% and 69%, respectively. The three-year pelvic failure rate and the distant failure rate were 14% and 17%, respectively. Estimates of acute and late grade 3 toxicity or higher were 2% and 7%, respectively. The authors concluded that IMRT is associated with low toxicity and favorable outcomes, supporting its safety and efficacy for cervical cancer. Prospective clinical trials are needed to evaluate the comparative efficacy of IMRT vs. conventional techniques.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

In a 2020 ASTRO guideline for cervical cancer, 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, updated 2023) 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 technique is preferred to minimize toxicities (including acute and chronic GI and hematologic toxicity) in definitive treatment of the pelvis with or without para-aortic treatment and that regular use of IGRT with orthogonal imaging and/or routine volumetric imaging (such as cone beam CT) at the time of treatment delivery, is essential to ensure appropriate coverage of targets and sparing of normal tissues. The guideline also states that IMRT is 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 individuals with an intact cervix. Very careful attention to detail and reproducibility is required for proper delivery (NCCN, 2024).

Endometrial Cancer

Klopp et al. (2018) conducted a multicenter, phase III randomized clinical trial to evaluate patient-reported acute toxicity and QOL in individuals with invasive cervical or endometrial cancer and treated with standard four field pelvic RT or pelvic IMRT. The primary end point, change in acute GI toxicity, was measured at baseline and end of RT (five 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 toxicity impacted daily activities, the -Reported Outcomes–Common Terminology Criteria for Adverse Events (PRO-CTCAE), FACT-Cx, FACT-G and Trial Outcome Index were used. A total of 278 participants 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 participants 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 participant'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 in individuals with endometrial and cervical cancer and underwent post-operative pelvic RT with either 3D-CRT or IMRT. Individuals who received definitive or palliative RT, were diagnosed with bowel obstruction 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 bowel obstruction and secondary objective was to identify other potential risk factors for bowel obstruction. A total of 224 individuals 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 individuals with endometrial cancer and 40 individuals with cervical cancer and the 3D-CRT group (N = 104) consisted of 72 individuals with endometrial cancer and 32 individuals with cervical cancer. At five years, the bowel obstruction rate was lower in the IMRT group compared with the 3D-CRT group (0.9% vs. 9.3%, P = 0.006, respectively). Individual characteristics such as age, prior abdominal surgeries and cancer type did not impact the rate of bowel obstruction however, individuals with a BMI ≥ 30 were less likely to develop a bowel obstruction (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 bowel obstruction 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 individuals 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 study participants 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 participants were enrolled, at the end of IMRT, a total of 47 participants were available for analysis and at week 15, 46 participants remained. At the completion of IMRT, 13 participants (27.1%, 95% CI 14.5-39.7%) developed at least one grade 2 GI toxicity and no participants experienced grade 3 GI toxicity. Among the 36 participants who received brachytherapy, eight participants 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 participants 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).

American Society for Radiation Oncology (ASTRO)

An ASTRO guideline for endometrial cancer strongly recommends IMRT to reduce acute and late toxicity for individuals with endometrial carcinoma undergoing adjuvant EBRT. Additionally, a vaginal internal target volume is strongly recommended for treatment planning with daily IGRT for treatment verification (Harkenrider, 2023).

National Comprehensive Cancer Network (NCCN)

According to NCCN guidelines for uterine neoplasms, treatment with IMRT is appropriate for normal tissue sparing and is preferred to minimize toxicities in definitive treatment of the pelvis with or without para-aortic treatment. (NCCN, 2024).

Esophageal Cancer

Hulshof et al. (2021) conducted a RCT to compare a dose of 50.4 Gy with that of a dose-escalating regimen to the primary tumor in definitive chemoradiation for individuals with esophageal cancer. Two hundred and sixty participants with medically inoperable and/or irresectable esophageal carcinoma were randomized to either the standard dose group to receive 50.4 Gy for 5.5 weeks to the tumor and regional lymph nodes or to the high dose group to receive 61.6 Gy to the primary tumor. Carboplatin and Paclitaxel was given in both arms weekly for six weeks. Local progression-free survival was the primary end point. Squamous cell carcinoma (SCC) was present in 61% of participants, and 39% had adenocarcinoma. Radiation treatment was completed by 94%, and 85% had at least five courses of chemotherapy. The median follow-up time for all participants was 50 months. The three year local progression-free survival was 70% in the standard dose arm versus 73% in the high dose arm (not significant). The local progression-free survival for SCC and adenocarcinoma was 75% versus 79% and 61% versus 61% for standard dose and high dose, respectively (not significant). The three-year locoregional progression-free survival was 52% and 59% for the standard dose and high dose arms, respectively. Overall, grade 4 and 5 common toxicity criteria were 12% and 5% in the standard dose arm versus 14% and 10% in the high dose arm, respectively. The authors concluded radiation dose escalation up to 61.6 Gy to the primary tumor did not result in a significant increase in LC over 50.4 Gy or survival. Additionally, the absence of a dose effect was found in both adenocarcinoma and SCC.

Xu et al. (2017) performed a systematic review and meta-analysis to compare IMRT and 3D-CRT in the treatment of esophageal cancer in terms of dose-volume histograms and outcomes including survival and toxicity. A total of seven studies were included. Of them, five studies (80 participants) were included in the dosimetric comparison, three studies (871 participants) were included in the OS analysis, and two studies (205 participants) were included in the irradiation toxicity analysis. For the lung in participants receiving doses ≥ 20 Gy and the heart in participants 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 two 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 esophageal cancer, 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 individuals with distal esophageal cancer undergoing chemoradiation. Nineteen individuals 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 PTV, 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 or PBRT may be used in clinical settings where reduction in dose to OAR (e.g., heart and lungs) is required that cannot be achieved by 3D techniques and that IMRT is now standardly used in the preoperative, definitive and postoperative treatment of esophageal and esophagogastric cancer (NCCN, 2024).

Head and Neck Cancer (HNC)

Mun et al. (2024) conducted a retrospective cohort study to evaluate recurrence patterns and survival outcomes in individuals diagnosed with glioblastoma who were treated with either IMRT or 3D-CRT. The study included 91 individuals with 60 individuals (mean age 58; 54.8% male) treated with IMRT and 31 individuals (mean age 59 years; 58.3% male) treated with 3D-CRT. The authors reported that the median OS was 18.9 months, and the median PFS was 9.4 months with no significant difference between the two groups as the median OS and PFS in the 3D-CRT group was 19.3 and 10.8 months respectively, while it was 18.4 and 8.9 months respectively in the IMRT group. The authors also reported that individuals who underwent gross total resection had higher OS and PFS than those who underwent less extensive surgery as there were 78 relapse cases with 67 in-field, five marginal and 19 out-of-field recurrences. When the authors analyzed the radiotherapy given, they reported that, among the 3D-CRT treated cases, 24 were in-field, one was marginal and nine were out-of-field recurrences while the IMRT group had 43 in-field recurrences, four marginal recurrences and 10 out-of-field recurrences. The authors also reported that the out-of-field recurrence was less frequent in the IMRT group (16.2%) than in the 3D-CRT group (36.3%) with marginal significance when partial tumor removal or biopsy cases were analyzed. Limitations of the study include the single-center, retrospective design, the small sample size and the heterogeneity regarding the size and location of the tumors as well as the surgical resections performed. The authors concluded that IMRT and 3D-CRT effectively managed glioblastoma with no significant differences in OS and PFS, and that the survival benefit with gross total resection emphasized the importance of maximal surgical resection, while the reduced rate of out-of-field recurrence in IMRT-treated individuals with partial resection highlighted its potential in cases where complete tumor removal is not feasible.

Nutting et al. (2023) conducted a phase 3, double-blind, multi-center RCT to investigate if dysphagia-optimized IMRT (DO-IMRT) reduced radiation dose to the dysphagia and aspiration related structures and improved swallowing function compared with standard IMRT. The study included 112 adults (80% male, median age 57 years) with biopsy-confirmed SCC of the oropharynx or hypopharynx with no clinical evidence of metastatic disease (stage I–IVB; T1–4, N0–3, M0) and no pre-existing swallowing dysfunction. Participants were randomly assigned 1:1 to receive DO-IMRT (N = 56, 73% male) or standard IMRT (N = 56; 88% male). Participants and speech language therapists were masked to treatment allocation. Swallowing function was evaluated by a speech and language therapist or a trained delegate at baseline and at three, six,

12, 18, and 24 months after treatment using a water swallowing test. All participants in both groups with adequate hematological and renal function were given concomitant intravenous cisplatin on day one and day 29 of radiotherapy. In participants where cisplatin was contraindicated, concurrent intravenous carboplatin was given., or they were treated with radiotherapy alone. Median follow up was 39.5 months. There were 52 (93%) participants in the DO-IMRT group and 45 (80%) participants in the standard IMRT group that completed the 12-month MDADI questionnaire. The authors reported that participants in the DO-IMRT group had significantly higher MD Anderson Dysphagia Inventory (MDADI) composite scores at 12 months than participants in the standard IMRT group, and that the difference in the MDADI composite score persisted at 24 months. The authors also reported that there were two serious adverse reactions in the DO-IMT group and seven in the standard IMRT group with the most common grade 3-4 late AEs being hearing impairment (nine in the DO-IMRT group versus seven in the standard IMRT group), dry mouth (three versus eight), and dysphagia (three versus eight). Limitations of the study include the heterogeneity of concomitant treatments received (such as chemotherapy, and swallowing exercises), and the variability in the standards of care rendered at the different treatment sites. The authors concluded that reducing dose to the pharyngeal constrictor muscle translates as was done with DO-IMRT improved patient-reported swallowing function compared with standard IMRT for the treatment of pharyngeal cancers.

Céspedes-Ajún et al. (2022) conducted a systematic review to compare the incidence of mandibular osteoradionecrosis (MORN) following head and neck radiotherapy delivered either by IMRT or 3D-CRT. Eight publications were included in the review. The primary outcome was presence or diagnosis of MORN of jaws, secondary explanatory variables including radiation dose, disease onset, jaw location and follow-up time, were noted. The authors found that IMRT had a lower risk incidence of MORN development and enhanced dose constraint than 3D-CRT (> 10%) which may translate into fewer complications after RT treatment. Limitations include small sample sizes in some included studies, inconsistent follow-up time, and uneven dose administration. The authors recommend additional future studies.

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. Participants (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 seven weeks (3D-CRT) or 66Gy/30 fractions over six weeks (IMRT). At a median follow-up of 140 months for surviving participants, 10-year Kaplan-Meier estimates of 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 participants in the IMRT arm experienced ≥ grade 2 late xerostomia and subcutaneous fibrosis at all time-points. At longer follow-up, fewer participants 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 five and ten years).

Oertel and colleagues (2019) conducted a single-center retrospective analysis investigating the impact of different radiation dose regimens on LC and OS in individuals with extramedullary head and neck plasmacytoma (EMP). A total of 33 radiation courses were administered to 27 individuals between January 2005 and January 2017 (IMRT N = 14, CRT N = 19). The median RT dose was 45 Gy (range: 12-55.8), the LC rate was 76% (93% for primary vs. 61% for secondary EMP lesions). A complete response rate to local RT was achieved for 42% of lesions (67% for primary vs. 22% for secondary EMP lesions). The overall response rate 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 individuals treated with high-dose RT had a non-significant higher overall response rate (100% vs. 80%, respectively) with longer duration of LC and longer survival than individuals in the low-dose group. There were no significant differences detected in secondary EMP individuals treated with high-dose RT regarding overall response rate and survival (60% vs. 62%, respectively). RT was well tolerated without significant AEs. The authors concluded that compared with secondary EMP, individuals with primary tumor manifestations were associated with better outcomes with a dose ≤ 45 Gy, resulting in a complete response rate that is comparable to high-dose regimens. Lower-dose RT also appeared 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). Participants with stage I-IVB disease were randomized to receive SEQ-IMRT (2 Gy × 25 fractions to low-risk 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 participants completed treatment (SEQ N = 102, SIB N = 107) and were included in the analysis. The majority had undifferentiated SCC (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, three-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 participants 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 participants received weekly cisplatin-based concurrent chemotherapy at 40 mg/m2. In the control arm, participants received 70, 63 and 56 Gy in 35 fractions to clinical target volumes (CTV) one, two and three, respectively. In the study arm, participants received 60 and 50 Gy to CTV one and CTV three, respectively. Toxicities, PFS, and OS were compared between both arms. Baseline participants-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 two -year late toxicities were observed. The median follow-up duration was 25.5 months (range 1.8 - 39.9 months). The two year PFS was 53.3% and 80%, and the two-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 individuals 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 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 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 individuals with NPC. Modalities studied included 2D-RT (N = 350), 3D-CRT (N = 390), and IMRT (N = 497). At five 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, five-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 individuals with T1-2N0 SCC of the glottic larynx treated with definitive RT. None of the individuals 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 individuals. The RT field extended from the hyoid bone to the cricoid cartilage. The median age was 60 years, and 155 individuals (70%) had T1 disease. The five-year rates of local recurrence-free survival and ultimate local recurrence-free survival 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 local recurrence-free survival . In 34 individuals with local recurrence, tumors recurred in the ipsilateral vocal cord in 28 individuals. 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 five years. Secondary endpoints were DFS, OS and toxicity associated with each schedule. SFX consisted of two Gy per fraction, once a day to a total dose of 70 Gy in 35 fractions in seven weeks. Two-dimensional RT using two or three 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 six hours, to a total dose of 79.2 Gy in 66 fractions in 6.5 weeks. A total of 250 participants with T2 (stratified by substage T2a vs T2b) glottic cancer enrolled and were randomly assigned to SFX or HFX. Of 239 participants (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 participants was 7.9 years (range, 0.6 to 13.1). The five-year LC rate was eight 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 five 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 (five-year: T2b 63.3% vs. T2a 74.1%) (HR 1.65 (1.05-2.59); P = 0.03), DFS (5-year: T2b 31.4% vs. T2a 52.4%) (HR 1.62 (1.19-2.22); P = 0.002) and OS (five-year: T2b 50.0% vs. T2a 77.5%) (2.06 (1.43-2.97); P = 0.0001). The authors concluded that five year LC was modestly higher with HFX compared to SFX for T2 glottic carcinoma, but the difference was not statistically significant, and substaging 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.

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 participants with pharyngeal SCC were randomly assigned to receive IMRT (N = 47) or CRT (N = 47). The primary endpoint was the proportion of participants with grade 2 or worse xerostomia at 12 months. Median follow-up was 44 months. Six participants from each group died before 12 months; seven participants from the CRT and two from the IMRT group were not assessed at 12 months. At 12 months, xerostomia side effects were reported in 73 of 82 participants. 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 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.

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). 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 participants with early glottic carcinoma (T1N0M0) participated in the study. Participants 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 six 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 five weeks for minimal tumor or 63 Gy in 28 fractions within 5.6 weeks for larger than minimal tumors in Arm B. The five-year LC rate was 77% for Arm A and 92% for Arm B (P = 0.004). The corresponding five-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 preferred in reducing long-term toxicity in oropharyngeal, nasal cavity, paranasal sinus, salivary gland, and nasopharyngeal cancers by reducing the dose to salivary glands, temporal lobes, auditory structures (including cochlea), and optic structures. The guidelines also state that IMRT is preferred for thyroid cancers because of its ability to spare the larynx, brachial plexus, and esophagus, and that the application of IMRT to other sites (e.g., oral cavity, larynx, hypopharynx) is preferred and may be used at the discretion of treating physicians. Advanced RT technologies such as IMRT are also recommended in the guidelines as they may offer clinically relevant advantages in specific instances to spare important OARs, such as brain, brain stem, cochlea, semicircular canals, optic chiasm and cranial nerves, retina, lacrimal glands, cornea, spinal cord, brachial plexus, mucosa, salivary glands, bone (skull base and mandible), pharyngeal constrictors, larynx, and esophagus, and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control (NCCN, 2024).

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

Gondi et al. (2024) published their final results of the NRG Oncology CC001 phase III, multi-center RCT (Brown et al. study below) with complete cognition, patient-reported outcomes, and longer-term follow-up exceeding one year. In the study, 518 adult participants were randomly assigned to receive either HA-WBRT + memantine (N = 261) or WBRT + memantine (N = 257). Median follow-up was 12.1 months with 63 participants in the WBRT + memantine group and 51 participants in the HA-WBRT + memantine group completing the12 month Hopkins Verbal Learning Test-Revised (HVLT-R) follow up assessment. The authors reported that the addition of HA to WBRT+ memantine prevented cognitive failure and was associated with less deterioration in Trail Making Tests (TMT) B at four months and HVLT-R at four and six months. The authors also reported that longitudinal modeling of imputed data showed better preservation of all HVLT-R domains and that participants who received HA-WBRT + Memantine reported less symptom burden at six and 12 months, less symptom interference at six and 12 months, and fewer cognitive symptoms over time; however, the treatment arms did not differ significantly in OS (median of 6.3 months HA-WBRT + memantine versus 7.6 months WBRT + memantine), intracranial PFS (median of 5.0 months HA-WBRT + memantine versus 5.3 months WBRT), or grade 3+ toxicity without regard to attribution (62.1% vs 58.7%) or related to treatment (19.8% vs 19.3%) between the WBRT + Memantine and HA-WBRT + memantine arms, respectively. Finally, the authors reported that the addition of an interaction term between age and treatment arm was not significant, indicating that the effect of HA was independent of age. Limitations of the study include the lack of blinding, and missing data as only 34% of study participants completed the HVLT-R assessment at 12 months. The authors concluded that HA-WBRT + memantine for brain metastases led to sustained preservation of cognitive function and continued prevention of patient-reported neurologic symptoms, symptom interference, and cognitive symptoms with no difference in survival or toxicity.

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 participants 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 participants 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 four months and learning and memory at six months. Treatment arms did not differ significantly in OS, intracranial PFS, or toxicity. At six months, using all data, participants 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 spared the hippocampal neuroregenerative niche to better preserve cognitive function and patient-reported symptoms and should be considered a standard of care for individuals with good performance status who plan to receive WBRT for brain metastases with no metastases in the hippocampal-avoidance 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 individuals with brain metastases from solid tumors recommends memantine and hippocampal avoidance should be offered to individuals who receive WBRT, and have no hippocampal lesions, and four months or more expected survival. Individuals with asymptomatic brain metastases with either KPS ≤ 50 or KPS < 70 with systemic therapy options do not derive benefit from RT (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 individuals with a better prognosis (≥ 4) and no metastases within 5mm of the hippocampus or leptomeningeal disease (NCCN, 2024).

Mediastinal Tumors

Buglione et al. (2021) performed a systematic review to evaluate the benefits and risks of the use of conformal radiotherapy involving the mediastinum for the treatment of lymphoma. The study included 29 articles (including the Besson 2016 study below) that compared IMRT and conventional proton beam therapy (PBT), or between different IMRT techniques, for the treatment of mediastinal lymphoma. The authors reported that IMRT allowed superior, or at least equivalent, PTV coverage compared to anterior-posterior/posterior-anterior (APPA) plans and/or 3D-CRT and that the conformity index was constantly improved by the use of IMRT, while the homogeneity index was also better, or at least equivalent except that fewer high dose hot-spots were obtained in IMRT plans. The authors also reported that a substantial reduction of the mean RT dose to the heart, the esophagus and to the spinal cord was achieved with IMRT, compared to APPA and 3D-CRT, while most studies reported that the use of IMRT led to breast mean and/or median doses significantly higher than those obtained with APPA or 3D-CRT. The mean reported dose to the lungs was reported by the authors to be mostly similar for IMRT compared to APPA or 3D-CRT as was the mean dose to the thyroid in the majority of the studies. Limitations of this systematic review included the small population sizes in many of the studies (median number of enrolled participants was 12), the heterogeneity of the study designs and the comparators, and the wide range of values and standard deviations of the doses to the OARs within the studies. The authors concluded that IMRT allowed a substantial reduction of the volumes of OARs exposed to high doses, which reduces the risk of long-term toxicity; however, the low doses could potentially increase the risk of secondary malignant neoplasms.

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 = five). Of interest, between 2003 and 2006, 16 individuals were treated by 3D-CRT vs zero individuals treated by IMRT. Between 2007-2009, 16 individuals were treated by 3D-CRT vs one individual receiving IMRT. Between 2010-2015, 19 individuals were treated by IMRT, and zero received 3D-CRT. All individuals were followed for five years alternately by a radiation oncologist or a hematologist. Results demonstrated LC 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 individuals. 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)

NCCN guidelines for Hodgkin lymphoma state that advanced RT technologies, such as IMRT/VMAT, DIBH or respiratory gating, IGRT and PBT may offer significant and clinically relevant advantages in specific instances to spare important normal OARs and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. The guidelines also state that, although the advantages of tightly conformal dose techniques, such as IMRT, include steep dose gradients between targets and OARS, the "low-dose bath" to normal structures is often increased and that particular treatment to treatment technique and adherence to dose constraints is essential to minimize dose to high-risk OARS. 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 OARs in a clinically meaningful way without compromising target coverage should be considered in these individuals, who are likely to enjoy long life expectancies following treatment (NCCN, 2024).

NCCN guidelines for T-Cell lymphomas state that advanced RT technologies such as IMRT, breath hold or respiratory gating, IGRT, or PBT may offer significant and clinically relevant advantages in specific instances to spare important OARs and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. The guidelines also state that achieving highly conformal dose distributions is especially important for individuals who are being treated with curative intent or who have long life expectancies following therapy, and that the use of IMRT has been associated with favorable locoregional control and improved survival outcomes (OS and PFS) with mild toxicity in individuals with early-stage disease.

NCCN guidelines for thymomas and thymic carcinomas state that a minimum technological standard for RT is CT-planned 3D-CRT and that more advanced technologies (such as four-dimensional computed tomography (4D CT), PET/CT

simulation, IMRT, VMAT, IGRT, motion management and PBT) are appropriate when needed to deliver curative RT safely. The guidelines also state that since individuals with thymomas and thymic carcinomas 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 and that IMRT is preferred over 3D-CRT and may further improve the dose distribution and decrease the dose to the normal tissue as indicated (NCCN, 2024).

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

Chun et al. (2024) conducted a secondary analysis of the NRG Oncology-RTOG 0617 RCT to compare long-term prospective outcomes of study participants receiving IMRT and 3D-CRT with concurrent carboplatin/paclitaxel for locally advanced NSCLC. The RCT included 483 participants (median age 64 years, 40.2% female) who were randomized to receive chemotherapy and either 3D-CRT (N = 255) or IMRT (N = 228) with a median follow-up of 5.2 years. The IMRT group had more tumors in unfavorable cardiac locations (145 versus 139), larger mean PTVs (486.2ml versus 426.7ml), greater PTV-to-lung ratios (0.15 versus 0.13), and larger lung V5 (61.6% versus 54.8%), than the 3D-CRT group. The authors reported that the IMRT group achieved significantly lower heart V40 than 3D-CRT (16.5% versus 20.5%) and that IMRT was associated with a two-fold reduction in grade 3 or higher pneumonitis AEs (per CTCAE version three). The authors also reported that participants in both groups similar OS, PFS, time to local failure, and DMFS at five years. A limitation of the study was that it was based on trial stratification as a secondary end point rather than randomized as a primary end point. The authors concluded that the findings from their analysis supported the use of IMRT for locally advanced NSCLC.

Another secondary analysis of the NRG Oncology RTOG 0617 RCT (Chun et al. 2017) was conducted to evaluate OS, PFS, LF distal metastasis and AEs between those who received IMRT vs. 3D-CRT. A total of 482 participants 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 participants in the IMRT group had stage IIIB/N3 disease than participants in the 3D-CRT group (38.6% vs. 30.3%; P = 0.056), more participants in the IMRT group had staging by positron emission tomography than participants in the 3D-CRT group (94.3% vs. 88.2%, P = 0.019). After treatment, there were no differences in two-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 RTOG 0617, toxicity and dosimetry data were analyzed on 322 participants with a multivariate analysis performed on 251 participants. Primary endpoints were OS, DFS survival, and toxicity. Participants were treated with RT 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 one and two 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 one year OS rates were 70.2% versus 46.8% and the two year OS rates were 45.9% versus 26.7% (P < 0.0001). Median heart V50 was significantly higher for participants with cardiac toxicity with a CTCAE grade of one or higher. Based on the authors conclusion, for participants 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 three months. Of 424 eligible stage III NSCLC participants, 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 participants (70%) completed the three-month QOL assessments, and 137 of the living participants (57%) completed the 12-month assessment. Individual demographics and baseline QOL scores were comparable between the 74-Gy and 60-Gy arms. Significantly more participants in the 74-Gy arm than in the 60-Gy arm had clinically meaningful decline in FACT-LCS at three months (45% vs 30%; P = .02). At 12 months, fewer participants 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 three 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 individuals with locally advanced NSCLC receiving 3D-CRT and IMRT between 2002 and 2010, from a single academic center. Overall survival, LRPFS, DMFS, and PFS were compared among individuals (IMRT, N = 446, and 3D-CRT, N = 206) irradiated with different techniques. The median OS of the 3D-CRT and IMRT groups were 19.4 and 23.3 months, with the five-year rate of 13% and 19%, respectively (P = .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 individuals 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 individuals, 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 participants received standard-dose chemoradiotherapy, 121 participants received high-dose chemoradiotherapy, 147 participants received standard-dose chemoradiotherapy and cetuximab, and 110 participants received high-dose chemoradiotherapy and cetuximab. Participants who received standard-dose radiotherapy had a longer median OS compared with participants 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 individuals 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, 2024).

Pancreatic Cancer

Umezawa et al. (2022) conducted a retrospective, single-center cohort study to analyze the incidences of acute GI toxicities in individuals who underwent 3D-CRT and IMRT in CRT with S-1 including prophylactic regions for pancreatic cancer. The study included 56 individuals with locally advanced pancreatic cancer without distant metastases who received S-1 daily (five days per week) during treatment with either 3D-CRT (N = 25; median age 69; 52% male) or IMRT (N = 31; median age 69; 65% male) administered in a hungry state for at least three hours and shallow free breathing. Administration of S-1 was discontinued in four individuals (16%) in the 3D-CRT group and in one individual (3.3%) in the IMRT group. Acute toxicities were evaluated according to CTCAE v5 and were defined as symptoms that occurred from the start of CRT to 14 days after the completion of CRT. GI toxicities were defined as acute toxicities related to the stomach and the duodenum. The authors reported that the values of ST V50, V40, and V30, and DU V50 were lower in the IMRT group than in the 3D-CRT group and that the dose coverage for the PTV was more sufficient in the IMRT group than in the 3D-CRT group; however, there was no significant difference in the liver V30 and kidney V18 between the two groups. The authors also reported that the frequencies of acute GI toxicity of grade 2 or higher were 36% in the 3D-CRT group and 9.7% in the IMRT group and that PTV was smaller in the IMRT group than in the 3D-CRT group. Finally, the authors reported that the PTV was smaller in the IMRT group than in the 3D-CRT group and that IMRT was able to reduce the dose to the stomach and duodenum while maintaining a sufficient dose coverage. Limitations of the study include the single-center, retrospective design, the differences in induction chemotherapy and RT dose between the 3D-CRT group and the IMRT group, and the difference in PTV between the 3D-CRT group and the IMRT group. The authors concluded that the incidence of GI toxicity was significantly reduced in the IMRT group.

Bittner et al. (2015) conducted a systematic review to determine whether toxicities can be reduced by using IMRT rather than 3D-CRT in individuals 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 individual survival (OS and PFS). A total of 13 IMRT and seven 3D-CRT studies were included in the final analysis. For acute toxicities, nausea, and vomiting ≥ grade 3 were 13.4% (109/747 participants) vs. 7.8% (35/446 participants) 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 GI: 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 participants 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 and metastatic pancreatic cancer. Participants were identified from the medical record database, selecting 63 individuals 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 individuals prior to therapy. Pain elimination or reduction was achieved in 100% of those reporting symptoms prior to RT or CCRT. The median OS for locally advanced pancreatic cancer and metastatic pancreatic cancer individuals were 15.7 months and eight 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 locally advanced pancreatic cancer and metastatic pancreatic cancer.

Clinical Practice Guidelines

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 3D-CRT, IMRT, and SBRT can result in improved PTV coverage with decreased dose to OARs. The guidelines also state that 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, 2024).

Prostate Cancer

Maggio et al. (2024) conducted a prospective, multi-center, longitudinal observational study to evaluate the evolution of QOL in the first five years following IMRT for prostate cancer. The study included 391 men (median age 71) who were treated with conventional or moderately hypofractionated IMRT while QoL was evaluated with the of EORTC QLQ-C30 at baseline, at the completion of RT, and every six months up to five years after IMRT ended. The authors reported that the longitudinal analysis on the 160 participants who completed their questionnaires at 60 months showed a trend toward the significant worsening of QOL at RT end for global health, physical and role functioning, fatigue, appetite loss, diarrhea, and pain, and that QOL worsening was recovered within six months from RT end except for physical functioning. The authors also reported that the most impaired time point was at the end of RT and that QOL dimension analysis indicated that acute Grade 2 or higher GI toxicity significantly impacted global health, physical and role functioning, fatigue, appetite loss, diarrhea, and pain, and that acute Grade 2 or higher GU toxicity resulted in lower role functioning and higher pain. Limitations include the high attrition rate and the use of concomitant therapies that may have impacted the participants' symptoms. The authors concluded that high radiation IMRT doses delivered for prostate cancer led to a temporary worsening of QOL that tended to resolve completely at six months without affecting long-term QOL, and that acute Gi and GU toxicity were the most common systems affected.

Abu-Gheida et al. (2019) presented 10-year outcomes and toxicities for individuals with localized prostate cancer who underwent IMRT with 70 Gy in 28 fractions at 2.5 Gy per fraction. Eight hundred and fifty-four participants were included in the study. Participants with multiple intermediate risk factors were considered unfavorable risk (UIR) and those with a single intermediate risk factor were considered favorable intermediate-risk (FIR) disease. The median follow-up was 11.3 years (maximum, 19 years). For participants with low-risk, FIR, UIR, and high-risk disease, the 10-year biochemical relapse free survival rates were 88%, 78%, 71%, and 42%, respectively, (P < .0001). The 10-year clinical relapse free survival were 95%, 91%, 85%, and 72% for participants with low-risk , FIR, UIR, and high-risk , respectively, (P < .0001). For all participants, the 10-year actuarial OS rate was 69% (95% confidence interval, 66%-73%), and the 10-year prostate cancer-specific mortality was 6.8% (95% confidence interval, 5.1%-8.6%) overall. For participants with low-risk , FIR, UIR and high-risk disease, the 10-year prostate cancer-specific mortality rates were 2%, 5%, 5%, and 15%. Long-term grade 3 GU or GI toxicity remained low with 10- year cumulative incidences of 2% and 1%, respectively. The authors concluded the dose-escalated moderately hypofractionated IMRT with daily IGRT resulted in acceptable tumor control rates with a very low occurrence of late grade 3 toxicity over 10 years of follow-up time and the fractionation schedule appeared to be

acceptable for participants across all risk groups. Limitations include lack of randomization, physician-reported toxicity outcomes rather than patient-reported, and some participants were lost to follow-up.

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 participants 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 three 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 five-year rate of freedom from biochemical failure was 95.4% in the IMRT arm and 94.3% in the 3D-CRT 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. Individuals who underwent IMRT were also less likely to receive additional cancer therapy. In a comparison between IMRT and proton therapy (N = 1,368), individuals who underwent IMRT 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 individuals 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 individuals with localized prostate cancer.

Clinical Practice Guidelines

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 six MV is recommended for prostate IMRT, and five to nine fields are typically used for a plan encompassing the prostate gland (Zaorsky et al., 2017).

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 individuals with low, intermediate, and high-risk disease. The guideline strongly recommends that dose escalation should be utilized when 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).

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, 2024).

Vulvar Cancer

Richman et al. (2020) conducted a retrospective, single-center review of women treated with dose-escalated IMRT for locally advanced vulvar cancer to assess the response to the therapy. The study included 49 women with a median age

68 years, and a median follow up of 20 months. The study included 25 individuals with a clinical tumor stage of T2 or greater, while 27 individuals had evidence of positive inguinal or pelvic lymph nodes and 12 individuals had evidence of positive pelvic lymph nodes. The authors reported that the overall rate of clinical complete response was 76%, while the response rate for pathologic complete response was 70%, and that DFS at two years was 65% for all individuals 81% for definitive IMRT and 55% for preoperative IMRT. The authors also reported that grade 3 toxicity was seen in 29% of individuals while late RT toxicity was seen in 6% of individuals. Limitations of the study include the single-center, retrospective design, the lack of a comparison group and the small sample size. The authors conclude that dose-escalated IMRT and concurrent cisplatin for locally advanced vulvar cancer was well tolerated and improved clinical and pathologic response relative to historical controls.

Rishi et al. (2020) conducted a retrospective, single-center study to evaluate the clinical outcomes, patterns of failure, and toxicity after high-dose IMRT for advanced vulvar cancer. Twenty-six individuals were included in the study (23 were unresectable and three refused surgery), of which 15 had inguinal node metastases and 10 had pelvic node metastases. Individuals also received platinum-based chemotherapy in addition to the IMRT. The authors reported that complete response was achieved in 80.7% of the individuals and that recurrent disease occurred inside the irradiated volume in five individuals who had persistent disease following treatment. The authors also reported that actuarial one year local, regional and distant controls were 72.4%, 85.4%, and 86%, respectively, while one and two year OSs were 91% and 62%, respectively. Finally, the authors reported that complete response at three months was a strong predictor for OS, and that lymph node metastases adversely affected OS. Grade 3 and 4 late urinary and soft-tissue toxicity was reported by the authors to be seen in five individuals and was related to tumor doses > 66 Gy and prior pelvic radiation. The study was limited by the single-center, retrospective design, the small sample size, and the lack of a comparator group. The authors concluded that high dose IMRT for vulvar cancer achieved high rates of LC with acceptable dose-dependent long-term toxicity.

In a retrospective, single-center study to evaluate treatment techniques and clinical outcomes after IMRT for vulvar cancer, Rao et al. (2017) reviewed the records of 39 women (median age 62 years) with SCC of the vulva treated with IMRT, which included 21 individuals treated with postoperative IMRT, 13 with definitive IMRT and five with preoperative IMRT. Fourteen individuals also received concurrent chemotherapy with cisplatin (N = 13) or cisplatin and 5-fluorouracil. The individuals were seen at six weeks, three, six and 12 months, and at least annually after completion of RT with a median follow-up of 34 months. The authors reported that the three year LRC was 42% and the OS was 49% for those who received definitive IMRT while individuals who received neoadjuvant IMRT achieved a 69% complete clinical response rate and 44% had complete pathologic response. The authors also reported that there were no acute grade 3 or 4 hematological, GI, or GU toxicities, nor were there any late grade 3-4 GI or GU toxicities. This study was limited by the small sample size, the single-center, retrospective design, the lack of a comparator group and the heterogeneity of the treatments provided to the study participants. The authors concluded that IMRT for vulvar cancer was associated with high rates of LRC in the postoperative setting and limited radiation-related toxicity, and that durable LRC of disease after definitive IMRT remains challenging.

Clinical Practice Guidelines

European Society of Gynaecological Oncology (ESGO)

The 2023 updated ESGO guidelines for management of vulvar cancer notes that adjuvant radiotherapy should be performed by IMRT techniques with daily set-up verification especially in cases when there is a simultaneous integrated boost used (Oonk et al., 2023).

National Comprehensive Cancer Network (NCCN)

NCCN guidelines state that advanced techniques such as IMRT, IGRT, and interstitial high dose-rate HDR brachytherapy should be used to maximize dose to the target and minimize the dose to the normal tissues. The guidelines also state that image-guided IMRT is an essential component of treatment (to account for vulvar edema or marked tumor regression) (NCCN 2024).

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 the following website for more information (use product codes MUJ and IYE): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 8, 2024)

References

Abu-Gheida I, Reddy CA, Kotecha R, et al. Ten-year outcomes of moderately hypofractionated (70 gy in 28 fractions) intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2019 Jun 1;104(2):325-333.

Alicikus ZA, Yamada Y, Zhang Z, et al. Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. Cancer. 2011 Apr 1;117(7):1429-37.

American College of Radiology (ACR). Radiation Oncology Resources. External beam therapy (EBT). Updated May, 2024. https://www.radiologyinfo.org/en/info.cfm?pg=ebt. Accessed November 6, 2024.

American College of Radiology (ACR). Radiation Oncology Resources. Intensity-modulated radiation therapy (IMRT). Updated May 2023. https://www.radiologyinfo.org/en/info.cfm?pg=imrt. Accessed November 6, 2024.

American College of Radiology. ACR-ARS. Practice Parameter for image-guided radiation therapy (IGRT). 2024; Available at: https://www.acr.org/Clinical-Resources/Practice-Parameters-and-Technical-Standards. Accessed November 6, 2024.

American College of Radiology. ACR-ARS . Practice Parameter for intensity modulated radiation therapy (IMRT). 2021. Available at: https://www.acr.org/Clinical-Resources/Practice-Parameters-and-Technical-Standards. Accessed November 6, 2024.

American Society for Radiation Oncology (ASTRO). Clinical Practice Guidelines. Radiation therapy for treatment of soft tissue sarcoma in adults. July 2021. Available at: https://www.astro.org/Patient-Care-and-Research/Clinical-Practice-Statements/Clinical-Practice-Guidelines. Accessed November 6, 2024.

Barillot I, Tavernier E, Peignaux K, et al. Impact of post-operative intensity modulated radiotherapy on acute gastro-intestinal toxicity for patients with endometrial cancer: results of the phase II RTCMIENDOMETRE French multicenter trial. Radiother Oncol. 2014 Apr;111(1):138-43.

Besson N, Pernin V, Zefkili S, et al. Evolution of radiation techniques in the treatment of mediastinal lymphoma: from 3D conformal radiotherapy (3DCRT) to intensity-modulated RT (IMRT) using helical tomotherapy (HT): a single-center experience and review of the literature. Br J Radiol. 2016;89(1059):20150409.

Bittner MI, Grosu AL, Brunner TB. Comparison of toxicity after IMRT and 3D-conformal radiotherapy for patients with pancreatic cancer - a systematic review. Radiother Oncol. 2015 Jan;114(1):117-21.

Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomized, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16(2):187–199.

Brown PD, Gondi V, Pugh S, et al.; for NRG Oncology. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG Oncology CC001. J Clin Oncol. 2020 Apr 1;38(10):1019-1029.

Bryant AK, Huynh-Le MP, Simpson DR, et al. Intensity modulated radiation therapy versus conventional radiation for anal cancer in the veterans affairs system. Int J Radiat Oncol Biol Phys. 2018 Sep 1;102(1):109-115.

Buglione M, Guerini AE, Filippi AR, et al. A systematic review on intensity modulated radiation therapy for mediastinal Hodgkin's lymphoma. Crit Rev Oncol Hematol. 2021 Nov;167:103437.

Céspedes-Ajún CA, Amghar-Maach S, Gay-Escoda C. Incidence of mandibular osteoradionecrosis (MORN) after intensity modulated radiotherapy (IMRT) versus 3D conformal radiotherapy (3D-CRT): a systematic review. Med Oral Patol Oral Cir Bucal. 2022 Nov 1;27(6):e539-e549.

Chen H, Rao H, Huang Y. The effect on quality of life after three-dimensional intensity-modulated radiation therapy in patients with low-grade glioma. Comput Math Methods Med. 2022 Aug 13;2022:5854013.

Chino J, Annunziata CM, Beriwal S, et a.. The ASTRO Clinical Practice Guidelines in cervical cancer: optimizing radiation therapy for improved outcomes. Gynecol Oncol. 2020 Dec;159(3):607-610.

Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial. J Clin Oncol. 2017 Jan;35(1):56-62.

Chun SG, Hu C, Komaki RU, et al. Long-term prospective outcomes of intensity modulated radiotherapy for locally advanced lung cancer: a secondary analysis of a randomized clinical trial. JAMA Oncol. 2024 Aug 1;10(8):1111-1115.

Cibula D, Pötter R, Planchamp F, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. Radiother Oncol. 2018 Jun;127(3):404-416.

Donovan E, Bleakley N, Denholm E, et al. Breast Technology Group. Randomized trial of standard 2D radiotherapy (RT) versus intensity-modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol. 2007 Mar;82(3):254-64.

Eastham JA, Auffenberg GB, Barocas DA, et al. Clinically localized prostate cancer: AUA/ASTRO guideline, part III: principles of radiation and future directions. J Urol. 2022 Jul;208(1):26-33.

Elshaikh MA, Yashar CM, Wolfson AH, et al. ACR Appropriateness Criteria®. Advanced stage endometrial cancer. Am J Clin Oncol. 2014 Aug;37(4):391-6.

Gondi V, Deshmukh S, Brown PD, et al. Sustained preservation of cognition and prevention of patient-reported symptoms with hippocampal avoidance during whole-brain radiation therapy for brain metastases: final results of NRG Oncology CC001. Int J Radiat Oncol Biol Phys. 2023 Nov 1;117(3):571-580.

Gupta T, Sinha S, Ghosh-Laskar S, et al. Intensity-modulated radiation therapy versus three-dimensional conformal radiotherapy in head and neck squamous cell carcinoma: long-term and mature outcomes of a prospective randomized trial. Radiat Oncol. 2020 Sep 16;15(1):218.

Halasz LM, Attia A, Bradfield L, et al. Radiation therapy for IDH-mutant grade 2 and grade 3 diffuse glioma: an ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2022 Sep-Oct;12(5):370-386.

Han K, Cummings BJ, Lindsay P, et al. Prospective evaluation of acute toxicity and quality of life after IMRT and concurrent chemotherapy for anal canal and perianal cancer. Int J Radiat Oncol Biol Phys. 2014 Nov 1;90(3):587-94.

Harkenrider MM, Abu-Rustum N, Albuquerque K, et al. Radiation therapy for endometrial cancer: an American Society for Radiation Oncology Clinical Practice Guideline. Pract Radiat Oncol. 2023 Jan-Feb;13(1):41-65.

Hasselle MD, Rose BS, Kochanski JD, et al. Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys. 2011 Aug 1;80(5):1436-45.

Hong TS, Pretz JL, Herman JM, et al. ACR Appropriateness Criteria®. Anal cancer. Gastrointest Cancer Res. 2014 Jan;7(1):4-14.

Hulshof MCCM, Geijsen ED, Rozema T, et al. Randomized study on dose escalation in definitive chemoradiation for patients with locally advanced esophageal cancer (ARTDECO Study). J Clin Oncol. 2021 Sep 1;39(25):2816-2824.

Jagsi R, Griffith KA, Moran JM, et al. A randomized comparison of radiation therapy techniques in the management of node-positive breast cancer: primary outcomes analysis. Int J Radiat Oncol Biol Phys. 2018 Aug 1;101(5):1149-1158.

Jhaveri J, Rayfield L, Liu Y, et al. Impact of intensity modulated radiation therapy on survival in anal cancer. J Gastrointest Oncol. 2018 Aug;9(4):618-630.

Joseph K, Balushi MA, Ghosh S, et al. Long-term patient-reported quality of life of anal cancer survivors treated with intensity modulated radiation therapy and concurrent chemotherapy: results from a prospective phase II trial. Int J Radiat Oncol Biol Phys. 2023 Oct 1;117(2):434-445.

Kachnic LA, Tsai HK, Coen JJ, et al. Dose-painted intensity-modulated radiation therapy for anal cancer: a multi-institutional report of acute toxicity and response to therapy. Int J Radiat Oncol Biol Phys. 2012 Jan 1;82(1):153-8.

Kachnic LA, Winter KA, Myerson RJ, et al. Long-term outcomes of NRG Oncology/RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-Fluorouracil and Mitomycin-C for the reduction of acute morbidity in anal canal cancer. Int J Radiat Oncol Biol Phys. 2022 Jan 1;112(1):146-157.

Karim AB, Afra D, Cornu P, et al. Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BRO4: an interim analysis. Int J Radiat Oncol Biol Phys. 2002 Feb 1;52(2):316-24.

Klopp AH, Yeung AR, Deshmukh S, et al. Patient-reported toxicity during pelvic intensity-modulated radiation therapy: NRG Oncology-RTOG 1203. J Clin Oncol. 2018 Aug 20;36(24):2538-2544.

Kole TP, Aghayere O, Kwah J, et al. Comparison of heart and coronary artery doses associated with intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy for distal esophageal cancer. Int J Radiat Oncol Biol Phys. 2012 Aug 1;83(5):1580-6.

Landsteiner A, Sowerby C, Ullman K, et al. Hypofractionation radiation therapy for definitive treatment of selected cancers: a systematic review. Washington (DC): Department of Veterans Affairs (US); 2023 May. PMID: 37769054.

Lei RY, Leonard CE, Howell KT, et al. Four-year clinical update from a prospective trial of accelerated partial breast intensity-modulated radiotherapy (APBIMRT). Breast Cancer Res Treat. 2013 Jul;140(1):119-33.

Lertbutsayanukul C, Prayongrat A, Kannarunimit D, et al. A randomized phase III study between sequential versus simultaneous integrated boost intensity-modulated radiation therapy in nasopharyngeal carcinoma. Strahlenther Onkol. 2018 May;194(5):375-385.

Lim YJ, Wu HG, Kwon TK, et al. Long-term outcome of definitive radiotherapy for early glottic cancer: prognostic factors and patterns of local failure. Cancer Res Treat. 2015 Oct;47(4):862-70.

Lin Y, Chen K, Lu Z, Zhao L, Tao Y, Ouyang Y, Cao X. Intensity-modulated radiation therapy for definitive treatment of cervical cancer: a meta-analysis. Radiat Oncol. 2018 Sep 14;13(1):177.

Maggio A, Rancati T, Gatti M, et al. Quality of life longitudinal evaluation in prostate cancer patients from radiotherapy start to 5 years after IMRT-IGRT. Curr Oncol. 2024 Feb 1;31(2):839-848.

Manfrida S, Fionda B, Mariani S, et al. High-tailored anal canal radiotherapy (HIT-ART): outcomes of a 10-year single center clinical experience. In Vivo. 2024 May-Jun;38(3):1306-1315.

Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: long-term results of the randomized phase III APBI-IMRT-Florence Trial. J Clin Oncol. 2020 Dec 10;38(35):4175-4183.

Meattini I, Saieva C, Miccinesi G, et al. Accelerated partial breast irradiation using intensity modulated radiotherapy versus whole breast irradiation: health-related quality of life final analysis from the Florence phase 3 trial. Eur J Cancer. 2017 May;76:17-26.

Mell LK, Sirák I, Wei L, et al. Bone marrow-sparing intensity modulated radiation therapy with concurrent cisplatin for stage IB-IVA cervical cancer: an international multicenter phase II clinical trial (INTERTECC-2). Int J Radiat Oncol Biol Phys. 2017 Mar 1;97(3):536-545.

Milker-Zabel S, Zabel-du Bois A, Huber P, et al. Intensity-modulated radiotherapy for complex-shaped meningioma of the skull base: long-term experience of a single institution. Int J Radiat Oncol Biol Phys. 2007 Jul 1;68(3):858-63.

Mills D, Horsley P, Venkatasha V, Back M. Volumetric response and survival of patients with bulky IDH-mutated Grade 3 glioma managed with FET-FDG-guided integrated boost IMRT. Clin Oncol (R Coll Radiol). 2024 Jun;36(6):343-352.

Moon SH, Cho KH, Lee CG, et al. IMRT vs. 2D-radiotherapy or 3D-conformal radiotherapy of nasopharyngeal carcinoma: survival outcome in a Korean multi-institutional retrospective study (KROG 11-06). Strahlenther Onkol. 2016 Jun;192(6):377-85.

Movsas B, Hu C, Sloan J, et al. Quality of life analysis of a radiation dose-escalation study of patients with non-small-cell lung cancer: a secondary analysis of the radiation therapy oncology group 0617 randomized clinical trial. JAMA Oncol. 2016 Mar;2(3):359-67.

Mun SH, Jang HS, Choi BO, et al. Recurrence pattern of glioblastoma treated with intensity-modulated radiation therapy versus three-dimensional conformal radiation therapy. Radiat Oncol J. 2024 Sep;42(3):218-227.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Anal carcinoma. V1.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. B-cell lymphoma. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast cancer. V5.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Central nervous system cancers. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Cervical cancer. V4.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Esophageal and esophagogastric junction cancers. V4.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Head and neck cancers. V4.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Hodgkin lymphoma. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Multiple myeloma. V1.2025.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. V11.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Pancreatic adenocarcinoma. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Prostate cancer. V4.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. T-cell lymphoma. V4.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Thymomas and thymic carcinomas. V1.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Uterine neoplasms. V3.2024.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Vulvar cancer. V4.2024.

Nutting C, Finneran L, Roe J, et al. Dysphagia-optimised intensity-modulated radiotherapy versus standard intensity-modulated radiotherapy in patients with head and neck cancer (DARS): a phase 3, multicentre, randomised, controlled trial. Lancet Oncol. 2023 Aug;24(8):868-880.

Nutting CM, Morden JP, Harrington KJ, et al.; PARSPORT trial management group. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicenter randomized controlled trial. Lancet Oncol. 2011 Feb;12(2):127-36.

Oertel M, Elsayad K, Kroeger KJ, et al. Impact of radiation dose on local control and survival in extramedullary head and neck plasmacytoma. Radiat Oncol. 2019 Apr 15;14(1):63.

Oonk MHM, Planchamp F, Baldwin P, et al. European Society of Gynaecological Oncology guidelines for the management of patients with vulvar cancer - update 2023. Int J Gynecol Cancer. 2023 Jul 3;33(7):1023-1043.

Padhi S, Mahapatra BR, Pati KC, et al. Comparison of acute gastrointestinal toxicity of intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy in patients of carcinoma cervix. Cureus. 2023 Nov 16;15(11):e48876.

Palta M, Godfrey D, Goodman KA, et al. Radiation therapy for pancreatic cancer: Executive Summary of an ASTRO Clinical Practice Guideline. Pract Radiat Oncol. 2019 Sep - Oct;9(5):322-332.

Rao S, Guren MG, Khan K, et al.; ESMO Guidelines Committee. Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2021 Sep;32(9):1087-1100.

Rao YJ, Chundury A, Schwarz JK, et al. Intensity modulated radiation therapy for squamous cell carcinoma of the vulva: treatment technique and outcomes. Adv Radiat Oncol. 2017 Feb 28;2(2):148-158.

Ratko TA, Douglas GW, de Souza JA, et al. Radiotherapy treatments for head and neck cancer update. Comparative Effectiveness Review No. 144. (prepared by Blue Cross and Blue Shield Association Evidence-based Practice Center under Contract No. 290-2007-10058.) AHRQ Publication No. 15-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2014.

Richman AH, Vargo JA, Ling DC, et al. Dose-escalated intensity modulated radiation therapy in patients with locally-advanced vulvar cancer - does it increase response rate? Gynecol Oncol. 2020 Dec;159(3):657-662.

Rieken S, Mohr A, Habermehl D, et al. Outcome and prognostic factors of radiation therapy for medulloblastoma. Int J Radiat Oncol Biol Phys. 2011;81:e7–e13.

Rishi A, Rollins M, Ahmed KA, et al. High-dose intensity-modulated chemoradiotherapy in vulvar squamous cell carcinoma: Outcome and toxicity. Gynecol Oncol. 2020 Feb;156(2):349-356.

Samson DJ, Ratko TA, Rothenberg BM, et al. Comparative effectiveness, and safety of radiotherapy treatments for head and neck cancer. Comparative Effectiveness Review No. 20. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-02-0026.) Rockville, MD: Agency for Healthcare Research and Quality, May 2010.

Sarmiento JM, Venteicher AS, Patil CG. Early versus delayed postoperative radiotherapy for treatment of low-grade gliomas. Cochrane Database Syst Rev. 2015 Jun 29;(6):CD009229. Updated January 20, 2020.

Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA. 2012 Apr 18;307(15):1611-20.

Shih KK, Hajj C, Kollmeier M, et al. Impact of postoperative intensity-modulated radiation therapy (IMRT) on the rate of bowel obstruction in gynecologic malignancy. Gynecol Oncol. 2016 Oct;143(1):18-21.

Speirs CK, DeWees TA, Rehman S, et al. Heart dose is an independent dosimetric predictor of overall survival in locally advanced non-small cell lung cancer. J Thorac Oncol. 2017 Feb;12(2):293-301.

Tandon S, Gairola M, Ahlawat P, et al. Randomized controlled study comparing simultaneous modulated accelerated radiotherapy versus simultaneous integrated boost intensity modulated radiotherapy in the treatment of locally advanced head and neck cancer. J Egypt Natl Canc Inst. 2018 Sep;30(3):107-115.

Trotti A 3rd, Zhang Q, Bentzen SM, et al. Randomized trial of hyperfractionation versus conventional fractionation in T2 squamous cell carcinoma of the vocal cord (RTOG 9512). Int J Radiat Oncol Biol Phys. 2014 Aug 1;89(5):958-963.

Tsang RW, Campbell BA, Goda JS, et al. Radiation therapy for solitary plasmacytoma and multiple myeloma: guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2018 Jul 15;101(4):794-808.

Tsuchida K, Murakami N, Kato T, et al. Postoperative pelvic intensity-modulated radiation therapy reduced the incidence of late gastrointestinal complications for uterine cervical cancer patients. J Radiat Res. 2019 Jun 28.

Umezawa R, Nakagawa K, Mizuma M, et al. Comparison of acute gastrointestinal toxicities between 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy including prophylactic regions in chemoradiotherapy with S-1 for pancreatic cancer-importance of dose volume histogram parameters in the stomach as the predictive factors. J Radiat Res. 2022 Dec 6;63(6):856-865.

Vendrely V, Lemanski C, Pommier P, et al.; for FFCD investigators/collaborators. Treatment, outcome, and prognostic factors in non-metastatic anal cancer: The French nationwide cohort study FFCD-ANABASE. Radiother Oncol. 2023 Jun;183:109542.

Viani GA, Viana BS, Martin JE, et al. Intensity-modulated radiotherapy reduces toxicity with similar biochemical control compared with 3-dimensional conformal radiotherapy for prostate cancer: a randomized clinical trial. Cancer. 2016 Jul 1;122(13):2004-11.

Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for brain metastases: ASCO-SNO-ASTRO guideline. J Clin Oncol. 2022 Feb 10;40(5):492-516.

Wahl AO, Gaffney DK, Jhingran A, et al. ACR Appropriateness Criteria®. Adjuvant management of early-stage endometrial cancer. Oncology (Williston Park). 2016 Sep 15;30(9):816-22.

Wang J, Zhou Z, Liang J, et al. Intensity-modulated radiation therapy may improve local-regional tumor control for locally advanced non-small cell lung cancer compared with three-dimensional conformal radiation therapy. Oncologist. 2016 Dec;21(12):1530-1537.

Wang Z, Ren ZG, Ma NY, et al. Intensity modulated radiotherapy for locally advanced and metastatic pancreatic cancer: a mono-institutional retrospective analysis. Radiat Oncol. 2015 Jan 10;10:14.

Xu D, Li G, Li H, et al. Comparison of IMRT versus 3D-CRT in the treatment of esophagus cancer: a systematic review and meta-analysis. Medicine (Baltimore). 2017 Aug;96(31):e7685.

Yamazaki H, Nishiyama K, Tanaka E, et al. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. Int J Radiat Oncol Biol Phys. 2006 Jan 1;64(1):77-82.

Zaorsky NG, Showalter TN, Ezzell GA, et al. ACR Appropriateness Criteria®. External beam radiation therapy treatment planning for clinically localized prostate cancer, part II of II. Adv Radiat Oncol. 2017 Mar 20;2(3):437-454.

Policy History/Revision Information

Date	Summary of Changes

03/01/2025	**Coverage Rationale**
	• Replaced language indicating “intensity-modulated radiation therapy (IMRT) is covered without further review for *persons 18 years and younger*” with “IMRT is covered without further review for *individuals younger than 19 years of age*”
	Intensity-Modulated Radiation Therapy (IMRT) for Definitive Therapy
	• Revised list of conditions for which IMRT for Definitive Therapy for the primary site is proven and medically necessary:
	  ○ Added “vulvar cancer”
	  ○ Replaced “anal cancer” with “*anus*/anal *canal* cancer”
	Definitions
	• Updated definition of “Definitive Therapy”
	Supporting Information
	• Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information

Date	Summary of Changes
	• Archived previous policy version 2025T0407DD

Instructions for Use

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

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

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