Intensity-Modulated Radiation Therapy

Policy Number: CS064.T
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➲ Instructions for Use

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Commercial Policy

- Intensity-Modulated Radiation Therapy

Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Idaho	Intensity-Modulated Radiation Therapy (for Idaho Only)
Indiana	None
Kansas	Intensity-Modulated Radiation Therapy (for Kansas Only)
Kentucky	Intensity-Modulated Radiation Therapy (for Kentucky Only)
Nebraska	Intensity-Modulated Radiation Therapy (for Nebraska Only)
New Jersey	Intensity-Modulated Radiation Therapy (for New Jersey Only)
New Mexico	Intensity-Modulated Radiation Therapy (for New Mexico Only)
North Carolina	Intensity-Modulated Radiation Therapy (for North Carolina Only)
Ohio	Intensity-Modulated Radiation Therapy (for Ohio Only)
Pennsylvania	Intensity-Modulated Radiation Therapy (for Pennsylvania Only)
Tennessee	Intensity-Modulated Radiation Therapy (for Tennessee Only)

Coverage Rationale

Note: This policy applies to individuals 19 years of age or 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 when any of the following criteria are met:
    - When the left-sided internal mammary nodes are being treated; or
    - Accelerated partial-breast irradiation of up to five fractions
  - Central nervous system tumors (primary or benign), including the brain, brainstem, and spinal cord
  - Cervical cancer

    - Endometrial cancer
    - Esophageal cancer
    - Head and neck cancers, including lymphoma and solitary plasmacytomas, when treatment includes the following areas: pharynx (nasopharynx, oropharynx, and hypopharynx), larynx, salivary glands, oral cavity (includes the tongue), nasal cavity, and paranasal sinuses
    - Hepatocellular carcinoma, unresectable
    - Intrahepatic cholangiocarcinoma, unresectable
    - Hodgkin lymphoma
    - Mediastinal tumors (e.g., lymphomas, thyroid, thymomas, tracheal cancer)
    - Non-small cell lung cancer when any of the following criteria are met:
        - Stage I to II undergoing hypofractionated radiation therapy up to 10 fractions; or
        - Stage III, undergoing chemoradiation therapy
    - Pancreatic cancer
    - Prostate cancer
    - Rectal cancer when treatment involves inguinal lymph nodes
    - Small cell lung cancer, limited stage
    - Soft tissue sarcoma, retroperitoneal/intra-abdominal location
    - Vulvar cancer
- Hippocampal-avoidance whole-brain radiation therapy of up to 10 fractions is considered proven and medically necessary when all the following criteria are met:
    - Brain metastasis; and
    - Eastern Cooperative Oncology Group performance status of ≤ 2 or Karnofsky performance status of ≥ 70; and
    - Prognosis of 4 months or greater; and
    - Absence of leptomeningeal disease
- IMRT may be considered medically necessary for a condition that is not defined above, including recurrences or metastases in selected cases. Requests for an exception 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 (i.e., as specified by the Radiation Therapy Oncology Group or QUANTEC guidelines) and is demonstrated on a comparison of treatment plans for the IMRT and non-IMRT technique (e.g., 3D conformal treatment plan)
    - The same or an immediately adjacent area has been previously irradiated, and the dose distribution in 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 federal, state, or contractual requirements, 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 guidelines titled Medical Records Documentation Used for Reviews.

Definitions

Definitive Therapy: Radiation treatments for cancer with a curative intent (National Comprehensive Cancer Network, 2025; Landsteiner et al., 2023). The National Cancer Institute defines curative-intent therapy as a treatment designed to eliminate a disease or illness, aiming for a full recovery while maintaining satisfactory quality of life. In cancer care, the suitability of a curative approach depends on the specific type and stage of cancer (National Cancer Institute, 2025).

Applicable Codes

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

Coding Clarification:
Standard single-isocenter IMRT or VMAT should be billed under CPT code 77407 (radiation treatment delivery, intermediate). CPT code 77412 (radiation treatment delivery, complex) should be used for treatments that require multiple isocenters or single-isocenter delivery with active motion-management techniques. When CPT code 77412 is reported, documentation must clearly describe the circumstances that justify Level 3 rather than Level 2 treatment delivery (AMA, 2026; CMS, 2026).

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
77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
77407	Radiation treatment delivery; Level 2, single-isocenter (e.g., 3D or IMRT), photons, including imaging guidance, when performed
77412	Radiation treatment delivery; Level 3, multiple isocenters with photon therapy (e.g., 2D, 3D, or IMRT) or a single-isocenter photon therapy (e.g., 3D or IMRT) with active motion management, or total skin electrons, or mixed-electron/photon field(s), including imaging guidance, 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

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 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. External beam radiation therapy is used to treat many types of cancer and may be used to relieve symptoms in individuals with advanced cancer or cancer that has metastasized (American College of Radiology, 2024).

Intensity-modulated radiation therapy (IMRT) is an advanced mode of high-precision radiation therapy that uses computer-controlled linear accelerators to deliver precise radiation doses to a malignant tumor or specific areas in the tumor. IMRT allows the radiation dose to conform more precisely to the 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 (American College of Radiology, 2023).

Image-guided radiation therapy uses 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 anatomical, biological, and positional changes over time in individuals. It is often used in conjunction with IMRT and other advanced forms of radiation therapy (American College of Radiology/American Radium Society, 2024).

Clinical Evidence

Intensity-modulated radiation therapy (IMRT) has become widely used for a variety of clinical indications such as tumors of the central nervous system, head and neck, breast, prostate, gastrointestinal (GI) tract, lung, and gynecologic system as well as sites that were previously irradiated. In general, the ability of IMRT to deliver the dose preferentially to target structures in close proximity to organs at risk (OARs) and other nontarget tissues makes it a valuable tool that enables the radiation oncologist to deliver the dose to target volumes while minimizing the dose to adjacent normal tissues (American College of Radiology, 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 patients (72.7% female; median age, 64.3 years) who were diagnosed with squamous cell anal cancer (60.9% were staged cT3-4; 70.9% were node positive) and treated with long-course IMRT and concurrent chemotherapy. The authors reported that 68.2% of the patients received a sequential boost (administered by IMRT or interventional radiotherapy to obtain a total equivalent dose in 2 Gy of 54-60 Gy) and that the acute grade ≥ 3 toxicity rate was 36.4%, with a median follow-up of 35.4 months. The authors also reported that a total of 83% of patients achieved a clinical complete response, while locoregional recurrence occurred in 20.9% of patients, and distant metastases occurred in 6.4% of cases. Salvage surgery was reported by the authors to have occurred in 12.7% of the patients, while a total of 25.5% (n = 28) of the patients had grade ≥ 2; of these patients, 4.5% (n = 5) had grade 3 late toxicity. The authors reported that the estimated 3-year overall survival (OS) rate was 92%, disease-free survival (DFS) rate was 72%, and colostomy-free survival (CFS) rate was 84%, with a 3-year locoregional recurrence of 22%. Limitations of the study include the single-center retrospective design and lack of data related to patients' risk factors, such as smoking history and human papillomavirus (HPV) status. The authors concluded that IMRT was confirmed to be effective in patients with locally advanced squamous cell anal cancer, with favorable acute and late toxicity rates and excellent long-term rates of tumor control and CFS compared with patients who received historical 3D 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 2, single-center clinical trial in participants with anal squamous cell carcinoma who were treated with IMRT and concurrent 5-fluorouracil (5FU)/mitomycin-C (MMC). The study included 54 adults (34% male; median age, 58 years) who underwent a QOL evaluation with the European Organisation 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 the QLQ-C30 and QLQ-CR29 questionnaires were 100%, 88%, 83%, 74%, 74%, and 74% at baseline and 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 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 the 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, lack of a comparator, heterogeneity of concurrent treatments (such as surgery), use of nonspecific questionnaires, and small sample size. The authors concluded that, when compared with historical data, IMRT is associated with reduced long-term effects on QOL; additionally, the majority of participants who were treated with IMRT experienced clinically significant recovery of function and improvement in QOL over 5 years after completion of treatment, although chronic diarrhea, fecal incontinence, and urinary and sexual dysfunction were primarily responsible for deterioration of 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 nonmetastatic squamous cell carcinoma of the anus using chemoradiotherapy or radiation therapy as first-line treatment to evaluate treatment characteristics, CFS, DFS, OS, and prognostic factors. Among 1,015 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 in 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. DFS, CFS, and OS rates at 3 years were 84.3%, 85.6%, and 91.7%, respectively, in the early-stage group compared with 64.4%, 66.9%, and 78.2% in the locally advanced group ($p < 0.001$). In multivariate analyses, male sex, a locally advanced stage, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≥ 1 were associated with poorer DFS, CFS, and OS. IMRT was significantly associated with better CFS in the whole cohort and nearly reached significance in the locally advanced group. The authors stated that the treatment of participants with squamous cell carcinoma of the anus 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 patients who were diagnosed with nonmetastatic, stage I or II anal squamous cell carcinoma and treated with concurrent chemoradiation therapy between 2000 and 2015. Patients were stratified into two groups based on radiation type: IMRT and conventional radiation therapy (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; 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 included a total of 779 patients (403 received chemoradiotherapy,

and 376 received IMRT), with a median follow-up period of 5.9 years. Results showed that treatment with IMRT was associated with decreased treatment breaks for 5 or more days [hazard ratio (HR), 0.58; 95% CI, 0.37-0.91; p = 0.02], increased rates of receiving two cycles of MMC chemotherapy [odds ratio (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, and cancer-specific survival. The authors concluded that in the real-world setting, use of IMRT offers substantial benefits compared with CRT for individuals with anal cancer who are undergoing concurrent chemoradiation therapy.

Jhaveri et al. (2018) conducted a retrospective cohort analysis using the National Cancer Database to identify patients with nonmetastatic anal cancer. Patients were required to have histologically 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 end point was OS. A total of 8,108 patients were identified, with a median follow-up time of 54.4 months. After propensity score matching, 2,334 IMRT patients were matched to 2,334 non-IMRT patients, with no imbalances in demographics, tumor characteristics, and treatment variables. The multivariable Cox proportional hazards model for OS showed that the IMRT group had superior survival compared with the non-IMRT group (HR, 0.83; 95% CI, 0.74-0.94; p = 0.002). The adjusted Kaplan-Meier survival analysis showed that IMRT was associated with improved OS at 5 years (74.6% vs. 70.5%; p = 0.0022). The authors concluded that for the treatment of nonmetastatic anal cancer, concurrent IMRT-based conformal radiation therapy is associated with improved survival 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 who were 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. The 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 MMC. 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 that were most relevant to acute toxicities returned to baseline by 3 months after treatment.

Kachnic et al. (2013) conducted a prospective, multi-institutional, phase 2 trial, Radiation Therapy Oncology Group (RTOG) 0529, that assessed dose-painted intensity-modulated radiation therapy (DP-IMRT) for anal cancer. The primary outcome was reducing grade ≥ 2 combined acute GI and genitourinary (GU) adverse events (AEs) of 5FU and MMC chemoradiation for anal cancer by at least 15% compared with the CRT/5FU/MMC arm from RTOG 9811. Participants with stage T2 to T4, node-negative to node-positive (N0–N3), and nonmetastatic (M0) anal cancer were treated with a combination of 5FU and MMC, administered on days 1 and 29 of their radiation therapy course. The radiation was delivered using DP-IMRT, with dosing tailored to disease stage. For participants with T2N0 disease, the treatment included 42 Gy to elective lymph nodes and 50.4 Gy to the primary anal tumor, delivered in 28 fractions. For those with more advanced disease (T3–T4 or N-positive), the protocol prescribed 45 Gy to elective nodes, 50.4 Gy to metastatic lymph nodes measuring 3 cm or less, and 54 Gy to nodes larger than 3 cm, along with 54 Gy to the primary anal tumor, all delivered 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 end point, 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 52 participants, 54% were stage II, 25% were IIIA, and 21% were IIIB. The median follow-up was 7.9 years (0.02-9.2 years). Local-regional failures, colostomy failures, distant metastases, OS, DFS, and CFS at 5 years were 16% (95% CI, 7%-27%), 10% (4%-20%), 16% (7%-27%), 76% (61%-86%), 70% (56%-81%), and 74% (59%-84%), respectively, and at 8 years were 16% (7%-27%), 12% (5%-23%), 22% (12%-34%), 68% (53%-79%), 62% (47%-74%), and 66% (51%-77%). Eight participants experienced local-regional failure, with five having persistent disease at 12 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 14 participants (27%) with grade 2; eight (16%) with grade 3; zero with grade 4; and two (4%) with grade 5 (sinus bradycardia and myelodysplasia, possibly due to chemotherapy). Only 11 participants reported grade 0 to 3 sexual dysfunction. The authors concluded that 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 include a small study size.

Clinical Practice Guidelines

American College of Radiology (ACR)

The ACR Appropriateness Criteria state that in terms of the dosage of ionizing radiation, IMRT can reduce the dose to normal structures and is associated with decreased acute toxicity compared with 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).

American Society for Radiation Oncology (ASTRO)

In 2025, Feng et al. published an evidence-based guideline for ASTRO with recommendations for the definitive treatment of primary squamous cell carcinoma of the anal canal and anal margin. The guideline addressed key questions on indications for radiation therapy, concurrent systemic therapy, and surgery; appropriate techniques; suitable radiation therapy dose-fractionation regimens, target volumes, and dose constraints; and surveillance strategies after treatment. The recommendations are as follows (not all inclusive):

- For patients with localized anal cancer, definitive treatment with chemoradiation using concurrent 5FU plus MMC is recommended. Strength of recommendation: strong; quality of evidence: high.
- For select patients with cT1N0 anal margin and superficially invasive anal canal cancers without high-risk histological features, local excision is conditionally recommended if adequate surgical margins are obtained, sphincter function can be preserved, and when close follow-up will be ensured. Strength of recommendation: conditional; quality of evidence: low.
- For patients with anal cancer who are receiving external beam radiation therapy (EBRT), IMRT [including volumetric modulated arc therapy (VMAT)] is recommended. Implementation remark: daily image guidance is encouraged to verify target localization. Strength of recommendation: strong; quality of evidence: moderate.

European Society for Medical Oncology (ESMO)

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

National Comprehensive Cancer Network (NCCN)

The 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 in multiple studies (NCCN, 2025).

Breast Cancer

Meattini et al. (2020) presented the 10-year, long-term follow-up results of the Florence phase 3, single-center, randomized trial (NCT02104895) that assessed whether accelerated partial-breast irradiation (APBI) was a safe and effective alternative treatment compared with whole-breast irradiation (WBI) 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 nonconsecutive daily fractions at 6 Gy/fraction (2 weeks of treatment), and those randomized to the WBI arm (n = 260) received a total of 50 Gy in 25 fractions, followed by a boost on a surgical bed of 10 Gy in five fractions, delivered by direct external electron beam. The primary end point was the ipsilateral breast tumor recurrence (IBTR) rate, and secondary outcomes included OS, acute and late side effects, and cosmetic results. The median follow-up was 10.7 years. The 10-year cumulative incidence of IBTR was 2.5% (n = 6) in the WBI arm and 3.7% (n = 9) in the APBI arm (HR, 1.56; 95% CI, 0.55-4.37; p = 0.40). The OS rate at 10 years was 91.9% in both arms (HR, 0.95; 95% CI, 0.50-1.79; p = 0.86). Breast cancer–specific survival at 10 years was 96.7% in the WBI arm and 97.8% in the APBI arm (HR, 0.65; 95% CI, 0.21-1.99; p = 0.45). The APBI arm had significantly less acute toxicity (p = 0.0001), late toxicity (p = 0.0001), and improved cosmetic outcome, as evaluated by both the 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 the IMRT technique in five once-daily fractions was low and did not differ from that after WBI. They also stated that acute and late treatment-related toxicity and cosmesis outcomes were significantly in favor of APBI. Limitations include the single-center design and small sample size.

The Vicini et al. (2019) study, known as the NSABP B-39/RTOG 0413 trial, was a large, randomized, phase 3 equivalence trial designed to compare APBI with WBI following lumpectomy in participants with early-stage breast cancer. The aim of the trial was to determine whether APBI could provide equivalent local tumor control compared with WBI. The primary end point was the rate of IBTR, while secondary end points were recurrence-free interval, distant disease–free interval, OS, QOL, and any treatment toxicities. Between March 2005 and April 2013, the trial enrolled 4,216 adult women who were

randomly assigned to receive either WBI or APBI. WBI was delivered as 50 Gy in 25 daily fractions over 5 weeks, with an optional boost to the tumor bed. APBI was administered as either 34 Gy via brachytherapy or 38.5 Gy via EBRT in 10 fractions over 5 treatment days within an 8-day period. Of those enrolled, 2,109 participants were assigned to WBI and 2,107 to APBI. After accounting for withdrawals and loss to follow-up, 2,036 in the WBI group and 2,089 in the APBI group were evaluable for the primary outcome. At a median follow-up of 10.2 years, the rate of IBTR was 4.6% in the APBI group and 3.9% in the WBI group, with no significant difference in breast cancer–related deaths or treatment-related mortality. Second cancers and treatment-related toxicities were similar between the two groups. The highest toxicity grade reported was grade 1 in 845 (40%), grade 2 in 921 (44%), and grade 3 in 201 participants (10%) in the APBI group compared with grade 1 in 626 (31%), grade 2 in 1,193 (59%), and grade 3 in 143 (7%) in the WBI group. The authors concluded that APBI did not meet the criteria for equivalence to WBI in controlling local recurrence after breast-conserving therapy. Although the trial had broad eligibility and sufficient power overall, it was not designed to assess equivalence in specific participant subgroups or among different APBI techniques. Despite this, the small absolute difference in recurrence rates suggests that APBI may still be a reasonable option for some women with early-stage breast cancer. The trial had several limitations: HER2 status was not collected, subgroup analyses were underpowered, and differences between APBI techniques were not evaluated in the main study.

Whelan et al. (2019) conducted a multicenter, randomized, noninferiority trial across 33 cancer centers to determine whether external beam APBI delivered over 1 week was as effective as WBI in preventing local recurrence after breast-conserving surgery. The study's primary goal was to assess noninferiority in terms of recurrence prevention, while a key secondary objective was to compare late radiation-related toxicity between the two treatments. The trial included women aged 40 years or older who were diagnosed with ductal carcinoma in situ (DCIS) or invasive ductal carcinoma, all of whom had undergone breast-conserving surgery with clear margins and no axillary lymph node involvement. Eligibility extended to those with isolated tumor cells or micrometastases no larger than 2 mm. Participants were excluded if they had tumors larger than 3 cm, lobular carcinoma, multiple tumors in different breast quadrants, or radiation therapy plans that did not meet the protocol's dose-volume requirements for APBI. Participants in the WBI group received either 42.5 Gy in 16 daily fractions or 50 Gy in 25 daily fractions, with the use of wedges or limited forward-planning with IMRT allowed. In contrast, those assigned to APBI were treated with 38.5 Gy in 10 fractions, delivered twice daily with a 6- to 8-hour interval over a span of 5 to 8 days. Treatment techniques that were permitted for APBI included 3D-CRT or IMRT. Between February 2006 and July 2011, 2,135 participants were enrolled in the trial, with 1,070 assigned to receive APBI and 1,065 to WBI. Several participants did not complete treatment or were lost to follow-up: in the APBI group, six withdrew before treatment, four did not receive radiation therapy, 16 received WBI instead, 14 were lost to follow-up, and nine withdrew during follow-up. In the WBI group,16 withdrew before treatment, two did not receive radiation therapy, 20 were lost to follow-up, and 35 withdrew during follow-up. The median follow-up duration was 8.6 years. At 8 years, the cumulative rate of IBTR was 3.0% with APBI and 2.8% with WBI, with an HR of 1.27. Acute radiation toxicity (grade ≥ 2 within 3 months) was significantly lower in the APBI group (28%) than the whole-breast group (45%). However, late radiation toxicity (grade ≥ 2 after 3 months) was more frequent with APBI (32% vs 13%). Additionally, adverse cosmetic outcomes were more common in the APBI group at 3, 5, and 7 years. The authors concluded that external beam APBI was not inferior to WBI in preventing IBTR. While APBI resulted in lower acute toxicity, it was associated with a higher incidence of moderate late toxicity and poorer cosmetic outcomes, which may be linked to the twice-daily treatment schedule. The authors suggested that alternative approaches, such as once-daily treatment, could potentially improve cosmetic results and warrant further investigation. Limitations include a lower-than-expected rate of IBTR, which led to adjustments in the noninferiority margin and statistical power; additionally, blinding was not feasible for nurses and participants, potentially introducing bias in cosmetic assessments.

Jagsi et al. (2018) conducted a randomized controlled trial (RCT) that compared IMRT and deep inspiration breath-hold (DIBH) vs. standard, free-breathing, forward-planned 3D-CRT in participants 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 radiation therapy. End points included dosimetric parameters and changes in pulmonary and cardiac perfusion and function, measured by single-photon emission computed tomography (CT) scans and pulmonary function testing performed at baseline and 1 year post treatment. Of 62 participants who were randomized, 54 who completed all follow-up procedures were analyzed. The mean doses to the ipsilateral lung, left ventricle, whole heart, and left anterior descending coronary artery were lower with IMRT-DIBH; the percentage of the left ventricle receiving ≥ 5 Gy averaged 15.8% with standard radiation therapy and 5.6% with IMRT-DIBH. Single-photon emission CT revealed no differences in perfusion defects in the left anterior descending coronary artery territory, the study's primary end point, but did reveal statistically significant differences ($p = 0.02$) in left ventricular ejection fraction, which was a secondary end point. 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 in participants 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, 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 QOL in women with breast cancer who were treated with either APBI or standard WBI. Assessments were completed at the beginning and end of treatment and at the 2-year follow-up visit. A total of 205 women completed the health-related QOL protocol, of whom 105 received APBI-IMRT, and 100 received standard WBI. After adjusting for difference between the cohorts, at the end of treatment and 2 years later, women treated with APBI-IMRT reported better QOL related to physical, role, emotional, and social functioning as well as symptoms, including fatigue, pain, dyspnea, insomnia, and appetite loss compared with women treated with standard WBI ($p < 0.01$). The authors concluded that early breast cancer that was treated with APBI-IMRT showed improved short-term and 2-year health-related QOL and should be strongly considered for individuals at low risk.

Lei et al. (2013) used data from a multicenter, phase 2, nonrandomized clinical trial (NCT01185145) to provide a 4-year clinical update. This study's final study protocol included participants aged 40 years or older with stage 0/I DCIS breast cancer and negative margins of ≥ 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 4 to 6 weeks after treatment and every 3 to 4 months up to 4 years. The final analysis included 136 participants, with a median follow-up period of 53.1 months (range, 8.9-83.2 months). At 4 years, the Kaplan-Meier estimates were 0.7% for IBTRs, 0% for contralateral breast failure, 0.9% for distal failure, 96.8% for OS, and 100% for cancer-specific survival. At the last follow-up, 97.0% of participants rated breast pain as none/mild, and 88.2% rated cosmesis as excellent/good. Toxicities were mild edema (1.4%) and mild (2.2%) or moderate telangiectasia (1.4%). The authors concluded that 4-year results of APBI-IMRT demonstrate excellent local control, survival, cosmetic results, and toxicity profile and warrant further investigation.

In 2010, Livi et al. published preliminary findings from a phase 3 RCT that began in September 2008. The study enrolled 259 participants who were randomly assigned to receive either conventionally fractionated WBI (n = 128) or APBI using IMRT (n = 131). The researchers reported that RTOG grade 1 and 2 skin toxicities occurred in 22% and 19% of participants in the WBI group, respectively, compared with significantly lower rates of 5% and 0.8% in the APBI-IMRT group. These findings suggest that APBI delivered via IMRT was not only feasible but also associated with a more favorable acute skin toxicity profile. However, the authors emphasized the need for long-term follow-up to fully assess clinical outcomes and potential late effects. In 2015, Livi and colleagues published the 5-year survival analysis from their phase 3 RCT. The study ultimately enrolled a total of 520 participants, with 260 assigned to each treatment arm. Participants in the WBI group received CRT consisting of 50 Gy delivered in 25 fractions, followed by a tumor bed boost of 10 Gy in five additional fractions. In contrast, the APBI group received 30 Gy delivered in five consecutive daily fractions, targeting only the tumor bed using IMRT. The primary end point of the study was the incidence of IBTR, and the analysis was conducted on an intention-to-treat basis. At a median follow-up of 5 years (IQR, 3.4-7.0 years), the IBTR rate was 1.5% in both groups, with three cases in each arm. The 95% CI for the APBI group was 0.1% to 3.0% and for the WBI group was 0.0% to 2.8%. A log-rank test revealed no statistically significant difference between the two treatment arms ($p = 0.86$). Regarding OS, the 5-year OS rate was 99.4% in the APBI group and 96.6% in the WBI group. Importantly, participants in the APBI group experienced significantly fewer acute ($p \leq 0.0001$ Flow-risk) and late ($p = 0.004$) grade ≤ 2 skin toxicities than those in the WBI group. Additionally, cosmetic outcomes were rated more favorably in the APBI group ($p = 0.045$), supporting the potential advantages of this targeted, shorter-duration treatment approach. Limitations include a lack of blinding and a single-center design; additionally, over 90% of enrolled participants had low-risk features.

Donovan et al. (2007) conducted a prospective, multicenter, phase 3, randomized clinical trial to compare 3D-IMRT and standard 2D radiation therapy with wedge compensators to evaluate late AEs and QOL in participants who had early breast cancer (T1-3a N0-1 M0) and were judged to be at a 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 radiation therapy as 50 Gy in 25 fractions over 5 weeks and a boost of 10 Gy in five fractions to the 90% isodose (11.1 Gy to 100%) in five fractions. The primary end point was change in breast appearance (scored from serial photographs), and secondary end points included self-assessed breast discomfort and hardness and QOL. At 5 years, 240 participants (122 received standard 2D, and 118 received 3D-IMRT) completed photograph adherence. Participants treated with standard 2D radiation therapy 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 ($p = 0.006$), or inflammatory fold ($p = 0.009$) and at the boost site ($p < 0.001$). There were no significant differences in participant-reported breast discomfort, hardness, or QOL between the arms. The authors concluded that the use of 3D-IMRT reduces late radiation AEs.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

In 2023, Shaitelman et al. published an ASTRO guideline for partial-breast irradiation for those with DCIS and early-stage, invasive breast cancer. The guideline makes the following recommendations (not all inclusive):

- For patients with early-stage, invasive breast cancer or DCIS who are receiving partial-breast irradiation, IMRT is recommended. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with early-stage, invasive breast cancer or DCIS who are receiving external beam partial-breast irradiation, 3,000 cGy in five once-daily fractions delivered on nonconsecutive days within 2 weeks is recommended. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with early-stage, invasive breast cancer or DCIS who are receiving external beam partial-breast irradiation, 4,005 cGy in 15 once-daily fractions over 3 weeks is recommended. Strength of recommendation: strong; quality of evidence: moderate.

Correa et al. (2016) updated the ASTRO APBI Consensus Statement to guide the use of intraoperative radiation therapy for partial-breast irradiation in early-stage breast cancer. The statement categorized patients into three groups: suitable, cautionary, and unsuitable. Those considered suitable for APBI included patients aged 50 years or older with stage Tis or T1 tumors and surgical margins of at least 2 mm. For those with DCIS to be considered suitable, they must meet all the following: screen-detected disease, low to intermediate nuclear grade, tumor size of ≤ 2.5 cm, and resection margins of at least 3 mm.

American Society for Radiation Oncology (ASTRO)/American Society of Clinical Oncology (ASCO)/Society of Surgical Oncology (SSO)

Jimenez et al. (2025) released an evidence-based clinical guideline that outlined recommendations for the use of postmastectomy radiation therapy (PMRT) in breast cancer treatment. PMRT involves targeting the chest wall and ipsilateral regional nodes, specifically the at-risk axillary, supraclavicular, infraclavicular, and internal mammary nodes. The updated recommendations clarify when PMRT should be used, both in those undergoing initial surgery and those receiving neoadjuvant systemic therapy. They also offer guidance on selecting appropriate treatment areas, determining radiation doses, and choosing effective techniques. These recommendations were developed by a multidisciplinary task force and are as follows (not all inclusive):

- For patients with node-positive (pN+) breast cancer, PMRT is recommended. Implementation remarks: Omission of PMRT may be appropriate for select patients with pN1 mic or low nodal burden pN1a disease following axillary lymph node dissection who have favorable clinicopathologic features. Strength of recommendation: strong; quality of evidence: high.
- For patients with any pT4 breast cancer, PMRT is recommended, even in the absence of any other risk factors. Strength of recommendation: strong; quality of evidence: high.
- For patients with initial cT4 or cN2-3 breast cancer who receive neoadjuvant systemic therapy, PMRT is recommended, regardless of pathological response. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with positive lymph nodes after neoadjuvant systemic therapy (ypN+), PMRT is recommended. Strength of recommendation: strong; quality of evidence: moderate.
- For patients receiving PMRT, treatment to the ipsilateral chest wall/reconstructed breast and regional lymphatics (e.g., at-risk axillary nodes, supra-/infraclavicular nodes, internal mammary nodes) is recommended. Implementation remarks: Treatment to the chest wall/reconstructed breast alone may be used in select patients (e.g., pT3N0). Coverage of the internal mammary nodes may be individually determined based on tumor location (medial/central), tumor size, and extent of nodal involvement. Strength of recommendation: strong; quality of evidence: high.
- For patients without breast reconstruction who are receiving PMRT, moderate hypofractionation is recommended. Implementation remarks: Moderate hypofractionation is preferred, given equivalent oncological outcomes and reduced toxicity. Conventional fractionation may be an option in rare circumstances. Strength of recommendation: strong; quality of evidence: high.
- For patients with breast reconstruction who are receiving PMRT, moderate hypofractionation (preferred) or conventional fractionation is recommended. Strength of recommendation: strong; quality of evidence: high for conventional fractionation and moderate for moderate hypofractionation.
- For patients receiving PMRT, IMRT (including VMAT) is recommended when 3D-CRT is unable to achieve treatment goals (e.g., target coverage, normal tissue avoidance). Implementation remark: Use of IMRT (including VMAT) may increase OAR low-dose exposure compared with 3D-CRT. Strength of recommendation: strong; quality of evidence: moderate.

- For patients receiving PMRT treated with IMRT (including VMAT), daily image guidance, in conjunction with regular 3D assessments (e.g., cone-beam CT, surface-guided radiation therapy), is recommended. Strength of recommendation: strong; quality of evidence: low.
- For patients receiving PMRT, DIBH is recommended when lower doses to normal tissues, including the heart and lungs, can be achieved compared with free breathing. Strength of recommendation: strong; quality of evidence: moderate.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for breast cancer state that several studies suggest that APBI offers similar local cancer control as whole-breast radiation therapy in early-stage breast cancer. In RCTs, QOL, side effects, and cosmetic results with APBI have generally been similar to or slightly better than those seen with WBI. However, the best external beam APBI technique and schedule to minimize long-term cosmetic side effects remain unclear. For those who are *BRCA* negative, APBI is considered appropriate, based on the 2023 ASTRO criteria for patient selection. The NCCN preferred regimen for APBI is IMRT/VMAT, five fractions every other day. The guidelines also note 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 the dose to adjacent normal tissues, particularly the heart and lungs. According to the guideline, the decision to use radiation therapy for locoregional recurrence must consider any prior radiation to the area and the cumulative risk of late normal tissue toxicity from both past and planned treatments (NCCN, 2025).

Central Nervous System Tumors

Mills et al. (2024) evaluated volumetric response, survival, and functional outcomes in a subgroup of participants with isocitrate dehydrogenase (IDH)–mutant grade 3 gliomas. The authors divided a prospective database of 187 participants 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 cohort (LVC). Each participant received IMRT with FET-^{18}F-fludeoxyglucose–guided integrated boost. At the time of data analysis, the median follow-up in survivors was 71.5 months, and 61 participants had relapsed, with a median progression-free survival (PFS) of 105.1 months and a projected 10-year PFS rate of 50%. Of the original 187 participants, 47 had died, and the median OS had not been reached, with a projected 10-year OS rate of 62%. The authors reported that the LVC had a median planning target volume (PTV) of 320 cm^3 compared with 186.2 cm^3 in the total group and that the projected 10-year relapse-free survival rate was 40% in the LVC group and 53% in the overall cohort, while the OS rate was 62% in both the LVC group and the whole cohort; however, the impact of PTV reached significance when analyzed as a continuous variable. The authors also reported that in participants who were assessable at year 4 post IMRT, there were no late Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 toxicity events and that 92% of participants had an ECOG PS of 0 to 1, while 45% were employed at prior capacity, and 28% were working with impairment. Limitations of the study include the single-center design, heterogeneity of treatment that occurred at multiple locations prior to referral to the authors' institution for radiotherapy, and lack of a control group. The authors concluded that participants with large-volume, IDH-mutant, grade 3 glioma had significant tumor reduction post IMRT and good long-term outcomes with respect to survival and functional status.

Chen et al. (2022) conducted an RCT to analyze the effects of 3D-IMRT on QOL in participants with low-grade gliomas. Overall, 100 participants with low-grade gliomas, from February 2015 to December 2019, were randomized into two groups: the 3D-CRT control group (n = 50) and 3D-IMRT research group (n = 50). The cognitive function in the two groups was analyzed by the Mini-Cog Assessment and the Montreal Cognitive Assessment. The self-care ability score (BI), effect of symptom improvement, and QOL 36-Item Short Form Health Survey score were also compared between the two groups. After radiation therapy, the self-care ability of participants in the two groups was significantly improved, and the improvement in the 3D-IMRT group was better than that in the control group. The Mini-Cog Assessment and Montreal Cognitive Assessment scores in the 3D-IMRT group were significantly higher than those in the control group. Additionally, the symptom improvement effect and QOL of the participants in the 3D-IMRT group were also significantly better than those in the control group. The scores on the Self-Rating Depression Scale and Self-Rating Anxiety Scale in participants who underwent 3D conformal IMRT were significantly lower than those in the control group. Mortality was not significantly different between the two groups. The authors concluded that 3D conformal IMRT can delineate the target volume more accurately, regulate the intensity of radiation, and improve the symptoms and QOL in individuals with low-grade gliomas. Limitations include a single-institution study design and small study size.

A Cochrane Evidence Review sought to compare the efficacy of advanced forms of radiation therapy (including IMRT) delivered in the immediate postoperative period (early) vs at the point of disease recurrence in individuals with low-grade gliomas. The search identified one multi-institution RCT that included 311 individuals (Karim et al., 2002). While individuals from the group that was 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 determine whether early radiation therapy is better than delayed radiation therapy. 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) radiation therapy in patients with medulloblastomas. Overall, 66 patients (24 > 18 years of age) were treated at a single institution between 1985 and 2009. All patients underwent initial neurosurgical tumor resection (47% complete resection), and all underwent postoperative CSI, with additional boosts to the posterior fossa in all but two patients. Radiation therapy was delivered with Cobalt before 1991 and with linear accelerators afterward, according to standard protocols. Three patients were treated with helical IMRT via tomotherapy. Boosts to the posterior fossa were applied with conventional photon radiation therapy with two lateral opposing fields in 48 patients; in 15 patients, 3D cross-sectional image-based plans were used, with three using a stereotactic setting. Regarding chemotherapy, 47 of the 66 patients received chemotherapy prior to CSI, with adults representing less than half of that number. The median follow-up was 93 months. OS and local and distant PFS rates were 73%, 62%, and 77%, respectively, at 60 months. Macroscopic complete tumor resection, desmoplastic histology, and early initiation of postoperative radiation therapy within 28 days were associated with improved outcomes. The addition of chemotherapy was associated with slightly enhanced acute side effects, causing treatment delay or interruptions due to hematologic toxicity in 15% of patients opposed to 6% with radiation therapy alone. However, chemotherapy did not improve OS. Study limitations include the 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 a 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. In a 7-year period, 94 individuals were treated with IMRT. Overall, 26 individuals received radiation therapy as the primary treatment, 14 individuals received postoperative IMRT for residual disease, and 54 individuals were treated after local recurrence. The median total dose was 57.6 Gy given in 32 fractions. During a median follow-up period of 4.4 years, overall, local control was 93.6%. In total, 69 individuals had stable disease based on CT/magnetic resonance imaging (MRI), 19 had tumor volume reduction after IMRT, and six had local tumor progression at a median of 22.3 months after radiation therapy. In 39.8% of the individuals, preexisting neurological deficits improved. The authors concluded that IMRT is an effective and safe treatment modality for long-term local control of especially complex-shaped and otherwise difficult-to-treat meningiomas of the skull base, with a 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 2025, Yeboa et al. published an ASTRO evidence-based guideline to provide recommendations for the treatment of World Health Organization (WHO) grade 4 adult-type diffuse glioma. Four key questions focus on indications for radiation therapy and/or other adjunctive treatments; the best radiation therapy regimens after initial biopsy/resection; and factors like pretreatment characteristics, target volumes, technique, dose, reirradiation, and health disparities. The guideline recommends IMRT (including VMAT) over 3D-CRT to reduce toxicity in those with WHO grade 4 diffuse glioma. Strength of recommendation: strong; quality of evidence: moderate.

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

National Comprehensive Cancer Network (NCCN)

In its central nervous system cancer guideline, the NCCN states that lower doses of targeted conformal radiation therapy (including 3D-CRT and IMRT) are recommended for the treatment of gliomas, infiltrative astrocytomas, oligodendrogliomas, glioblastomas, and meningiomas. Higher doses of radiation therapy are found to be no more effective than lower doses. For medulloblastomas, the guidelines state that for patients at average risk, a regimen of IMRT or proton CSI alone or with chemotherapy is a viable treatment option (NCCN, 2025).

Cervical Cancer

In their single-center, prospective, randomized study, Padhi et al. (2023) analyzed dosimetry and the incidence of acute GI toxicity in participants who were 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 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, single-center design, subjectivity of the GI toxicity assessment tool used, and heterogeneity of the concurrent chemotherapy that 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.

The open-label, parallel-group, phase 3, randomized Postoperative Adjuvant Radiation in Cervical Cancer (PARCER) trial that was conducted by Chopra et al. (2021) evaluated whether image-guided IMRT reduces GI toxicity without compromising pelvic tumor control in women who are undergoing postoperative radiation for cervical cancer vs 3D-CRT. Overall, 300 participants with cervical cancer post hysterectomy and an indication for adjuvant postoperative radiation therapy were randomly assigned to either image-guided IMRT (n = 151) vs. 3D-CRT (n = 149). Three-year grade ≥ 2 late GI toxicity was the primary end point. Acute toxicity, health-related QOL, pelvic relapse-free survival, DFS, and OS were secondary end points. Participants were assessed every 3 months in the first 2 years, once every 6 months in the subsequent 3 years, and annually after that. Grade ≥ 2 toxicity-free survival was 78% with image-guided IMRT vs. 57% with 3D-CRT ($p = 0.0009$). Grade 3 toxicity-free survival was 97.6% with image-guided IMRT vs. 81.6% with 3D-CRT ($p = 0.001$). Serious GI toxicity at 4 years was 19% (image-guided IMRT) vs. 38% (3D-CRT) ($p = 0.005$). There were lower rates of acute diarrhea, abdominal bloating, bowel obstruction, and appetite loss in the image-guided IMRT group. There was no significant difference in pelvic relapse-free survival between the two groups, and greater benefit was observed in participants who received concurrent chemotherapy. The authors concluded that image-guided IMRT significantly reduced long-term GI toxicity while maintaining effective tumor control and should be considered as a new standard of care for postoperative radiotherapy in gynecologic cancers when resources allow. Limitations include a long recruitment time (8 years) and lack of blinding to the treatment allocation.

Tsuchida et al. (2019) conducted a retrospective cohort analysis to compare clinical outcomes and toxicity incidence in patients who were diagnosed with cervical cancer, 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 locoregional control. A total of 73 patients (33 received 3D-CRT, and 40 received IMRT) were included in the final analysis. The median follow-up period differed between the groups, with 82 months in the 3D-CRT group and 50 months in the IMRT group ($p < 0.001$). After 4 years, there was no difference in OS and DFS between the groups. Locoregional recurrence was more frequent in patients with vaginal invasion reported in the postoperative 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, those treated with IMRT showed a significantly reduced incidence of late toxicities greater than grade 2. Specifically, GU toxicity of grade 2 or higher was lower in the IMRT group ($p = 0.038$), and GI toxicity of grade 2 or higher was also less frequent ($p = 0.026$). The authors concluded that their results show that IMRT 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 of and toxicities with IMRT with 3D-CRT or 2D radiation therapy for the 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 individuals (350 IMRT and 658 CRT), were included in the final analysis. Three-year OS and 3-year DFS revealed no significant differences between IMRT and 3D-CRT or 2D radiation therapy (3-year OS: OR, 2.41; 95% CI, 0.62-9.39; $p = 0.21$; 3-year DFS: OR, 1.44; 95% CI, 0.69-3.01; $p = 0.33$). The incidence of acute GI toxicity and GU toxicity in individuals who received IMRT was significantly lower than that in the control group (GI: grade 2, OR, 0.5; 95% CI, 0.28-0.89; $p = 0.02$; grade 3 or higher, OR, 0.55; 95% CI, 0.32-0.95; $p = 0.03$; GU: grade 2, OR, 0.41; 95% CI, 0.2-0.84; $p = 0.01$; grade 3 or higher, OR, 0.31; 95% CI, 0.14-0.67; $p = 0.003$). Furthermore, individuals who received IMRT experienced fewer incidences of chronic GU toxicity than individuals in the control group (grade 3: OR, 0.09; 95% CI, 0.01-0.67; $p = 0.02$). The authors concluded that IMRT and conventional radiotherapy demonstrated equivalent efficacy in terms of 3-year OS and DFS and that IMRT significantly reduced acute GI and GU toxicities as well as chronic GU toxicity in individuals with cervical cancer. Small sample sizes and the retrospective nature of most of the studies were included in the limitations.

Mell et al. (2017) conducted an international, multicenter, single-arm, phase 2 clinical trial (NCT01554397) to evaluate the incidence of hematologic and GI toxicities in participants with stage IB to IVA, biopsy-proven, invasive carcinoma of the cervix who were treated with IMRT. All 83 participants received daily IMRT concurrently with weekly cisplatin for 6 weeks, with an intracavitary brachytherapy boost given at completion of the chemoradiation regimen. Additionally, the researchers conducted a subgroup analysis on whether the use of positron emission tomography (PET)–based image-guided IMRT had an influence on the development of neutropenia compared with standard IMRT. Post–simple hysterectomy participants were included, initiating the regimen within 8 weeks of surgery. Participants who underwent radical hysterectomy with extensive nodal involvement were excluded. The primary outcome measures were either acute grade ≥ 3 neutropenia or clinically significant GI toxicity that occurred within 30 days of regimen completion. The median follow-up was 26 months. The incidence of any primary event was 26.5%, which was 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 image-guided IMRT (n = 35) had a significantly lower incidence (8.6%) than the 48 participants who received standard IMRT (27.1%). The differences in the incidence of grade ≥ 3 leukopenia and any grade ≥ 3 hematologic toxicities 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 image-guided 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 who were treated with pelvic IMRT. Individuals 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 the dose to the bowel, bladder, and rectum. Toxicity was graded according to the RTOG system. The study included 111 individuals with stage I to IVA cervical carcinoma. Of them, 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 individuals, 63 had stage I to IIA disease, and 48 had stage IIB to IVA disease. The median follow-up time was 27 months. The 3-year OS rate and DFS rate were 78% and 69%, respectively. The 3-year pelvic failure rate and 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 that of conventional techniques.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

In a 2020 ASTRO guideline for cervical cancer, Chino et al. recommended IMRT for women with cervical cancer who were treated with postoperative radiation therapy, with or without chemotherapy, to decrease acute and chronic toxicity (strength of recommendation: strong). For women with cervical cancer who are treated with definitive radiation therapy, 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 to improve the quality of care for women with cervical cancer. The guideline recommended 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 OARs. Image-guided radiation therapy (IGRT) is recommended for IMRT to ensure safe dose application in the tumor-related targets, account for motion uncertainties, reduce margins, and achieve reduced doses to OARs.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for cervical cancer state that the 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 indicates that IMRT is beneficial for reducing radiation exposure to the bowel and other critical structures following a hysterectomy. It is particularly useful when treating para-aortic lymph nodes, if needed, and in cases that require high-dose radiation for gross regional lymph node disease. However, IMRT should not be routinely used as a substitute for brachytherapy in treating central disease in patients with an intact cervix. Accurate and consistent treatment planning and delivery are essential to ensure its effectiveness.

Endometrial Cancer

In 2022, Wortman et al. evaluated whether IMRT, compared with 3D-CRT, reduced treatment-related toxicity and participant-reported symptoms in women with high-risk endometrial cancer who participated in the randomized PORTEC-3 trial. A total of 559 participants received 3D-CRT, and 99 received IMRT. The median follow-up was 74.6 months. During treatment, no statistically significant difference in overall AEs was observed, although there was a trend toward more severe (grade ≥ 3) AEs with 3D-CRT (37.7%) compared with IMRT (26.3%), which were mostly hematologic and GI ($p = 0.03$). During follow-up, diarrhea (grade ≥ 2) occurred in 15.4% of 3D-CRT participants vs 4% with IMRT. Hematologic AEs (grade ≥ 2) were seen in 26.1% of 3D-CRT participants vs. 13.1% with IMRT. Both differences were statistically significant ($p < 0.01$). Regarding QOL, more participants reported bowel-related symptoms with 3D-CRT; diarrhea was 37.5% with 3D-CRT vs. 28.6% with IMRT, which was not statistically significant ($p = 0.125$), and bowel urgency was 22.1% with 3D-CRT vs. 10.0% with IMRT, which was significant ($p = 0.039$). Abdominal cramps were 18.2% with 3D-CRT vs. 8.6% with IMRT, which was borderline ($p = 0.058$). Other QOL measures showed no major differences. The authors concluded that IMRT or VMAT should be the standard for adjuvant radiation in high-risk endometrial cancer, as IMRT was associated with fewer severe and moderate side effects, especially diarrhea and blood-related issues, and fewer bowel symptoms reported by participants compared with 3D-CRT. Participants also reported fewer bowel symptoms with IMRT. Limitations include the small number of IMRT participants; additionally, a lack of detailed radiation dose data limited interpretation, and approximately only 60% of participants had 5-year toxicity and QOL data, so long-term results should be interpreted cautiously. Additionally, this was a secondary analysis of the PORTEC-3 trial, which was not designed to detect significant differences between radiation techniques.

Klopp et al. (2018) conducted a multicenter, phase 3, randomized clinical trial to evaluate participant-reported acute toxicity and QOL in participants who had invasive cervical or endometrial cancer and were treated with standard four-field pelvic radiation therapy or pelvic IMRT. The primary end point, change in acute GI toxicity, was measured at baseline and at the end of radiation therapy (5 weeks) using the bowel domain of the Expanded Prostate Cancer Index Composite (EPIC). The secondary end points, 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; to determine the extent to which GU toxicity impacted daily activities, the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events, Functional Assessment of Cancer Therapy – Cervix, Functional Assessment of Cancer Therapy – General, and Trial Outcome Index were used. A total of 278 participants were included in the final analysis; 149 received standard radiation therapy, and 129 received IMRT. Compared with baseline, the standard radiation therapy arm had larger mean EPIC bowel and urinary score declines than the IMRT arm (-26.3 vs. -18.6, $p = 0.05$ and -10.4 vs. -5.3, $p = 0.03$, respectively). The Functional Assessment of Cancer Therapy – Cervix mean scores showed a decline of 4.9 points in the standard radiation therapy group vs. 2.7 points in the IMRT group ($p = 0.015$). There was no difference between the arms in the Functional Assessment of Cancer Therapy – General subscale or Trial Outcome Index scores. In addition, the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events results showed that at the end of therapy, more participants in the standard radiation therapy 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 that based on the participants' 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 patients with endometrial and cervical cancer who underwent postoperative pelvic radiation therapy with either 3D-CRT or IMRT. Patients who received definitive or palliative radiation therapy, 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 the secondary objective was to identify other potential risk factors for bowel obstruction. A total of 224 patients were identified (152 were diagnosed with endometrial cancer, and 72 were diagnosed with cervical cancer), and the median follow-up time was 67 months. The IMRT group (n = 120) consisted of 80 patients with endometrial cancer and 40 patients with cervical cancer, and the 3D-CRT group (n = 104) consisted of 72 patients with endometrial cancer and 32 patients with cervical cancer. At 5 years, the bowel obstruction rate was lower in the IMRT group than 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, patients with a body mass index of ≥ 30 kg/m^2 were less likely to develop a bowel obstruction (2.6% vs. 8.3%; $p = 0.03$). The authors concluded that the use of postoperative IMRT for endometrial and cervical cancers is associated with a significant reduction in bowel obstruction.

Barillot et al. (2014) conducted a multicenter, single-arm, phase 2 clinical trial to test their hypothesis that individuals with stage I or II endometrial cancer who are treated with 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 end point was acute GI toxicity of grade 2 or higher; secondary

end points 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 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. Overall, 19% (95% CI, 8.9%-32.6%) experienced grade 2 cystitis or urinary frequency; however, these resolved by week 15. The investigators concluded that postoperative 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 that examines 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 the dose to critical structures in dosimetric studies, and retrospective reviews of IMRT for early-stage endometrial cancer have shown excellent local control rates, with low GI toxicity rates. The ACR Appropriateness Criteria for advanced-stage endometrial cancer state that IMRT may further improve treatment of areas at risk for tumor recurrence while sparing adjacent normal tissues. The authors noted that several studies of IMRT for gynecologic malignancies showed that compared with external beam pelvic radiation therapy, IMRT improved target coverage and reduced the volume of normal tissues receiving the prescription dose; additionally, the reduction in dose resulted in a decrease in both acute and chronic GI side effects compared with historical 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 in patients with endometrial carcinoma who are undergoing adjuvant EBRT. Additionally, a vaginal internal target volume is strongly recommended for treatment planning with daily IGRT for treatment verification (Harkenrider et al., 2023).

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

Concin et al. (2021) developed ESGO/ESTRO/ESP evidence-based guidelines that address the diagnosis and treatment of endometrial carcinoma. The guidelines note that regarding adjuvant radiotherapy, IMRT/VMAT techniques are preferred due to their ability to provide a more conformal dose distribution, which enhances the sparing of normal tissues compared with four-field conventional or 3D conformal plans. The approach to radiotherapy for recurrent endometrial carcinoma is influenced by the location of the recurrence and any prior treatments that the patient has undergone. Treatment options include EBRT, brachytherapy, or a combination of both techniques. Additionally, definitive treatment with IMRT is part of the preferred treatment for those with more advanced, inoperable disease.

National Comprehensive Cancer Network (NCCN)

According to the 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, 2025).

Esophageal Cancer

Hulshof et al. (2021) conducted an RCT to compare a dose of 50.4 Gy with that of a dose-escalating regimen to the primary tumor in definitive chemoradiation for participants with esophageal cancer. Overall, 260 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 were given in both arms weekly for 6 weeks. Local progression–free survival was the primary end point. Squamous cell carcinoma 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 in all participants was 50 months. The 3-year local progression–free survival was 70% in the standard-dose arm vs. 73% in the high-dose arm (not significant). The local progression–free survival for squamous cell carcinoma and adenocarcinoma was 75% vs. 79% and 61% vs. 61% for standard dose and high dose, respectively (not significant). The 3-year locoregional progression–free survival was 52% and 59% in 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 vs. 14% and 10% in the high-dose arm, respectively. The authors concluded that radiation dose escalation up to 61.6 Gy to the primary tumor did not

result in a significant increase in local control over 50.4 Gy or survival. Additionally, the absence of a dose effect was found in both adenocarcinoma and squamous cell carcinoma.

In a 2020 study using propensity score matching, Lan et al. compared IMRT and 3D-CRT in those with esophageal cancer who received definitive chemoradiation, focusing on survival outcomes and the risk of radiation pneumonitis. The study analyzed outcomes in a total of 388 individuals, including 297 treated with IMRT and 91 treated with 3D-CRT. Results showed that IMRT was significantly associated with better clinical outcomes, including improved OS ($p = 0.001$), PFS ($p = 0.008$), and distant metastasis–free survival (DMFS; $p = 0.011$), compared with 3D-CRT. However, there was no significant difference in locoregional failure–free survival between the two groups ($p = 0.721$). Importantly, the incidence of radiation pneumonitis was significantly lower in the IMRT group (5.4%) than the 3D-CRT group (23.1%), with a p value of less than 0.001. A multivariate analysis identified several independent predictors of radiation pneumonitis: smoking history (OR, 4.225; $p = 0.002$), primary tumor length (OR, 2.764; $p = 0.049$), radiation technique (IMRT vs. 3D-CRT; OR, 10.760; $p < 0.001$), PTV (OR, 1.004; $p < 0.001$), and lung V20 (OR, 1.286; $p = 0.002$). The authors concluded that these findings support the use of IMRT in esophageal cancer not only for its survival benefits but also for its ability to reduce the risk of lung toxicity. Despite the positive findings, the study had several limitations: (1) the design of the analysis was retrospective; (2) the IMRT group had more individuals with upper esophageal tumors, which could have influenced radiation exposure to the heart and lungs; (3) baseline PET staging was more common in the IMRT group; and (4) the follow-up time in the IMRT group was short.

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 individuals) were included in the dosimetric comparison, three studies (871 individuals) were included in the OS analysis, and two studies (205 individuals) were included in the irradiation toxicity analysis. For the lung in individuals who received doses of ≥ 20 Gy and the heart in individuals who received a dose of 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 in radiation toxicity.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for esophageal and esophagogastric junction cancers state that IMRT or proton beam radiation therapy (PBRT) may be used in situations in which minimizing radiation exposure to critical organs, such as the heart and lungs, is necessary and cannot be achieved using 3D techniques. IMRT has become the standard approach in preoperative, definitive, and postoperative treatment settings for these cancers due to its superior ability to target tumors while sparing surrounding healthy tissue (NCCN, 2025).

Society of Thoracic Surgeons (STS)/American Society for Radiation Oncology (ASTRO)

Worrell et al. (2024) collaborated with the STS, ASTRO, and ASCO to develop guidelines for the management of those with locally advanced, resectable thoracic esophageal cancer (excluding cervical location). The guidelines note that IMRT is being adopted more frequently for treating esophageal cancer than traditional 3D-CRT. When 3D techniques are unable to adequately limit radiation to surrounding healthy tissues and meet dose constraints, IMRT is the preferred approach.

Head and Neck Cancer

Mun et al. (2024) conducted a retrospective cohort study to evaluate recurrence patterns and survival outcomes in patients diagnosed with glioblastoma who were treated with either IMRT or 3D-CRT. The study included 91 patients, with 60 patients (mean age, 58 years; 54.8% male) treated with IMRT and 31 (mean age, 59 years; 58.3% male) treated with 3D-CRT. The authors reported that the median OS was 18.9 months, and median PFS was 9.4 months, with no significant difference between the two groups; the median OS and PFS in the 3D-CRT group were 19.3 and 10.8 months, respectively, and 18.4 and 8.9 months in the IMRT group. The authors also reported that patients 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; small sample size; and 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; additionally, 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 patients with partial resection highlighted its potential in cases in which complete tumor removal is not feasible.

Nutting et al. (2023) conducted a phase 3, double-blinded, multicenter RCT to investigate if dysphagia-optimized intensity-modulated radiation therapy (DO-IMRT) reduced the 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 squamous cell carcinoma of the oropharynx or hypopharynx, with no clinical evidence of metastatic disease (stage I-IVB; T1-4, N0-3, M0) and no preexisting 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 3, 6, 12, 18, and 24 months after treatment using a water swallowing test. All participants in both groups with adequate hematologic and renal function were given concomitant intravenous cisplatin on day 1 and day 29 of radiotherapy. In participants for whom cisplatin was contraindicated, concurrent intravenous carboplatin was given, or they were treated with radiotherapy alone. The median follow-up was 39.5 months. There were 52 participants (93%) in the DO-IMRT group and 45 participants (80%) in the standard IMRT group who completed the 12-month MD Anderson Dysphagia Inventory (MDADI) questionnaire. The authors reported that participants in the DO-IMRT group had significantly higher 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-IMRT group and seven in the standard IMRT group, with the most common grade 3 to 4 late AEs being hearing impairment (nine in the DO-IMRT group vs. seven in the standard IMRT group), dry mouth (three vs. eight), and dysphagia (three vs eight). Limitations of the study include the heterogeneity of concomitant treatments received (such as chemotherapy and swallowing exercises) and variability in the standards of care rendered at the different treatment sites. The authors concluded that reducing the dose to the pharyngeal constrictor muscle, as was done with DO-IMRT, improved participant-reported swallowing function compared with standard IMRT for the treatment of pharyngeal cancers.

Razavian et al. (2023) performed a systematic review and meta-analysis to assess the effectiveness of IMRT in individuals with early-stage, node-negative glottic larynx cancer. The primary focus was on evaluating local and regional failure rates associated with IMRT, while also examining clinical and pathological factors that influence outcomes, treatment-related toxicity, and salvage therapies. The review included peer-reviewed studies that were published between December 1, 2000, and September 2, 2022, that reported on at least 10 individuals who were treated with IMRT for early glottic cancer. Studies were excluded if they were case reports, systematic reviews, database analyses, or non-English publications or if they lacked full-text access. Additional exclusions applied to studies that involved chemoradiotherapy alone, recurrent or metastatic disease, reirradiation, or stereotactic body radiation therapy (SBRT). The primary outcome was the rate of local failure following IMRT, with secondary outcomes that included pooled regional failure rates following IMRT and local failure and regional failure rates following CRT. Overall, 15 studies that included 2,083 individuals were included in the analysis, with the majority being retrospective and having median follow-up periods that ranged from 18 to 66 months. Among the 873 individuals who were treated with IMRT, most had T1 disease, with 3.4% presenting with Tis tumors, 64% with T1 tumors, and 28% with T2 tumors. A variety of advanced techniques was used, including partial larynx targeting, single vocal cord carotid sparing, and IGRT. The pooled crude rate of local failure was 7.6%, with actuarial local failure rates of 6.3% at 3 years and 9.0% at 5 years. Regional failure following IMRT, with a pooled crude rate, was 1.5%. A metaregression analysis revealed that T2 disease and grade 2 to 3 histology were significantly associated with increased local failure rates. In comparison, 738 individuals were treated with chemoradiotherapy, with 76% having T1 disease and 22% having T2 disease. Among studies that reported both modalities, no statistically significant differences in local failure and regional failure rates were observed between IMRT and CRT. The authors concluded that IMRT offers strong local and regional control for individuals with early-stage squamous cell carcinoma of the glottic larynx. The treatment appears to have a favorable toxicity profile. However, they emphasized the need for further research to better understand the potential long-term effects of IMRT, particularly regarding radiation-induced cerebrovascular complications. This study was limited by its study-level design, which prevented detailed subgroup analysis and standardization of treatment techniques.

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 the presence or diagnosis of MORN of the jaw; 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 radiation therapy treatment. Limitations include the small sample sizes in some included studies, inconsistent follow-up time, and uneven dose administration. The authors recommended 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 end point was the incidence of physician-rated acute salivary gland toxicity (grade ≥ 2). Secondary end points included other acute toxicity (mucositis, dermatitis, and dysphagia), late radiation morbidity, patterns of failure, locoregional disease status, and OS. Participants (n = 60) who were previously untreated, had early to moderately advanced, nonmetastatic squamous carcinoma of the oropharynx, larynx, or hypopharynx, and were planned for comprehensive irradiation of the primary site and bilateral neck nodes were randomly assigned to either IMRT or 3D-CRT. Treatment consisted of 6-MV photons to a total dose of 70 Gy/35 fractions over 7 weeks (3D-CRT) or 66 Gy/30 fractions over 6 weeks (IMRT). At a median follow-up of 140 months in surviving participants, 10-year Kaplan-Meier estimates of locoregional control, PFS, and OS with 95% CI 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 locoregional control (79.2% vs. 68.7%), PFS (41.3% vs. 48.6%), and OS (44.9% vs. 55.0%). A significantly smaller proportion of participants in the IMRT arm experienced grade ≥ 2 late xerostomia and subcutaneous fibrosis at all time points. At the longer follow-up, fewer participants remained evaluable for late radiation toxicity, reducing statistical power and precision. The authors concluded that IMRT provides sustained, clinically meaningful benefit compared with 3D-CRT in reducing the late morbidity of radiation, without compromising disease-related outcomes in long-term survivors of non-nasopharyngeal HNSCC. Limitations include the lack of blinding to treatment arm and small study size, with even much lesser numbers in long-term follow-up (between 5 and 10 years).

In a 2020 RCT by Tao et al., researchers evaluated the efficacy and toxicity profiles of dose-escalated IMRT compared with those of conventional 3D radiation therapy in the setting of concurrent chemoradiotherapy in participants with locally advanced HNSCC. A total of 188 participants were enrolled and randomized to receive either 70 Gy in 35 fractions over 7 weeks using 3D radiation therapy or an escalated dose of 75 Gy in 35 fractions using IMRT. Both treatment arms received concurrent chemotherapy consisting of three cycles of cisplatin at a dose of 100 mg/m² that were administered during radiation therapy. Follow-up assessments were performed 3 months after treatment completion, then every 3 months for 2 years, and every 6 months thereafter. The primary end point was locoregional progression, and secondary end points were PFS, OS, and distant progression. The majority of participants (85%) had oropharyngeal tumors, and 73% were classified as stage IVa disease. The median follow-up duration was 60.5 months. A significant reduction in xerostomia was observed in the IMRT group compared with the 3D radiation therapy group. At 1 year, the incidence of grade ≥ 2 xerostomia was 63% in the 3D radiation therapy group vs. 23% in the IMRT group ($p < 0.0001$). This benefit persisted at 3 years, with rates of 45% and 11%, respectively. Despite the improvement in toxicity outcomes, no statistically significant differences were found between the two groups in terms of locoregional progression (adjusted HR, 1.13; 95% CI, 0.64-1.98; $p = 0.68$) and OS (adjusted HR, 1.19; 95% CI, 0.78-1.81; $p = 0.42$). The authors concluded that increasing the radiation dose to the gross tumor volume using IMRT did not improve locoregional control in those with locally advanced HNSCC who were treated with high-dose cisplatin and radiation therapy. However, IMRT did lead to better treatment tolerance and significantly reduced xerostomia. Limitations include that (1) as the follow-up period extended, fewer participants remained evaluable for late radiation toxicity and (2) the sample size was small.

Oertel and colleagues (2019) conducted a single-center retrospective analysis that investigated the impact of different radiation dose regimens on local control and OS in patients with extramedullary head and neck plasmacytoma (EMP). A total of 33 radiation courses were administered to 27 patients between January 2005 and January 2017 (IMRT: n = 14; CRT: n = 19). The median radiation therapy dose was 45 Gy (range, 12-55.8 Gy), and the local control rate was 76% (93% for primary vs. 61% for secondary EMP lesions). A complete response rate to local radiation therapy was achieved for 42% of lesions (67% for primary vs. 22% for secondary EMP lesions). The overall response rate for lesions that were treated with high-dose regimens (> 45 Gy) vs. low-dose regimens (≤ 45 Gy) was 87% vs. 67%, respectively. The median survival in the high-dose radiation therapy group was significantly longer. In a subgroup analysis, patients with primary EMP who were treated with high-dose radiation therapy had a nonsignificant, higher overall response rate (100% vs. 80%, respectively), with a longer duration of local control and longer survival than patients in the low-dose group. There were no significant differences detected in patients with secondary EMP who were treated with high-dose radiation therapy regarding overall response rate and survival (60% vs 62%, respectively). Radiation therapy was well tolerated, without significant AEs. The authors concluded that compared with secondary EMP, patients with primary tumor manifestations were associated with better outcomes with a dose of ≤ 45 Gy, resulting in a complete response rate that is comparable to that with high-dose regimens. Lower-dose radiation therapy 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 3 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 to 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 squamous cell carcinoma (82%).

Mucositis and dysphagia were the most common grade 3 to 5 acute toxicities. No statistically significant differences in the cumulative incidence of grade 3 to 4 acute toxicities were observed between the two arms (59.8% in SEQ vs. 58.9% in SIB). Common grade 3 to 4 late toxicities with SEQ and SIB included hearing loss (2.9% vs. 8.4%), temporal lobe injury (2.9% vs. 0.9%), cranial nerve injury (0% vs. 2.8%), and xerostomia (2% vs. 0.9%). With the median follow-up of 41 months, 3-year PFS and OS rates in the SEQ and SIB arms were 72.7% vs. 73.4% and 86.3% vs. 83.6%, respectively. The authors concluded that while both techniques provide excellent survival outcomes with few late toxicities, SIB-IMRT, with a satisfactory dose-volume constraint to nearby critical organs, is the technique of choice for NPC treatment due to its convenience.

Tandon et al. (2018) conducted a prospective, single-institution, nonblinded, randomized study that compared two fractionation schedules, SIB-IMRT and simultaneous modulated accelerated radiation therapy (SMART) boost, in participants with stage III or nonmetastatic stage IV, locally advanced head and neck cancer. Overall, 60 participants met the inclusion criteria and were randomized into the control arm using the standardized technique (SIB-IMRT) or the study arm, which received radiation therapy using the SMART boost technique. All participants received weekly cisplatin-based concurrent chemotherapy at 40 mg/m^2. In the control arm, participants received 70, 63, and 56 Gy in 35 fractions to clinical target volumes (CTVs) 1, 2, and 3, respectively. In the study arm, participants received 60 and 50 Gy to CTV 1 and CTV 3, respectively. Toxicities, PFS, and OS were compared between both arms. Baseline participant-related characteristics were comparable between the arms, except for primary site of the tumor. No significant differences were noted in acute toxicities, except for fatigue, which was statistically higher in the control arm. No significant differences in 2-year late toxicities were observed. The median follow-up duration was 25.5 months (range, 1.8-39.9 months). The 2-year PFS was 53.3% and 80%, and the 2-year OS was 60% and 86.7% in 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 and maintains comparable toxicity and survival compared with SIB-IMRT. However, given the lack of phase 3 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 that covered staging, workup, and radiation therapy management in individuals with plasma cell neoplasms. For a localized plasmacytoma in the bone or in extramedullary (extraosseous) soft tissues, definitive radiation therapy is the standard treatment. It provides long-term local control in solitary bone plasmacytomas and is potentially curative in 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, and 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 with different radiation therapy modalities in 1,237 patients with NPC. The modalities studied included 2D radiation therapy (n = 350), 3D-CRT (n = 390), and IMRT (n = 497). At 5 years, OS rates with 2D radiation therapy, 3D-CRT, and IMRT were 59.7%, 73.6%, and 76.7%, respectively. In patients with advanced primary tumors, the 5-year OS was 50.4%, 57.8%, and 70.7% with 2D radiation therapy, 3D-CRT, and IMRT, respectively. The authors concluded that the outcomes demonstrated that IMRT was superior to 2D radiation therapy or 3D-CRT in cases of advanced primary disease and that IMRT and 3D-CRT were associated with better outcomes than 2D radiation therapy.

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

Trotti et al. (2014) conducted a multicenter randomized trial (RTOG 9512) to compare hyperfractionation (HFX) with standard fractionation (SFX) for T2N0 vocal cord carcinoma. The primary end point was local control at 5 years. The

secondary end points were DFS, OS, and toxicity associated with each schedule. SFX consisted of 2 Gy per fraction, once a day, to a total dose of 70 Gy in 35 fractions in 7 weeks. 2D radiation therapy that used two or three coplanar portals was used. Field reduction at 50 Gy was permitted to reduce arytenoid dose. HFX consisted of 1.2 Gy per fraction, twice a day, with a minimum interval of 6 hours, to a total dose of 79.2 Gy in 66 fractions in 6.5 weeks. A total of 250 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 a Karnofsky performance status (KPS) of 90 to 100, and 62% had a T2a tumor. The median follow-up in all surviving participants was 7.9 years (range, 0.6-13.1 years). The 5-year local control rate was 8 points higher (but not statistically significant: p = 0.14) with HFX (78%) vs. SFX (70%), corresponding to a 30% HR reduction. The 5-year DFS was 49% vs. 40% (p = 0.13), and OS was 72% vs. 63% (p = 0.29). HFX had higher rates of acute skin, mucosal, and laryngeal toxicity. Grade 3 to 4 late effects were similar, with a 5-year cumulative incidence of 8.5% (3.4%-13.6%) after SFX and 8.5% (3.4%-13.5%) after HFX. In the subcategory analysis (T2b vs T2a), outcomes were significantly worse in T2b disease for locoregional control (5-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 (5-year: T2b, 50.0% vs. T2a, 77.5%; HR, 2.06; 1.43-2.97; p = 0.0001). The authors concluded that 5-year local control was modestly higher with HFX than SFX for T2 glottic carcinoma, but the difference was not statistically significant; additionally, substaging by T2a vs T2b carries prognostic value for DFS and OS. They also stated that their results were achieved with 2D 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, which is a common late side effect of radiation therapy to the head and neck. Overall, 94 participants with pharyngeal squamous cell carcinoma were randomly assigned to receive IMRT (n = 47) or CRT (n = 47). The primary end point was the proportion of participants with grade 2 or worse xerostomia at 12 months. The 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 nonxerostomia late toxicities, locoregional control, and 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 comparative effectiveness review of radiation therapy for head and neck cancer found that while IMRT is more successful than traditional radiation therapy in avoiding side effects, such as xerostomia (dry mouth), it is unknown whether IMRT is better or worse at reducing tumor size (Samson et al., 2010). A 2014 update found moderate-strength evidence that showed a reduction in the incidence of late grade 2 or higher xerostomia with IMRT compared with 3D-CRT. This increases the strength of evidence for 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, oncological outcomes, or comparisons (Ratko et al., 2014).

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

In 2024, ASTRO released updated clinical practice guidelines that specifically addressed the management of HPV-positive oropharyngeal squamous cell carcinoma. These guidelines provide evidence-based recommendations for both definitive and postoperative radiation therapy approaches. For patients who are undergoing postoperative radiation therapy following surgical resection of HPV-positive oropharyngeal squamous cell carcinoma, ASTRO strongly recommends the use of IMRT over 3D-CRT. IMRT is preferred due to its superior ability to precisely target tumor sites while minimizing radiation exposure to surrounding healthy tissues, thereby reducing treatment-related toxicity and preserving critical functions such as swallowing and speech (Margalit et al., 2024).

International Society of Oral Oncology (ISOO)/Multinational Association of Supportive Care in Cancer (MASCC)/American Society of Clinical Oncology (ASCO)

In 2024, Peterson et al. developed comprehensive, evidence-based clinical guidelines on behalf of the ISOO, the MASCC, and ASCO to guide the prevention and management of osteoradionecrosis of the jaw in patients who are undergoing radiation therapy for head and neck cancers. The guidelines emphasize the importance of using advanced radiation planning techniques – specifically IMRT and intensity-modulated proton therapy – to minimize the radiation dose

to the mandible and maxilla. This dose-sparing approach is strongly recommended as a preventive strategy to reduce the risk of osteoradionecrosis, particularly in patients with tumors that are located near osseous structures of the jaw.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for head and neck cancers recommend IMRT as the preferred radiation technique for several tumor sites, including the oropharynx, nasal cavity, paranasal sinuses, salivary glands, and nasopharynx, because it helps reduce long-term side effects by limiting radiation exposure to nearby critical structures like the salivary glands, temporal lobes, auditory structures (including the cochlea), and optic structures. The use of IMRT for other areas such as the oral cavity, larynx, and hypopharynx is also supported and may be used at the discretion of the treating physician. Additionally, the guidelines highlight that advanced radiation technologies like IMRT may offer clinically relevant advantages in sparing important OARs, such as the brain, brainstem, 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, while still effectively treating the tumor and reducing the risk of long-term damage (NCCN, 2025).

Hepatocellular Cancer

Jang et al. (2023) performed a systematic review and meta-analysis to evaluate the existing evidence that supports the use of IMRT for hepatocellular carcinoma (HCC) and identify its distinguishing clinical and technical characteristics. Studies were included if they involved IMRT for liver tumors, used inverse planning techniques (e.g., step-and-shoot, sliding-window, VMAT, helical tomotherapy), delivered IMRT in at least 10 fractions, included 10 or more individuals with HCC, and reported outcomes such as local control or survival. Studies were excluded if IMRT was used as neoadjuvant or adjuvant therapy for surgery; intended as a bridge to liver transplant; delivered using CyberKnife, GammaKnife, brachytherapy, or charged particle therapy; or if it targeted only distant metastatic lesions. Ultimately, 29 studies that involved 1,755 individuals met the criteria for inclusion. Four studies reported outcomes in separate treatment groups, resulting in a total of 33 cohorts. The studies varied in design, with six being prospective and the remainder being retrospective. Most individuals (median, 100%) had advanced-stage HCC (Barcelona Clinic Liver Cancer stage C). Nineteen studies used combination treatments. The pooled response rate was 58%, and 1-year local control was 84%. Median OS was 13 months, with 1- and 3-year survival rates of 59% and 23%, respectively. Rates of serious liver toxicity were low: 2% for classic radiation-induced liver disease, 4% for nonclassic radiation-induced liver disease, and 4% for grade ≥ 3 hepatic toxicity. These survival outcomes were comparable to those reported with other radiation therapy modalities. According to the authors, this meta-analysis is the first to assess IMRT specifically for liver HCC and showed comparable survival outcomes and low severe toxicity. Limitations include the lack of RCTs and limited data on long-term risks like secondary cancer from IMRT; additionally, the distinction between IMRT and SBRT remains unclear due to overlapping techniques and fractionation schemes. The authors suggested that further clinical trials are needed to optimize its use and identify individuals who may benefit most from fractionated IMRT.

Wei et al. (2023) conducted an open-label RCT to determine whether neoadjuvant radiation therapy could offer survival benefits to those diagnosed with hepatitis B virus–related HCC. The study specifically focused on participants with a single, small tumor (≤ 5 cm) who were predicted to have a high risk of microvascular invasion, which is a known factor that is associated with poor prognosis and early recurrence. A total of 60 eligible participants were randomly assigned to one of two groups: the neoadjuvant radiotherapy (IMRT) group or the up-front surgery group. The primary end point of the study was DFS, while OS and objective response rate were evaluated as secondary end points. In the neoadjuvant radiation therapy group, three participants deviated from the study protocol: two underwent up-front hepatectomy instead of radiation therapy, and one received radiofrequency ablation following radiation therapy. In the neoadjuvant radiation therapy group, the objective response rate was 25.0% (seven of 28 participants), although two participants experienced grade 3 liver toxicity. The median follow-up duration was 68 months in both the radiation therapy and up-front surgery groups, with IQRs of 58 to 70 months and 62 to 75 months, respectively. Based on the intention-to-treat analysis, the median DFS and OS were not reached in either group. The 1-, 2-, 3-, and 5-year DFS rates in the radiation therapy group were 86.7%, 76.7%, 60.0%, and 56.3%, respectively, compared with 90.0%, 66.7%, 52.8%, and 45.7% in the surgery group (p = 0.448). Corresponding OS rates were 96.7%, 86.7%, 83.3%, and 72.7% in the radiation therapy group vs. 100.0%, 93.3%, 79.6%, and 60.7% in the surgery group (p = 0.399). The authors concluded that among participants with a single, small, hepatitis B virus–related HCC who were predicted to have a high risk of microvascular invasion, neoadjuvant radiation therapy demonstrated a favorable response rate and manageable toxicity. However, the study found no statistically significant difference in survival outcomes between neoadjuvant radiotherapy and up-front surgery. According to the authors, these findings indicate that while neoadjuvant radiation therapy may be a feasible option, its role in this specific population requires further investigation to determine its potential clinical value. Limitations include the single-institution design, small sample size, and lack of blinding due to the nature of the intervention.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

The ASTRO guideline for primary liver cancers provides evidence-based recommendations for the treatment of HCC with EBRT. The recommendations are as follows (not all inclusive):

- Use of EBRT as a potential first-line treatment in those with liver-confined HCC who are not candidates for curative therapy and catheter-based therapies is being considered. EBRT is a potential first-line single therapy option. Strength of recommendation: strong; quality of evidence: moderate.
- For those with liver-confined HCC and incomplete response to thermal ablation or catheter-based therapies, EBRT is recommended as a consolidative treatment option. Strength of recommendation: strong; quality of evidence: moderate.
- EBRT is recommended as a salvage treatment option for those with locally recurrent HCC after surgery, thermal ablation, or catheter-based therapies. Strength of recommendation: strong; quality of evidence: low.
- For those with liver-confined HCC for whom EBRT is recommended, dose-escalated ultra- or moderately hypofractionated EBRT is recommended, with the choice of regimen based on tumor location, underlying liver function, and available technology. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with unresectable intrahepatic cholangiocarcinoma (IHC), induction chemotherapy followed by consolidation with EBRT, alone or in combination with chemotherapy, is recommended. Implementation remark: For patients who are not candidates for induction chemotherapy, EBRT, alone or in combination with chemotherapy, should be considered. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with HCC who are receiving dose-escalated ultra- or moderately hypofractionated EBRT, IMRT or proton therapy is recommended, with the choice of regimen based on tumor location, underlying liver function, and available technology. Strength of recommendation: strong; quality of evidence: moderate.
- Additionally, the authors recommended future high-quality RCTs to further define the role of EBRT in HCC treatment (Apisarnthanarax et al., 2022).

National Comprehensive Cancer Network (NCCN)

According to the NCCN guidelines for HCC, radiation therapy, such as 3D-CRT, IMRT, and SBRT, is recommended for patients with unresectable disease or those who are medically inoperable. It may be considered for tumors regardless of their anatomical location. The use of IGRT is strongly recommended when using radiation therapy techniques such as IMRT and SBRT, as it enhances treatment precision and minimizes radiation-related toxicity. Hypofractionated treatment using photons or protons is an acceptable approach for intrahepatic tumors; however, it is recommended that such therapy be delivered at centers with established expertise (NCCN, 2025).

Hippocampal-Avoidance Whole-Brain Radiation Therapy

In 2025, Surendran et al. performed a systematic review and meta-analysis aimed to synthesize high-quality evidence regarding the clinical efficacy of hippocampal-avoidance whole-brain radiation therapy (HA-WBRT) in mitigating cognitive dysfunction. It specifically examined the therapeutic impact and radiation dose parameters – both minimum and maximum – delivered to the hippocampus and surrounding contouring regions. The objective was to evaluate whether sparing the hippocampus during whole-brain radiation therapy (WBRT) could preserve neurocognitive function. The inclusion criteria encompassed individuals of any age or gender who had brain metastases and were undergoing HA-WBRT, delivered at varying doses, fractionation schedules, and contouring parameters. The primary and secondary end points included evaluating the effectiveness of HA-WBRT in reducing radiation-induced neurocognitive impairment; determining hippocampal dose thresholds that minimize cognitive damage; analyzing contouring accuracy and relapse risk; and comparing toxicity, OS, and PFS between HA-WBRT and standard WBRT. A total of nine studies (680 individuals) were included in the final synthesis and analysis, comprising five RCTs, three nonrandomized studies, and one cohort study. In WBRT, radiation exposure to the hippocampus, within a 3- to 7-mm margin, was deliberately avoided. Across studies, the maximum hippocampal dose ranged from 12.61 to 17 Gy, while minimum doses varied between 5.38 and 10 Gy. HA-WBRT demonstrated significant preservation of delayed recall compared with standard WBRT, with multiple studies reporting statistically significant results ($p < 0.001$ and $p = 0.048$). The standardized mean difference (-0.57; 95% CI, -1.27 to 0.12; $p = 0.59$; $I^2 = 0\%$) favored HA-WBRT. However, no significant differences were observed between the two groups in other cognitive domains, including psychomotor speed, visuospatial ability, executive function, and verbal fluency. The authors concluded that HA-WBRT shows potential in preserving delayed memory in those with brain metastases, but broader cognitive protection is needed to support daily function and employability. Limitations include evidence that was limited to short-term follow-up and phase 2 data, which underscores the need for long-term RCTs.

Gondi et al. (2023) published their final results of the NRG Oncology CC001 phase 3 multicenter RCT (Brown et al. study below), with complete cognition, participant-reported outcomes, and longer-term follow-up exceeding 1 year. In the study, 518 adult participants were randomly assigned to receive either HA-WBRT plus memantine (n = 261) or WBRT plus

memantine (n = 257). The median follow-up was 12.1 months, with 63 participants in the WBRT plus memantine group and 51 participants in the HA-WBRT plus memantine group completing the 12-month Hopkins Verbal Learning Test-Revised (HVLT-R) follow-up assessment. The authors reported that the addition of hippocampal avoidance to WBRT plus memantine prevented cognitive failure and was associated with less deterioration in Trail Making Test B at 4 months and HVLT-R at 4 and 6 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 plus memantine reported less symptom burden at 6 and 12 months, less symptom interference at 6 and 12 months, and fewer cognitive symptoms over time; however, the treatment arms did not differ significantly in OS (median of 6.3 months with HA-WBRT plus memantine vs. 7.6 months with WBRT plus memantine), intracranial PFS (median of 5.0 months with HA-WBRT plus memantine vs. 5.3 months with WBRT), and grade ≥ 3 toxicity, without regard to attribution (62.1% vs. 58.7%) or related to treatment (19.8% vs. 19.3%) between the WBRT plus memantine and HA-WBRT plus 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 hippocampal avoidance 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 plus memantine for brain metastases led to sustained preservation of cognitive function and continued prevention of participant-reported neurological symptoms, symptom interference, and cognitive symptoms, with no difference in survival or toxicity.

Brown et al. (2020) conducted a phase 3 trial to determine if hippocampal avoidance using IMRT during WBRT preserves cognition. Between July 2015 and March 2018, 518 participants were randomly assigned to two groups: one group with brain metastases that received HA-WBRT plus memantine and one group with WBRT plus memantine. Time to cognitive function failure, defined as a decline using the Reliable Change Index on at least one of the cognitive tests, was the primary end point. OS, intracranial PFS, toxicity, and participant-reported symptom burden were secondary end points. The median follow-up in alive participants was 7.9 months. The risk of cognitive failure was significantly lower after HA-WBRT plus memantine vs. WBRT plus memantine (adjusted HR, 0.74; 95% CI, 0.58-0.95; p = 0.02). This difference was attributable to less deterioration in executive function at 4 months and learning and memory at 6 months. Treatment arms did not differ significantly in OS, intracranial PFS, and toxicity. At 6 months, using all data, participants who received HA-WBRT plus memantine reported less fatigue (p = 0.04), less difficulty with remembering things (p = 0.01), and less difficulty with speaking (p = 0.049) and using imputed data, less interference of neurological symptoms with daily activities (p = 0.008) and fewer cognitive symptoms (p = 0.01). The authors concluded that HA-WBRT plus memantine effectively spared the hippocampal neuroregenerative niche to better preserve cognitive function and participant-reported symptoms and should be considered a standard of care for individuals with good PS 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, and OS. Limitations include a lack of blinding.

Clinical Practice Guidelines

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

The ASCO/SNO/ASTRO guideline for patients with brain metastases from solid tumors recommends that memantine and hippocampal avoidance should be offered to patients who receive WBRT, have no hippocampal lesions, and have 4 months or more of expected survival. Patients with asymptomatic brain metastases, with either a KPS of ≤ 50 or KPS of < 70 with systemic therapy options, do not derive benefit from radiation therapy (Vogelbaum et al., 2021).

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for central nervous system cancers state that HA-WBRT plus memantine 30 Gy in 10 fractions is preferred for patients with a better prognosis (≥ 4 months) and no metastases within 5 mm of the hippocampus or leptomeningeal disease (NCCN, 2025).

Intrahepatic Cholangiocarcinoma

Tao et al. (2016) conducted a single-institution retrospective study that investigated the impact of radiation therapy dose escalation on local control and OS in those with unresectable IHC. The study aimed to identify whether a specific radiation therapy dose threshold correlates with improved survival outcomes. A retrospective analysis was conducted in 79 patients with unresectable IHC who received definitive radiation therapy at The University of Texas MD Anderson Cancer Center between 2002 and 2014. Seven patients who were treated with palliative intent were excluded. All included patients completed their planned radiation therapy, which was delivered using either 3D-CRT, IMRT, or passive scatter proton therapy with 6-MV photon beams. The median follow-up in surviving patients was 33 months (range, 11-93 months), and the median OS was 30 months, with a 3-year OS rate of 44%. The radiation therapy dose emerged as the most significant prognostic factor. Patients receiving a biologically effective dose (BED) of > 80.5 Gy had markedly better outcomes: a 3-

year OS rate of 73% vs. 38% for lower doses (p = 0.017) and a 3-year local control rate of 78% vs. 45% (p = 0.04). BED as a continuous variable was significantly associated with both local control (p = 0.009) and OS (p = 0.004). No significant treatment-related toxicities were reported. The study concluded that high-dose radiation therapy improves both local control and OS in those with inoperable IHC. A BED of > 80.5 Gy may represent an ablative dose that can achieve survival outcomes that are comparable to those with surgical resection, especially when delivered with advanced techniques such as daily CT image guidance and breath-hold gating. Limitations include the retrospective design and single-institution setting.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

The ASTRO guideline for primary liver cancers provides evidence-based recommendations for the treatment of HCC and IHC with EBRT. The recommendations are as follows (not all inclusive):

- For patients with unresectable IHC, induction chemotherapy followed by consolidation with EBRT, alone or in combination with chemotherapy, is recommended. Implementation remark: For patients who are not candidates for induction chemotherapy, EBRT, alone or in combination with chemotherapy, should be considered. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with unresectable IHC who are receiving dose-escalated ultra- or moderately hypofractionated EBRT, IMRT or proton therapy is conditionally recommended, with the choice of regimen based on tumor location, underlying liver function, and available technology. Strength of recommendation: conditional; quality of evidence: low.
- For patients with IHC who underwent curative surgical resection and have high-risk features, adjuvant EBRT with concurrent chemotherapy, alone or sequenced after systemic chemotherapy, is conditionally recommended. Implementation remark: High-risk clinical features include positive lymph nodes and/or R1 resection. Strength of recommendation: conditional; quality of evidence: low.

Additionally, the authors recommended future high-quality RCTs to further define the role of EBRT in IHC treatment (Apisarnthanarax et al., 2022).

National Comprehensive Cancer Network (NCCN)

According to the NCCN guidelines for cancers of the biliary tract, radiation therapy, including modalities such as 3D-CRT, IMRT, and SBRT, may be considered for tumors, irrespective of their anatomical location. The use of IGRT is strongly recommended when implementing advanced radiation therapy techniques like IMRT and SBRT, as it improves targeting accuracy and helps reduce toxicity to surrounding healthy tissues. Radiation therapy dosing should be individualized based on the patient's liver function and the ability to meet normal organ dose constraints (NCCN, 2025).

Hodgkin Lymphoma

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 et al., 2016, study below) that compared IMRT and conventional proton beam therapy 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 with anterior-posterior/posterior-anterior (APPA) plans and/or 3D-CRT and that the Conformity Index was constantly improved with 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 in the mean radiation therapy dose to the heart, esophagus, and spinal cord was achieved with IMRT compared with APPA and 3D-CRT, while most studies reported that the use of IMRT led to breast mean and/or median doses that were 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 with APPA or 3D-CRT, as was the mean dose to the thyroid in the majority of the studies. Limitations of this systematic review include the small population sizes in many of the studies (median number of enrolled individuals was 12), heterogeneity of the study designs and the comparators, and wide range of values and SDs of the doses to the OARs in 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.

Filippi et al. (2014) compared 3D-CRT with optimized VMAT in individuals with early-stage mediastinal Hodgkin lymphoma (HL) treated with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy followed by 30-Gy involved node radiation therapy or involved-site radiation therapy. Among 38 individuals (mostly nonbulky disease), VMAT significantly reduced the absolute excess risk of cardiac and valvular disease across all disease extents. For second cancer risk, 3D-CRT showed lower lung cancer induction risk in mediastinal-only and mediastinal plus unilateral neck cases, while VMAT reduced breast cancer risk in mediastinal plus bilateral neck presentations. No significant

differences were observed for thyroid cancer. Overall, VMAT provided superior cardiac protection and comparable or improved secondary cancer risk profiles in selected scenarios. The authors reported that in those with limited disease at diagnosis, mostly nonbulky cases without axillary involvement, optimized VMAT lowers heart disease risk while maintaining similar thyroid and breast cancer risks. However, it slightly increases the likelihood of lung cancer. These outcomes vary significantly with anatomical differences, highlighting the need for personalized treatment planning. Limitations include the small sample size; additionally, the study mainly included individuals with favorable disease characteristics.

Clinical Practice Guidelines

International Lymphoma Radiation Oncology Group (ILROG)

The ILROG guidelines (Specht et al., 2014) highlight radiation therapy as the most effective single modality for achieving local control in HL and an essential component of treatment for many patients. Modern radiation therapy strategies emphasize smaller fields and lower doses to reduce toxicity while preserving disease control. Traditional extended-field and original involved-field techniques have been replaced by limited-volume approaches. Advanced technologies, including IMRT, breath-hold techniques, IGRT, and 4D imaging, are recommended when they significantly decrease normal tissue exposure without compromising tumor coverage. IMRT is particularly valuable for delivering highly conformal dose distributions in complex anatomical regions and minimizing high-dose exposure to OARs. However, careful planning is required to manage the potential increase in low-dose exposure to surrounding tissues. In patients with mediastinal involvement, IMRT can substantially lower pulmonary toxicity predictors (e.g., D_{mean} and V20) and improve cardiac and coronary artery protection, especially when the PTV is large and includes the anterior mediastinum. Its precision also enables safe retreatment in relapsed cases without exceeding tolerance limits of critical structures such as the spinal cord. The aim of modern, smaller-field radiation therapy is to limit both the treatment volume and radiation dose while preserving therapeutic effectiveness and reducing the risk of acute and long-term side effects.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for HL state that advanced radiation therapy techniques, such as IMRT/VMAT, DIBH, respiratory gating, IGRT, and PBRT, can offer meaningful benefits in select cases by sparing critical OARs and reducing long-term toxicity while maintaining effective tumor control. Although conformal techniques like IMRT provide precise dose delivery, they may increase low-dose exposure to surrounding tissues, making careful technique selection and strict adherence to dose constraints essential. Randomized trials are unlikely because these techniques aim to reduce late effects that take over a decade to appear. Therefore, modalities that effectively lower doses to OARs, without compromising target coverage, should be prioritized based on current evidence and best practices, especially for those with favorable prognoses and a long life expectancy (NCCN, 2025).

Mediastinal Tumors

In 2022, Falkson et al. conducted a systematic review to update the existing evidence on the most effective treatment strategies for thymic epithelial tumors. The findings from this review were intended to inform and refine clinical practice guidelines that were developed by Ontario Health's Program in Evidence-Based Care, ensuring that recommendations reflect current best practices for managing thymoma and related conditions. The working group identified OS, PFS or recurrence-free survival, and treatment-related toxicities as critical outcomes across systemic therapy, radiation therapy, and surgery for thymic epithelial tumors. For systemic therapy and radiation therapy, response rates and QOL were also considered important. In surgical treatment, a broader range of outcomes, including margin status, short-term mortality, recurrence patterns, complications, and recovery metrics, were deemed important to fully assess the impact and effectiveness of care. Studies were included if they were fully published or published abstracts of completed phase 2 or 3 RCTs. In the absence of high-quality RCTs, comparative studies were considered, followed by noncomparative studies with at least 25 individuals. Studies were excluded if they involved individuals with myasthenia gravis without thymoma or were published in languages other than English. A total of 106 studies, mostly observational, were reviewed. Postoperative radiotherapy was associated with improved OS in those with thymic carcinoma (HR, 0.65) and thymoma (HR, 0.70), particularly in those at a higher risk of death. Chemotherapy showed effectiveness in both tumor types. However, findings from studies on neoadjuvant chemotherapy and minimally invasive surgery were influenced by selection bias. Additionally, the survival benefit that was seen with adjuvant chemotherapy may have been confounded by concurrent use of postoperative radiotherapy. The authors concluded that the evidence base for treating thymoma and thymic carcinoma is limited and prone to bias. However, postoperative radiotherapy was associated with improved OS. The authors suggested that future large-scale, prospective studies that account for confounding factors are needed to strengthen the evidence. Limitations include low-quality evidence (most studies were observational) and the rarity of thymic epithelial tumors; additionally, the predominance of single-institution studies may limit the applicability of findings to broader populations of individuals.

A 2021 prospective, nonrandomized, phase 2 trial that was conducted by Romesser et al. investigated the effectiveness and tolerability of IMRT, with or without concurrent chemotherapy, in participants with locally advanced thyroid cancer. The primary outcome that was measured was 2-year locoregional progression–free survival, while secondary outcomes included OS, safety, participant-reported outcomes, and functional assessments. Among the 27 participants who were enrolled, 44.4% had unresectable disease, and 55.6% had gross residual disease. With a median follow-up of 45.6 months, the 2-year locoregional progression rate was 15.2%, and PFS and OS rates were 77.3%. Acute grade ≥ 3 toxicity occurred in 33.4% of participants, while late toxicity was observed in 3.7%. Functional assessments at 12 months showed no significant differences, and participant-reported QOL initially declined but returned to baseline within 6 months, improving thereafter. A post hoc analysis revealed that IMRT combined with chemotherapy significantly reduced locoregional failures at 2 years ($p = 0.001$), although it was associated with higher rates of acute grade ≥ 2 dermatitis, mucositis, and dysphagia, without affecting long-term toxicity, functionality, and QOL. The authors concluded that IMRT was well tolerated and showed promising efficacy in participants with locally advanced, nonanaplastic thyroid carcinoma. Adding concurrent doxorubicin to IMRT enhanced locoregional disease control, although it led to a modest increase in acute toxicity. Importantly, no differences in long-term toxicity, functional outcomes, and participant-reported QOL were observed. The authors suggested that given the strong locoregional control and manageable side effect profile, doxorubicin-based concurrent chemoradiation should be considered for those with gross residual or unresectable, nonanaplastic differentiated thyroid cancer. Limitations include the small sample size and lack of randomization.

Jackson et al. (2017) analyzed data from the National Cancer Database to assess outcomes and identify prognostic factors in individuals who might benefit from adjuvant radiotherapy. Their study focused on adults aged 18 years or older who were diagnosed with thymoma or thymic carcinoma between 2004 and 2012. Only individuals who had undergone surgery and had complete treatment data, including surgery, chemotherapy, and radiation therapy, were included. The analysis was limited to the initial course of treatment, excluding cases in which radiation was administered before or during surgery as well as those in which the individual died within 1 month of diagnosis. A total of 4,056 individuals met the criteria for inclusion in the study, with 49% receiving postoperative radiation therapy. A multivariate analysis of OS in the thymoma group, adjusted for age, WHO histological subtype, Masaoka-Koga stage, surgical margins, and chemotherapy, showed that postoperative radiotherapy was significantly associated with improved survival (HR, 0.72; $p = 0.001$). This survival benefit was further supported by propensity score–matched analyses. A subgroup analysis revealed that postoperative radiotherapy was linked to longer OS in those with stage IIB thymoma (HR, 0.61; $p = 0.035$) or stage III disease (HR, 0.69; $p = 0.020$) and those with positive surgical margins (HR, 0.53; $p < 0.001$). However, for individuals with stage I to IIA disease, the benefit of postoperative radiotherapy did not reach statistical significance (HR, 0.76; $p = 0.156$). Most presented with localized disease, although a higher percentage of thymic carcinoma cases (17.5%) were diagnosed at Masaoka-Koga stage IV. The study period (2004-2012) coincided with the widespread use of advanced radiation therapy techniques, including 3D-CRT and IMRT. The authors concluded that postoperative radiotherapy was linked to improved OS, with the most significant benefits seen in individuals with stage IIB to III disease and those with positive surgical margins. Although randomized trials are lacking, these findings offer valuable insights that may help guide clinical decision-making. Limitations include the retrospective nature of the study and lack of randomization.

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

Clinical Practice Guidelines

American Thyroid Association (ATA)

The 2021 ATA guidelines for the management of anaplastic thyroid cancer by Bible et al. provided strong recommendations for the use of IMRT in specific clinical scenarios, despite the overall low quality of supporting evidence. These recommendations are as follows (not all inclusive):

- Postoperative IMRT following R0 or R1 resection: For patients with no evidence of metastatic disease, good PS, and a preference for aggressive treatment, the guidelines recommend SFX IMRT that is administered concurrently with systemic therapy. Strength of recommendation: strong; quality of evidence: low.

- IMRT for R2 resection or unresectable, nonmetastatic disease: Patients who have undergone an R2 resection or have unresectable but nonmetastatic disease, have a good PS, and wish to pursue aggressive therapy should also be offered SFX IMRT in combination with systemic therapy. Strength of recommendation: strong; quality of evidence: low.
- General recommendation for IMRT: Among all patients who are receiving radiation therapy for unresectable thyroid cancer or in the postoperative setting, IMRT is the preferred modality due to its ability to deliver conformal radiation while minimizing exposure to adjacent critical structures. Strength of recommendation: strong; quality of evidence: low.

National Comprehensive Cancer Network (NCCN)

The advanced radiation therapy techniques for treating B-cell lymphomas, including IMRT/VMAT, DIBH, respiratory gating, IGRT, and PBRT, can offer meaningful advantages in certain cases by reducing radiation exposure to critical organs such as the heart, lungs, liver, kidneys, spinal cord, and others. This reduction helps lower the risk of long-term tissue damage while maintaining effective tumor control. For mediastinal and abdominal lymphomas, managing respiratory motion through breath-hold or gating techniques is particularly beneficial, especially in minimizing radiation to the heart, liver, and kidneys. Because late effects from radiation may take over a decade to develop, randomized trials to validate these approaches are unlikely. Therefore, guidelines recommend using radiation therapy methods that effectively reduce exposure to OARs, without compromising tumor coverage, especially for patients with favorable prognoses and a long life expectancy (NCCN, 2025).

The NCCN guidelines for T-cell lymphomas emphasize that advanced radiation therapy techniques, such as IMRT, PBRT, IGRT, and respiratory motion management strategies like breath-hold or gating, can offer meaningful benefits in select cases. These technologies help spare critical OARs and reduce the likelihood of long-term tissue damage while maintaining effective tumor control. Achieving highly conformal dose distributions is particularly important for those treated with curative intent or those expected to have long survival. IMRT has been associated with favorable locoregional control and improved OS and PFS in early-stage disease, with minimal toxicity. For mediastinal lymphomas, the use of 4D-CT simulation and respiratory motion management during treatment delivery is also recommended to enhance precision and minimize exposure to surrounding healthy tissues (NCCN, 2025).

The NCCN guidelines for treating thymomas and thymic carcinomas recommend that radiation therapy should meet a minimum standard of CT-based 3D-CRT. More advanced technologies, such as 4D-CT, PET/CT simulation, IMRT, VMAT, IGRT, motion management, and PBRT, are considered appropriate when needed to safely deliver curative treatment. Because patients with these conditions are typically younger and are often long-term survivors, the guidelines emphasize minimizing the average radiation dose to the heart to help optimize survival outcomes. IMRT is preferred over 3D-CRT, as it can offer better dose distribution and reduce exposure to surrounding healthy tissue (NCCN, 2025).

The NCCN guidelines for the management of thyroid cancer highlight the critical role of advanced EBRT techniques in both adjuvant and definitive treatment settings. These recommendations advocate for the use of highly conformal approaches, particularly IMRT with SIB and image guidance, due to their ability to deliver highly precise radiation doses to tumor sites while minimizing exposure to surrounding healthy tissues (NCCN, 2025).

Non-Small Cell Lung Cancer

Chun et al. (2024) conducted a secondary analysis of the NRG Oncology-RTOG 0617 RCT to compare long-term prospective outcomes in study participants who were receiving IMRT and 3D-CRT with concurrent carboplatin/paclitaxel for locally advanced non-small cell lung cancer (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 vs. 139), larger mean PTVs (486.2 ml vs. 426.7 ml), greater PTV-to-lung ratios (0.15 vs. 0.13), and larger lung V5 (61.6% vs. 54.8%) than the 3D-CRT group. The authors reported that the IMRT group achieved significantly lower heart V40 than 3D-CRT (16.5% vs. 20.5%) and that IMRT was associated with a two-fold reduction in grade 3 or higher pneumonitis AEs (per CTCAE version 3). The authors also reported that participants in both groups had similar OS, PFS, time to local failure, and DMFS at 5 years. A limitation of the study is 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 support the use of IMRT for locally advanced NSCLC. A key limitation is that this was a secondary analysis that used data that were originally collected for a different primary objective. Another secondary analysis of the NRG Oncology RTOG 0617 RCT (Chun et al., 2017) was conducted to evaluate OS, PFS, local failure 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 them, 53% (n = 254) received 3D-CRT (57.1% received standard-dose and 42.9% received high-dose radiation therapy), and 47% (n = 228) received IMRT (59.2% received standard-dose and 52.6% received high-dose radiation therapy). 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), and more participants in the IMRT group had staging by PET than participants in the 3D-CRT group (94.3% vs. 88.2%; p = 0.019). After treatment, there were no differences in 2-year rates of OS, PFS, local failure, and distal metastasis–free survival between the IMRT and 3D-CRT groups. IMRT was associated with less grade ≥ 3 pneumonitis (7.9% vs. 3.5%; p = 0.039) and lower doses of radiation to the heart (V20, V40, and V60; p < 0.5). Furthermore, after differences between the groups were adjusted for, the volume of the heart that was receiving 40 Gy was significantly associated with OS (p < 0.05). The authors concluded that IMRT was associated with lower rates of severe pneumonitis and lower doses of radiation to the heart; by reducing these, IMRT may be associated with improved OS in the long term. They also stated that continued follow-up in this population is essential to further clarify whether differences in long-term survival exist between treatment with IMRT and 3D-CRT. A key limitation is that this was a secondary analysis that used data that were originally collected for a different primary objective.

Speirs et al. (2017) analyzed the clinical and dosimetric parameters that affected OS in individuals (n = 416) with locally advanced NSCLC, with a focus on heart dose. Treatment plans were recontoured using normal tissue guidelines from RTOG 0617; toxicity and dosimetry data were analyzed for 322 individuals, with a multivariate analysis performed in 251 individuals. The primary end points were OS, DFS, and toxicity. Individuals were treated with radiation therapy to prescribed doses of 50.0 to 84.9 Gy (median, 66.0 Gy). The median follow-up was 14.5 months. Median OS was 16.8 months. The 1- and 2-year OS rates were 61.4% and 38.8%, respectively. On multivariate analysis, factors that were 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 < 25% vs. ≥ 25%, the 1-year OS rates were 70.2% vs. 46.8%, and the 2-year OS rates were 45.9% vs. 26.7% (p < 0.0001). The median heart V50 was significantly higher in individuals with cardiac toxicity with a CTCAE grade of 1 or higher. Based on the authors' conclusion, in individuals with locally advanced NSCLC who are treated with chemoradiotherapy, the heart dose is associated with OS and cardiac toxicity. Limitations include the 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 radiation therapy arm at 3 months. Of 424 eligible participants with stage III NSCLC, 360 (85%) consented to QOL, with 313 completing the baseline QOL assessments. QOL was collected prospectively, and data were presented at baseline and 3 and 12 months. Overall, 219 participants (70%) completed the 3-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 the FACT-LCS at 3 months (45% vs. 30%; p = 0.02). At 12 months, fewer participants who received IMRT (vs. 3D-CRT) had a clinically meaningful decline in FACT-LCS (21% vs. 46%; p = 0.003). Baseline Fact-Trial Outcome Index was associated with OS in a multivariate analysis. The authors concluded that the QOL analysis demonstrated a clinically meaningful decline in QOL in the 74-Gy arm at 3 months, despite few differences in clinician-reported toxic effects between treatment arms. A key limitation is that this was a secondary analysis that used data that were originally collected for a different primary objective.

Wang et al. (2016) retrospectively compared the clinical outcomes and radiation-related toxicities between patients with locally advanced NSCLC who were receiving 3D-CRT and IMRT between 2002 and 2010 from a single academic center. OS, local-regional progression–free survival (LRPFS), DMFS, and PFS were compared among patients (IMRT, n = 446; 3D-CRT, n = 206) who were irradiated with different techniques. The median OS in the 3D-CRT and IMRT groups was 19.4 and 23.3 months, with a 5-year rate of 13% and 19%, respectively (p = 0.043). A multivariate analysis identified IMRT as an independent favorable factor that was associated with LRPFS and DMFS. A propensity score matching analysis further verified the beneficial effect of IMRT on LRPFS. No difference in OS and PFS was observed between the two techniques. A subgroup analysis revealed that IMRT might have been differentially more effective for both OS and LRPFS among patients who were female, were nonsmokers, had adenocarcinoma, or did not have weight loss. There was a significant reduction in lung toxicity and similar esophagus toxicity in the IMRT group compared with the 3D-CRT group. The authors concluded that pulmonary toxicity was reduced with IMRT. Additionally, IMRT may provide superior LRPFS and similar OS compared with 3D-CRT. Limitations include the retrospective study design.

Bradley et al. (2015) conducted a multi-institution, open-label, randomized, two-by-two factorial, phase 3 clinical trial in which participants, who were diagnosed with unresectable, stage III NSCLC, were randomized to receive concurrent chemotherapy comprising carboplatin and paclitaxel with or without cetuximab and either 60-Gy (standard dose) or 74-Gy (high dose) radiation therapy. The primary outcome was OS, and secondary outcomes included PFS, local-regional tumor control, and toxicity. In this study, 166 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 than participants who received high-dose radiotherapy (28.7 vs. 20.3 months; HR, 1.38; 95% CI, 1.09-1.76; p = 0.004). In addition, the use of cetuximab was associated with a higher rate of grade 3 or worse toxicity: 86% (205/237) vs. 70% (160/228), with 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)

The NCCN guidelines for NSCLC recommend IMRT over 3D-CRT for stage III disease, based on the RTOG 0617 trial, which showed that IMRT significantly reduced high-grade radiation pneumonitis while maintaining similar survival and tumor control, despite being used in patients with more advanced disease and larger treatment volumes. In early-stage NSCLC, if a stereotactic ablative body radiotherapy referral is not feasible, alternatives include modestly hypofractionated or dose-intensified conventionally fractionated, highly conformal radiation (IMRT with IGRT preferred), although these are less favored. Highly conformal radiation therapy, such as IMRT, is also preferred in retreatment settings to help minimize toxicity (NCCN, 2025).

Pancreatic Cancer

Umezawa et al. (2022) conducted a retrospective, single-center cohort study to analyze the incidences of acute GI toxicities in patients who underwent 3D-CRT and IMRT in CRT with S-1, including prophylactic regions for pancreatic cancer. The study included 56 patients with locally advanced pancreatic cancer, without distant metastases, who received S-1 daily (5 days per week) during treatment, with either 3D-CRT (n = 25; median age, 69 years; 52% male) or IMRT (n = 31; median age, 69 years; 65% male) administered in a hungry state for at least 3 hours and with shallow free breathing. Administration of S-1 was discontinued in four patients (16%) in the 3D-CRT group and in one patient (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 that were related to the stomach and 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, differences in induction chemotherapy and radiation therapy dose between the 3D-CRT group and the IMRT group, and 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 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. Grade ≥ 3 acute toxicities, nausea, and vomiting were 13.4% (109/747 individuals) vs. 7.8% (35/446) with 3D-CRT and IMRT, respectively (p < 0.001). Grade ≥ 3 diarrhea was 11.6% (87/747) vs. 2.0% (9/446) with 3D-CRT and IMRT, respectively (p < 0.001). Late toxicities were predominantly GI: grade ≥ 3 toxicities were 10.6% (22/207) and 5.0% (19/381) with 3D-CRT and IMRT, respectively (p = 0.017). However, those were mainly attributed to the group of individuals with GI bleeding/duodenal ulcer. There were no differences in hematologic 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 are no significant differences in OS and PFS; however, treatment-related toxicities such as nausea, vomiting, diarrhea, and late GI toxicity are significantly reduced with IMRT.

Wang et al. (2015) conducted a single-institution, retrospective analysis that evaluated efficacy and pain control when IMRT is used for locally advanced pancreatic cancer and metastatic pancreatic cancer. Patients were identified from the medical record database, with 63 patients who were treated between May 2006 and April 2013 selected. All patients received IMRT. Among the 63, 36 received radiation therapy alone, and 27 received concurrent chemoradiotherapy. Nonhematologic toxicities of grade ≤ 2 were 44% in both groups, while grade ≥ 3 hematologic toxicities in both groups were approximately 14%. Moderate to severe abdominal and/or back pain was reported by 44 patients prior to therapy. Pain elimination or reduction was achieved in 100% of those reporting symptoms prior to radiation therapy or concurrent chemoradiotherapy. The median OS in patients with locally advanced pancreatic cancer and metastatic pancreatic cancer was 15.7 months and 8 months, respectively. The authors concluded that while both radiation therapy and concurrent

chemoradiotherapy provided marked pain relief, the use of concurrent chemoradiotherapy 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 guideline states that modulated treatment techniques such as IMRT and VMAT for the planning and delivery of both conventionally fractionated and hypofractionated radiation therapy are recommended for the treatment of localized pancreatic cancer (strength of recommendation: strong) (Palta et al.).

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for pancreatic adenocarcinoma state that 3D-CRT, IMRT, and SBRT can result in improved PTV coverage, with a decreased dose to OARs. The guidelines also state that IMRT is increasingly being applied in the treatment of locally advanced pancreatic adenocarcinoma and in the adjuvant setting, with the aim of increasing the radiation dose to the gross tumor while minimizing toxicity to surrounding tissues. There is no clear consensus on the appropriate maximum dose of radiation when IMRT is used (NCCN, 2025).

Prostate Cancer

Maggio et al. (2024) conducted a prospective, multicenter, longitudinal, observational study to evaluate the evolution of QOL in the first 5 years following IMRT for prostate cancer. The study included 391 men (median age, 71 years) who were treated with conventional or moderately hypofractionated IMRT; QOL was evaluated by the EORTC QLQ-C30 at baseline, at the completion of radiation therapy, and every 6 months up to 5 years after IMRT ended. The authors reported that (1) the longitudinal analysis in the 160 participants who completed their questionnaires at 60 months showed a trend toward the significant worsening of QOL at the end of radiation therapy for global health, physical and role functioning, fatigue, appetite loss, diarrhea, and pain and (2) QOL worsening was recovered within 6 months from the end of radiation therapy, except for physical functioning. The authors also reported that (1) the most impaired time point was at the end of radiation therapy; (2) a 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 (3) acute grade 2 or higher GU toxicity resulted in lower role functioning and higher pain. Limitations include the high attrition rate and use of concomitant therapies that may have impacted the participants' symptoms. The authors concluded that high radiation IMRT doses that were delivered for prostate cancer led to a temporary worsening of QOL that tended to resolve completely at 6 months, without affecting long-term QOL; additionally, acute GI and GU toxicity were the most common systems affected.

Abu-Gheida et al. (2019) presented 10-year outcomes and toxicities in individuals with localized prostate cancer who underwent IMRT with 70 Gy in 28 fractions at 2.5 Gy per fraction. Overall, 854 individuals were included in the study. Individuals 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). In individuals with low-risk, FIR, UIR, or high-risk disease, the 10-year biochemical relapse–free survival rates were 88%, 78%, 71%, and 42%, respectively ($p < 0.0001$). The 10-year clinical relapse–free survival rates were 95%, 91%, 85%, and 72% in individuals with low-risk, FIR, UIR, or high-risk disease, respectively ($p < 0.0001$). In all individuals, the 10-year actuarial OS rate was 69% (95% CI, 66%-73%), and the 10-year prostate cancer–specific mortality was 6.8% (95% CI, 5.1%-8.6%) overall. In individuals with low-risk, FIR, UIR, or 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 that 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; additionally, the fractionation schedule appeared to be acceptable for individuals across all risk groups. Limitations include a lack of randomization, toxicity outcomes that were reported by the physicians rather than the individuals, and some individuals being lost to follow-up.

Viani et al. (2016) compared IMRT with 3D-CRT for the treatment of prostate cancer through a randomized phase 3 clinical trial (NCT02257827). In total, 215 participants were enrolled in the study and randomly selected for the IMRT group (n = 109) or the 3D-CRT group (n = 106). The primary outcome measures included early and late GU and GI toxicities as well as freedom from biochemical failure, determined using the Phoenix criteria (prostate-specific antigen +2 ng/mL nadir). The median follow-up period was 3 years. The 3D-CRT arm had incidences of grade ≥ 2 acute GU and GI toxicities at 27% and 24%, respectively, compared with 9% and 7% 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 had 12.3% and 21%, respectively, compared with the IMRT arm, which had 3.7% and 6.4%. The 5-year rate of freedom from biochemical failure was 95.4% in the IMRT arm and 94.3% in the 3D-CRT arm ($p = 0.678$). 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 with 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. The 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 the 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. The 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% in the low-risk group, 78% in the intermediate-risk group, and 62% in the high-risk group. The 10-year DMFS 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 associated with excellent long-term tumor control outcomes in individuals with localized prostate cancer.

Clinical Practice Guidelines

American College of Radiology (ACR)

The ACR Appropriateness Criteria state that external beam radiation is a key component of the curative management of T1 and T2 prostate cancer. IMRT is widely used for prostate cancer treatment, achieving highly conformal dose distributions and a high level of precision in treatment delivery. Photon energy of at least 6 MV is recommended for prostate IMRT, and 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 guidelines note that various radiation therapy options, including IMRT, can be considered an appropriate option for patients with low-, intermediate-, or high-risk disease. The guideline strongly recommends that dose escalation should be used when EBRT is the primary treatment for prostate cancer; 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 use IMRT with doses between 45 and 52 Gy. Of note, the SUO endorsed this guideline (Eastham et al., 2022).

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines note that IMRT is preferred over 3D-CRT and should be used to treat prostate cancer due to its superior ability to shape radiation doses to the tumor. IMRT has been shown to lower the risk of GI side effects and reduce the need for additional treatments in some older studies, although not consistently across all of them. Additionally, moderately hypofractionated, image-guided IMRT has demonstrated comparable effectiveness and safety to traditional IMRT schedules in several randomized trials (NCCN, 2025).

Rectal Cancer

The RAPIDO trial, which was conducted by Bahadoer et al. (2021), was a multicenter, randomized, open-label, phase 3 study that was designed to evaluate whether total neoadjuvant therapy could improve outcomes in those with high-risk, locally advanced rectal cancer. The trial compared two treatment strategies; the experimental arm received short-course radiotherapy, followed by chemotherapy (either six cycles of capecitabine and oxaliplatin or nine cycles of 5FU, leucovorin, and oxaliplatin) and then total mesorectal excision surgery. The control arm followed the conventional approach of long-course chemoradiotherapy (50 Gy over 25-28 fractions with concurrent capecitabine), followed by total mesorectal excision and optional adjuvant chemotherapy based on institutional protocols. Eligible participants were adults who had an ECOG PS of 0 to 1; newly diagnosed, biopsy-confirmed rectal adenocarcinoma that exhibited high-risk features on pelvic MRI, such as cT4 or cN2 staging; mesorectal fascia involvement; or lateral lymph node enlargement. Participants with metastatic disease, prior rectal cancer treatment, or extensive sacral nerve involvement were excluded. The primary end point was disease-related treatment failure at 3 years, which included locoregional recurrence, distant metastases, new primary colorectal tumor, and treatment-related death. A total of 912 participants were enrolled and randomized: 462 in the experimental group and 450 in the standard-of-care group. The RAPIDO trial found that the cumulative probability of disease-related treatment failure at 3 years was significantly lower in the experimental group (23.7%) than the standard treatment group (30.4%) (HR, 0.75; p = 0.019). During preoperative therapy, the most frequent severe AE (grade 3 or higher) was diarrhea, which affected 18% of participants in the experimental group and 9% in the

standard group. In the standard group, neurological toxicity was also notable during adjuvant chemotherapy and occurred in 9% of those who received it. Serious AEs were reported in 38% of participants in the experimental group and in 34% of participants in both subgroups of the standard group who did and did not receive adjuvant chemotherapy. Treatment-related deaths occurred in both groups, with four in each; causes included cardiac arrest, pulmonary embolism, infectious complications, neutropenic sepsis, and aspiration, and one suicide occurred due to severe depression. According to the authors, for those with high-risk, locally advanced rectal cancer, the RAPIDO trial demonstrated that short-course radiation therapy, followed by 18 weeks of chemotherapy before surgery, significantly lowers the risk of disease-related treatment failure compared with standard chemoradiotherapy with or without adjuvant chemotherapy. This benefit is mainly due to a reduction in distant metastases. The high rate of pathological complete response that was observed in the experimental group also suggests potential for organ preservation. Limitations include the change in the primary end point during the study from DFS to disease-related treatment failure. Another limitation is the lack of centralized review of baseline MRI scans, which may have led to staging inaccuracies.

Wee et al. (2018) conducted a meta-analysis to evaluate and compare the acute toxicity profiles of IMRT and 3D-CRT in individuals with rectal cancer. Two radiation oncologists performed a thorough literature search using the Embase and PubMed databases to identify relevant studies that were published up to March 24, 2017. Only studies with English-language abstracts were considered. The analysis included studies that directly compared toxicity outcomes between IMRT and 3D-CRT. Excluded from the review were case reports, review articles, abstracts that lacked full articles, studies without a comparative radiation technique group, and those with insufficient toxicity data to calculate ORs. Six studies, involving a total of 859 individuals, met the inclusion criteria for analysis, with the vast majority (98.7%) of individuals receiving neoadjuvant chemoradiotherapy. The meta-analysis revealed that IMRT significantly reduced the incidence of grade ≥ 2 acute GI toxicities, including overall GI toxicity, diarrhea, and proctitis, compared with 3D-CRT, with ORs of 0.38, 0.32, and 0.60, respectively (all statistically significant). IMRT also showed a notable reduction in grade ≥ 3 acute proctitis (OR, 0.24; $p = 0.03$). No significant heterogeneity or publication bias was found. The pooled analysis further supported these findings, showing that IMRT lowered the rates of both grade ≥ 2 and grade ≥ 3 acute GI toxicities as well as GU toxicity (all $p < 0.05$). According to the authors, although randomized trials are lacking, the evidence suggests that IMRT significantly reduces acute GI and potentially GU toxicities in those with locally advanced rectal cancer that has been treated with 5FU-based neoadjuvant chemoradiotherapy, without negatively affecting pathological complete response rates. The study acknowledges several limitations. Firstly, all included studies were retrospective and conducted across different institutions, which may introduce variability in data collection and reporting. Secondly, some studies had relatively small cohorts of individuals, which potentially affected the robustness of the findings.

Ng et al. (2016) retrospectively reviewed records of 318 patients with biopsy-confirmed primary rectal adenocarcinoma who underwent preoperative chemoradiation with either IMRT or 3D-CRT. Patients who underwent induction chemotherapy received either 5FU, leucovorin, and oxaliplatin or capecitabine and oxaliplatin. During chemoradiation, clinicians conducted weekly evaluations and documented acute toxicities. The study focused on pelvic radiation–related side effects, including diarrhea, proctitis, GU symptoms (such as dysuria, urinary frequency, and cystitis), and vaginal discharge. Of 301 patients, 67.4% received IMRT, and 32.6% received 3D-CRT. Those treated with 3D-CRT had significantly higher rates of moderate to severe diarrhea (22% vs 10%; $p = 0.004$), with a 2.7-fold increased risk, even after adjusting for individual characteristics and chemotherapy (OR, 2.71; $p = 0.01$). IMRT was associated with fewer cases of grade 2 GU toxicity (6% vs. 13%; $p = 0.04$) and showed a trend toward reduced grade 2 proctitis (22% vs. 32%; $p = 0.07$). Additionally, patients aged over 55 years had 45% lower odds of developing proctitis compared with those aged under 55 years. The authors concluded that IMRT significantly reduced grade ≥ 2 diarrhea and GU toxicity during chemoradiation, with a possible trend toward reduced proctitis. The authors suggested that prospective studies using appropriate chemotherapy agents are needed to better assess IMRT's impact on treatment-related side effects. Limitations include the retrospective design and potential selection bias; favoring those who are more likely to benefit from IMRT may have underestimated its true effect.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

The ASTRO evidence-based guideline developed by Wo et al. (2025) for radiation therapy for rectal cancer focused on updating three key questions that include indications for neoadjuvant radiation therapy, selection of neoadjuvant regimens, and indication for nonoperative management. The guideline recommends the following (not all inclusive):

- For patients with stage II or III rectal cancer, neoadjuvant radiation therapy is recommended. Implementation remark: For patients at lower risk of locoregional recurrence, neoadjuvant radiation therapy may not always be appropriate. Strength of recommendation: strong; quality of evidence: high.
- For patients with rectal cancer for whom radiation is indicated, radiation therapy should be performed prior to the operation rather than post operation. Strength of recommendation: strong; quality of evidence: high.

- For patients with rectal cancer who are treated with radiation therapy, an IMRT/VMAT technique is conditionally recommended. Implementation remark: IMRT/VMAT may be beneficial when the external iliac nodes and/or the inguinal nodes require treatment or when 3D conformal techniques may confer a higher risk for toxicity. Strength of recommendation: conditional; quality of evidence: low.
- For patients with rectal cancer who are receiving IMRT/VMAT, daily image guidance to verify localization is conditionally recommended. Strength of recommendation: conditional; quality of evidence: expert opinion.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for rectal cancer state that IMRT is preferred for reirradiation in those with recurrent disease who have been previously treated, those undergoing postoperative treatment due to increased acute or late toxicity, or in specific anatomical situations, such as when the external iliac lymph nodes are invading pelvic organs or inguinal lymph nodes involving the anal canal. For ablative radiotherapy that targets a limited number of liver or lung metastases, the guidelines advise that radiotherapy should be administered in a highly conformal manner, using techniques such as IMRT (NCCN, 2025).

Small Cell Lung Cancer

Yang et al. (2023) conducted a retrospective analysis in patients with limited-disease small cell lung cancer (SCLC) who were undergoing definitive concurrent chemoradiation with etoposide and cisplatin to evaluate the effectiveness and safety of escalating the radiation dose with a once-daily treatment approach. Between January 2016 and March 2021, patients who were diagnosed with limited-disease SCLC, confirmed by pathology, and treated with definitive concurrent chemoradiation therapy using IMRT at doses of 50 Gy or higher were included in the study. Exclusion criteria were the lack of follow-up chest CT scans, prior thoracic radiation or surgery, and a history of other cancers within 2 years before the SCLC diagnosis. Patients were categorized into standard and dose-escalated groups based on a BED ($\alpha/\beta = 10$) of 70 Gy. All treatments used IMRT, with total doses ranging from 50 to 66 Gy, and conventional fractionation. Chemotherapy consisted of four cycles of platinum-based combination therapy. After concurrent chemoradiotherapy was completed, chest CT scans were performed 1 month later, then every 3 months for the first 2 years, and every 6 months up to 5 years to monitor treatment response and disease progression. A total of 122 patients were included in the analysis, with a median follow-up time of 27.8 months (ranging from 4.4-76.9 months). The median age was 63 years, and most (86%) had a history of smoking. Patients in the dose-escalated group had significantly better outcomes than those in the standard group, with 1- and 3-year OS rates of 93.5% and 50.5% compared with 76.7% and 33.3%, respectively ($p = 0.008$). Similarly, freedom from in-field failure rates at 1 and 3 years were higher in the dose-escalated group (91.4% and 66.5%) than in the standard group (73.8% and 46.9%; $p = 0.018$). There were no statistically significant differences between the groups in the incidence of grade 2 or higher acute or late pneumonitis ($p = 0.062$ and 0.185). The authors concluded that delivering dose-escalated, once-daily concurrent chemoradiation using IMRT at a BED_{10} that exceeded 70 Gy significantly improved survival and local tumor control, without increasing treatment-related toxicity. The retrospective nature of the study and small samples size are key limitations.

A secondary analysis of the NRG Oncology RTOG 0617 trial (Chun et al., 2017) evaluated outcomes in participants with stage III NSCLC who were treated with either IMRT or 3D-CRT. Among 482 participants, 47% received IMRT, and 52.8% received 3D-CRT, with the IMRT group having slightly more advanced disease and higher use of PET staging. While no significant differences were found in 2-year OS, PFS, local failure, and distant metastasis, IMRT was associated with lower rates of severe pneumonitis and reduced radiation exposure to the heart. According to the authors, these findings suggest that IMRT may offer long-term survival benefits, although continued follow-up is needed to confirm its impact compared with that of 3D-CRT. In 2024, long-term results of the secondary analysis of the NRG Oncology RTOG 0617 trial were assessed by Chun et al. The analysis in 483 participants with stage III NSCLC (median age, 64 years) found that 47.2% received IMRT and 52.8% received 3D-CRT, with a median follow-up of 5.2 years. IMRT was linked to a two-fold reduction in grade ≥ 3 pneumonitis compared with 3D-CRT (3.5% vs. 8.2%). IMRT also delivered significantly lower radiation doses to the heart V40 (16.5% vs. 20.5%). Higher heart V40 (≥ 20%) was associated with worse OS, while lower heart exposure correlated with better outcomes. Lung V5 and age were not associated with survival. Rates of secondary cancers were similar between groups. The authors emphasized that IMRT should focus on minimizing radiation exposure to critical structures, specifically lung V20 and heart V20 to V60, rather than limiting low-dose radiation spread. They noted that lung V5 and participant age were not associated with OS and therefore should not be considered as contraindications for receiving chemoradiotherapy. A key limitation is that this was a secondary analysis that used data that were originally collected for a different primary objective.

Clinical Practice Guidelines

American Radium Society (ARS)

Chun et al. (2020) developed evidence-based guidelines for the ARS for radiation therapy in limited-stage small cell lung cancer (LS-SCLC) and recommended that IMRT is appropriate when it offers clear advantages in target coverage and

normal tissue sparing compared with 3D conformal techniques. Radiation therapy for unresectable, node-positive LS-SCLC is generally considered most appropriate when delivered using IMRT with motion management and daily image guidance. The recommended dose is either 45 Gy in 1.5-Gy twice-daily fractions or 60 to 70 Gy in 1.8- to 2-Gy once-daily fractions.

American Society for Radiation Oncology (ASTRO)

Simone II et al. (2020) developed a guideline for ASTRO regarding thoracic radiation therapy and prophylactic cranial irradiation (PCI) for LS-SCLC and extensive-stage SCLC. The guideline notes that radiation therapy is a key component of curative treatment for LS-SCLC, with survival benefits supported by both historical and recent data. For those in good health and with an adequate PS, concurrent chemoradiation is the standard of care, even for older adults or those with comorbidities, if carefully selected. Advanced radiation therapy techniques like IMRT and VMAT are preferred over 3D-CRT to reduce normal tissue toxicity, along with motion management and image guidance when appropriate. However, unlike for NSCLC, evidence supporting these advanced techniques in SCLC is limited. Similarly, data on postoperative radiation therapy for SCLC are sparse, so recommendations in this setting are largely extrapolated from NSCLC literature. According to the guideline (not all inclusive):

- For patients with LS-SCLC who can tolerate definitive therapy, thoracic radiation therapy is recommended. Strength of recommendation: strong; quality of evidence: high.
- For patients with LS-SCLC, highly conformal techniques are recommended to minimize normal tissue dose. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with LS-SCLC, twice-daily radiation therapy in 150-cGy fractions to 4,500 cGy is recommended. Strength of recommendation: strong; quality of evidence: high.
- For patients with LS-SCLC, daily radiation therapy in 200-cGy fractions to 6,000 to 7,000 cGy is conditionally recommended as an acceptable alternative to twice-daily radiation therapy. Strength of recommendation: conditional; quality of evidence: moderate.
- For patients with stage I or II, node-negative LS-SCLC who are medically inoperable, either SBRT or conventional fractionation is recommended. Ultracentral tumors may be more appropriately treated with conventional fractionation schema. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with stage I SCLC, PCI is conditionally not recommended. In lieu of PCI, surveillance using brain MRI with contrast can serve as an alternative. Strength of recommendation: conditional; quality of evidence: low.
- For patients with stage II to III LS-SCLC who are less than 70 years of age, have a good PS (ECOG PS 0-2), and respond to thoracic chemoradiation, PCI is recommended. Strength of recommendation: strong; quality of evidence: high.
- For patients with extensive-stage SCLC with a response to chemotherapy alone but a residual tumor in the thorax, thoracic radiation therapy is recommended. Strength of recommendation: strong; quality of evidence: high.

National Comprehensive Cancer Network (NCCN)

According to the NCCN guidelines for SCLC, the use of advanced radiation technologies is appropriate when necessary to ensure adequate tumor coverage while maintaining safe dose limits to surrounding normal tissues. Recommended technologies include 4D-CT and/or ^{18}F-fludeoxyglucose-PET/CT simulation, IMRT, VMAT, IGRT, and motion management strategies. IMRT is preferred over 3D-CRT, specifically in the setting of concurrent chemotherapy and radiation therapy, due to its ability to reduce treatment-related toxicity (NCCN, 2025).

Soft Tissue Sarcoma

Wang et al. (2019) retrospectively compared outcomes between postoperative IMRT and 2D radiation therapy in 274 patients with primary, localized soft tissue sarcomas of the extremities and trunk who were treated at a single institution between 2005 and 2015. Patients who were included had no prior radiation and underwent function-preserving surgery. A total of 274 patients had received either IMRT (n = 187) or 2D radiation therapy (n = 87) following surgery. Exclusion criteria were amputation, metastatic disease, or radiation performed elsewhere. The study evaluated OS, DFS, local recurrence–free survival, and DMFS from the date of surgery. With a median follow-up of 58.1 months, the study reported 30 local recurrences, 66 distant metastases, and 40 deaths. Patients treated with IMRT had significantly better 5-year outcomes than those who received 2D radiation therapy, including higher rates of local recurrence–free survival (91.1% vs. 80.8%), DMFS (80.0% vs. 69.7%), DFS (75.2% vs. 59.2%), and OS (90.2% vs. 81.0%). A multivariate analysis confirmed IMRT as an independent positive predictor for all survival metrics. Additionally, IMRT was associated with lower rates of grade ≥ 2 joint stiffness and grade ≥ 3 fractures, while edema rates were similar between groups. The authors concluded that compared with conventional radiation techniques, postoperative IMRT was associated with improved local control and OS, along with reduced severity of late toxicities in patients with soft tissue sarcoma of the extremities and trunk. They recommended further validation of these findings through prospective randomized trials to confirm the clinical benefits of IMRT over 2D radiation therapy. Limitations include the study's retrospective design, which could introduce

potential bias. Additionally, the IMRT group had a shorter median follow-up than the 2D radiation therapy group, which may have led to an overestimation of survival and local control outcomes and an underestimation of late toxicities.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

The 2021 ASTRO guideline by Salerno et al. offers evidence-based recommendations on the role of radiation therapy in treating soft tissue sarcoma and includes but is not limited to the following points:

- For those with localized extremity and truncal soft tissue sarcoma, IMRT, including VMAT, is recommended to reduce the dose to OARs and minimize toxicity. In certain cases, 3D-CRT may be preferred to better spare critical structures or lower the overall radiation dose. Strength of recommendation: strong; quality of evidence: moderate.
- For patients with primary, localized retroperitoneal sarcomas who are receiving preoperative radiation, IMRT, including VMAT, is recommended to reduce the dose to OARs and minimize toxicity. In select cases, 3D-CRT may be used if it offers comparable or improved sparing of critical structures or lowers the overall radiation dose. Strength of recommendation: strong; quality of evidence: moderate.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines state that radiation therapy for soft tissue sarcomas should be delivered using the most appropriate technique that ensures comprehensive coverage of the target volume while adhering to dose constraints for surrounding normal tissues, including bone, lymphatics, and soft tissue. Techniques such as 3D-CRT, IMRT, and PBRT are all acceptable options, depending on the clinical scenario. Daily image guidance is recommended to maintain precise targeting and minimize exposure to adjacent healthy structures. For retroperitoneal/intra-abdominal sarcoma, use of advanced planning methods, such as IMRT, IGRT, and PBRT, can improve the therapeutic ratio by enhancing tumor control while reducing toxicity. In those who have previously received radiation to the treatment site, IMRT or SBRT may offer a safer approach to reirradiation (NCCN, 2025).

Vulvar Cancer

Richman et al. (2020) conducted a retrospective single-center review in 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 of 68 years and median follow-up of 20 months. The study included 25 patients with a clinical tumor stage of T2 or greater; 27 patients had evidence of positive inguinal or pelvic lymph nodes, and 12 patients 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 pathological complete response was 70%; DFS at 2 years was 65% in all patients, 81% with definitive IMRT, and 55% with preoperative IMRT. The authors also reported that grade 3 toxicity was seen in 29% of patients, while late radiation therapy toxicity was seen in 6% of patients. Limitations of the study include the single-center, retrospective design, lack of a comparison group, and small sample size. The authors concluded that dose-escalated IMRT and concurrent cisplatin for locally advanced vulvar cancer was well tolerated and improved clinical and pathological 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. Overall, 26 patients were included in the study (23 were unresectable, and three refused surgery), of whom 15 had inguinal node metastases and 10 had pelvic node metastases. Patients also received platinum-based chemotherapy in addition to the IMRT. The authors reported that complete response was achieved in 80.7% of the patients and that recurrent disease occurred inside the irradiated volume in five patients who had persistent disease following treatment. The authors also reported that actuarial 1-year local, regional, and distant controls were 72.4%, 85.4%, and 86%, respectively, while 1- and 2-year OS was 91% and 62%, respectively. Finally, the authors reported that complete response at 3 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 observed in five patients and was related to tumor doses of > 66 Gy and prior pelvic radiation. The study was limited by the single-center, retrospective design, small sample size, and lack of a comparator group. The authors concluded that high-dose IMRT for vulvar cancer achieved high rates of local control, 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 squamous cell carcinoma of the vulva who were treated with IMRT, which included 21 patients who were treated with postoperative IMRT, 13 with definitive IMRT, and five with preoperative IMRT. Fourteen patients also received concurrent chemotherapy with cisplatin (n = 13) or cisplatin and 5FU. The patients were seen at 6 weeks; 3, 6, and 12 months; and at least annually after the completion of radiation therapy, with a median follow-up of 34 months. The authors reported that the 3-year locoregional control was 42%, and the OS was 49% in those who received definitive IMRT; patients who received neoadjuvant IMRT achieved a 69% complete clinical response rate, and 44% had complete pathological response. The authors also reported that no

acute grade 3 or 4 hematologic, GI, or GU toxicities were observed as well as any late grade 3 to 4 GI or GU toxicities. This study was limited by the small sample size; single-center, retrospective design; lack of a comparator group; and heterogeneity of the treatments provided to the study patients. The authors concluded that IMRT for vulvar cancer was associated with high rates of locoregional control in the postoperative setting and limited radiation-related toxicity and that durable locoregional control of disease after definitive IMRT remains challenging.

Clinical Practice Guidelines

European Society of Gynaecological Oncology (ESGO)

The 2023 updated ESGO guidelines for the management of vulvar cancer note that adjuvant radiotherapy should be performed by IMRT techniques, with daily setup verification, especially in cases in which an SIB is used (Oonk et al., 2023).

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines state that IMRT is the preferred technique due to its superior ability to deliver precise doses to the target while minimizing exposure to surrounding healthy tissues. 2D/3D techniques may be used for urgent or emergent treatment starts, but patients should be transitioned promptly to IMRT for definitive therapy. Image-guided IMRT is essential to accommodate anatomical changes such as vulvar edema and significant tumor shrinkage during treatment. Special attention must be given to protect normal tissues, including the rectum, bladder, small bowel, and femoral head/neck, within tolerance limits (NCCN 2025).

Combined Therapies

No evidence was identified in the clinical literature that supports the combined use of IMRT and PBRT 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 August 14, 2025)

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Policy History/Revision Information

Date	Summary of Changes

05/01/2026	**Coverage Rationale**
	• Revised list of conditions for which **Intensity-Modulated Radiation Therapy (IMRT) for Definitive Therapy** for the primary site is proven and medically necessary:
	  ○ Replaced “breast cancer *in* the [listed] *circumstances*” with “breast cancer *when any of* the [listed] *criteria are met*”
	  ○ Added:
	  ▪ Hepatocellular carcinoma, unresectable
	  ▪ Hodgkin lymphoma
	  ▪ Intrahepatic cholangiocarcinoma, unresectable
	  ▪ Rectal cancer when treatment involves inguinal lymph nodes
	  ▪ Small cell lung cancer, limited stage
	  ▪ Soft tissue sarcoma, retroperitoneal/intra-abdominal location
	  ▪ Stage I to II non-small cell lung cancer undergoing hypofractionated radiation therapy up to 10 fractions
	  ○ Revised list of treatment areas for head and neck cancers; replaced “larynx *(stage III or IV cancer)*” with “larynx”
	  ○ Revised list of examples of mediastinal tumors; added “thyroid”
	• Removed language indicating compensator based beam modulation treatment is proven and medically necessary when done in combination with an IMRT indication listed [in the policy] as proven
	• Replaced language indicating:
	  ○ “Hippocampal-avoidance whole brain radiation therapy of up to 10 fraction is proven and medically necessary [when] all the [listed criteria are met]“ with “hippocampal-avoidance whole brain radiation therapy of up to 10 fractions is *considered* proven and medically necessary when all the [listed] criteria are met”

Date	Summary of Changes
	○ "IMRT may be *covered* for a condition that is not *listed* [in the policy] *as proven*, including recurrences or metastases in selected cases" with "IMRT may be *considered medically necessary* for a condition that is not *defined* [as proven and medically necessary in the policy], including recurrences or metastases in selected cases" **Definitions** • Updated definition of "Definitive Therapy" **Applicable Codes** • Added CPT codes 77407 and 77412 • Removed CPT/HCPCS codes 77385, 77386, G6015, G6016, and G6017 • Added notation to indicate: ○ Standard single-isocenter IMRT or VMAT should be billed under CPT code 77407 (radiation treatment delivery, intermediate) ○ CPT code 77412 (radiation treatment delivery, complex) should be used for treatments that require multiple isocenters or single-isocenter delivery with active motion-management techniques; when CPT code 77412 is reported, documentation must clearly describe the circumstances that justify level 3 rather than level 2 treatment delivery **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version CS064.S

Instructions for Use

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

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