Radiation Therapy: Fractionation, Image-Guidance, and Special Services

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Instructions for Use

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Related Commercial/Individual Exchange Policies

- Intensity-Modulated Radiation Therapy
- Proton Beam Radiation Therapy
- Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery

Community Plan Policy

- Radiation Therapy: Fractionation, Image-Guidance, and Special Services

Medicare Advantage Policy

- Radiation and Oncologic Procedures

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

Radiation Therapy Fractionation

Bone Metastases

When providing palliative external beam radiation therapy (EBRT) for the treatment of bone metastases, the following are medically necessary:

- Delivery of up to 10 fractions of radiation therapy
- Delivery of greater than 10 fractions for the treatment of a site that has previously received radiation therapy

Breast Adenocarcinoma

When providing EBRT for breast adenocarcinoma, the following are medically necessary:

- Delivery of up to five fractions for accelerated partial-breast irradiation with intensity-modulated radiation therapy
- Delivery of up to 10 fractions for accelerated partial-breast irradiation with 3D technique
- Delivery of up to 21 fractions (inclusive of a boost to the tumor bed)
- Delivery of up to 33 fractions (inclusive of a boost to the tumor bed) when any of the following criteria are met:
  - Treatment of supraclavicular and/or internal mammary lymph nodes; or
  - Postmastectomy radiation therapy; or
  - Individual has received previous thoracic radiation therapy; or
  - Individual has a connective tissue disorder such as systemic lupus erythematosus or scleroderma

When providing EBRT for breast cancer, delivery of greater than 33 fractions (inclusive of a boost to the tumor bed) is not medically necessary.

Locally Advanced Non-Small Cell Lung Cancer

When providing EBRT, with or without chemotherapy, for locally advanced non-small cell lung cancer, the following is medically necessary:

- Delivery of up to 35 fractions

When providing EBRT, with or without chemotherapy, for locally advanced non-small cell lung cancer, delivery of greater than 35 fractions is not medically necessary.

Prostate Adenocarcinoma

When providing EBRT for prostate adenocarcinoma, the following are medically necessary:

- Delivery of up to 20 fractions for Definitive Treatment in an individual with Limited Metastatic Disease
- Delivery of up to 28 fractions for localized prostate cancer
- Delivery of up to 45 fractions for localized prostate cancer when any of the following criteria are met:
  - Individual with high-risk prostate cancer is undergoing radiation treatment to pelvic lymph nodes; or
  - Radiation therapy is delivered post prostatectomy; or
  - Individual has a history of inflammatory bowel disease such as ulcerative colitis or Crohn disease; or
  - Individual has received previous pelvic radiation therapy

When providing EBRT for localized prostate cancer, delivery of greater than 45 fractions is not medically necessary.

Image-Guided Radiation Therapy (Refer to the Coding Clarifications in the *Applicable Codes* section)

Image guidance for radiation therapy is medically necessary under any of the following circumstances:

- When used with intensity-modulated radiation therapy (IMRT; e.g., prostate cancer); or
- When used with proton beam radiation therapy (PBRT); or
- When the target has received prior radiation therapy or abuts a previously irradiated area; or
- When implanted fiducial markers are being used for target localization; or
- During Definitive Treatment, using 3D conformal radiation therapy (3D-CRT) for the following:
  - Breast cancer and any of the following:
    - Accelerated partial-breast irradiation
    - Breast boost with the use of photons
    - Hypofractionated radiation therapy delivered up to five fractions to the whole breast or chest wall
    - Individual is being treated in the prone position
    - Left breast cancer and deep inspiration breath-hold technique is being used
  - During boost treatment of rectal and bladder cancer
  - Esophageal cancer
  - Gastric cancer
  - Head and neck cancer
  - Hepatobiliary cancer
  - Lung cancer
  - Pancreatic cancer
  - Soft tissue sarcoma
  - Image-guided radiation therapy (IGRT) when used with 3D-CRT may be medically necessary for a condition that is not listed above when documentation is provided, showing one or more of the following:
    - Clinically significant difference in normal tissue sparing between deep inspiration breath-hold and free breathing, as documented by comparison plans and dose-volume histogram (DVH; e.g., right-sided breast cancer)
    - Member unable to tolerate immobilization during computed tomography (CT) simulation
    - Significant target motion, as documented by imaging
    - Smaller clinical target volume (CTV) margins are required than what is traditionally used for 3D-CRT

When the above criteria are not met, IGRT is not medically necessary, including but not limited to the following circumstance:

- To align bony landmarks without implanted fiducials (i.e., during palliative radiation therapy)

Note: Refer to the Coding Clarification section for special services and the use of IGRT with brachytherapy, stereotactic radiosurgery, and stereotactic body radiation therapy.

Medical Records Documentation Used for Reviews

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

Definitions

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

Limited Metastatic Disease (Applicable to prostate cancer only): Absence of visceral metastasis or less than four bone metastases, with no metastasis outside the vertebral bodies or pelvis (Parker et al., 2018).

Applicable Codes

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

Coding Clarifications:

- Radiation treatment delivery should be reported using the appropriate level of complexity. Conventional single electron field, multiple electron fields or 2D photons should be reported under CPT code 77402 (Level 1). Standard single-isocenter 3D or IMRT/VMAT treatments should be reported under CPT code 77407 (Level 2). CPT code 77412 should be used only when delivery requires multiple isocenters with photon therapy, single-isocenter treatment with active motion-management techniques, total-skin electrons, or mixed electron/photon fields (Level 3). 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).
- Image-guided radiation therapy cannot be reported separately with stereotactic body radiation therapy (SBRT) or stereotactic radiosurgery (SRS) (ASTRO, 2025).
- When image-guided radiation therapy is used with 2D, 3D, IMRT techniques, the technical component is included under CPT codes 77402, 77407, and 77412 and should not be reported separately. The professional component of IGRT should be reported as 77387-26 (AMA, 2026; CMS, 2026).
- Image-guided radiation therapy codes should not be used for imaging that is performed during brachytherapy. Verification of applicator position should be reported using simple simulation CPT code 77280 (ASTRO, 2025).
- Regardless of the number of treatment sites, megavoltage planning, imaging, and treatment delivery codes should not be reported during superficial, surface, or orthovoltage radiation therapy (ASTRO Coding Resource, 2025). CPT codes 77436, 77437, 77438, 77439 should be reported for superficial, surface, or orthovoltage radiation therapy (AMA, 2026; CMS, 2026).
- Special dosimetry CPT code 77331 should be used to document the measurement of radiation dose at a specific point within a treatment area using specialized devices such as thermoluminescent dosimeters, optically simulated dosimeters, diode probes, special dosimetry probes, film dosimetry, and implanted markers. CPT code 77331 is used when radiation dose measurements are needed in treatment areas that fall outside the standard parameters of the treatment planning system or equipment calibration. When special dosimetry is requested, the number of measurements typically ranges from one to six, depending on the clinical need. Any requests beyond this standard range must be supported with documentation and will be considered on a case-by-case basis. Intensity-modulated radiation therapy (IMRT) planning (CPT code 77301) includes special dosimetry (ASTRO Coding Resource, 2025).
- Special medical radiation physics consultation CPT code 77370 should be reported once under the following circumstances such as complex interrelationship of photons and electrons; brachytherapy; stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT); analysis of customized beam modification devices and special blocking procedures; computing the dose to the fetus of a pregnant individual; specialized brachytherapy equipment

developed by the qualified medical physicist (QMP) to treat a specific individual; radioisotope treatment; individuals with implanted cardiac devices; or fusion by a QMP of 3D image sets from multiple modalities (computed tomography/positron emission tomography/magnetic resonance imaging) in non-IMRT treatment plans (ASTRO Coding Resource, 2025).

- Special treatment procedure CPT code 77470 should be reported once under the following circumstances: pediatric individuals requiring daily anesthesia; total body and hemibody irradiation, per oral or endocavitary irradiation; individuals very difficult to set up; combination of external beam radiation therapy and brachytherapy; concurrent cytotoxic chemotherapy and/or targeted therapy; radioimmunotherapy when combined with external beam radiation therapy; hyperthermia; or yttrium microsphere radiotherapy. Circumstances in which the routine use of CPT code 77470 should not be reported include but are not limited to contouring for 3D conformal radiation therapy and IMRT and routine use for SBRT or SRS, unless there was cause for extra time/effort with supporting documentation. There is no situation in which 77470 may be routinely used (ASTRO Coding Resource, 2025).
- Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services CPT code 77399 should only be reported if no other code appropriately describes the procedure or service in question (ASTRO Coding Resource, 2025).

Note: CPT codes 77331, 77370, 77470, and 77399 are considered for coverage only when the primary radiation procedure is proven and medically necessary.

CPT Code	Description
77331	Special dosimetry (e.g., TLD, microdosimetry) (specify), only when prescribed by the treating physician
77370	Special medical radiation physics consultation
77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
77402	Radiation treatment delivery; Level 1 (e.g., single-electron field, multiple-electron fields, or 2D photons), including imaging guidance, 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
77436	Surface radiation therapy; superficial or orthovoltage, treatment planning and simulation-aided field setting
77437	Surface radiation therapy; superficial, delivery, 150 kV, per fraction (e.g., electronic brachytherapy)
77438	Surface radiation therapy; orthovoltage, delivery, > 150-500 kV, per fraction
77439	Surface radiation therapy; superficial or orthovoltage, image guidance, ultrasound for placement of radiation therapy fields for treatment of cutaneous tumors, per course of treatment (List separately in addition to code for primary procedure)
77470	Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation)
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

Description of Services

A course of radiation therapy comprises a series of distinct activities, which include consultation, treatment planning, technical preparation and special services, treatment delivery, treatment management, and follow-up care management. The radiation oncologist leads a team, which includes a medical radiation physicist, dosimetrist, radiation therapist, oncology nurses, and ancillary staff, throughout the individual's course of treatment. The team works together to

coordinate the individual's clinical treatment plan, including consultations and evaluations; develops the appropriate dosimetry calculations and isodose plan; builds treatment devices to refine treatment delivery, as needed; delivers the radiation therapy; and performs any other special services that are required to ensure the safe and precise delivery of radiation therapy. Radiation treatment involves a prescribed total dose, which can be delivered in a single session or spread across multiple sessions. When given over several sessions, the dose is divided into smaller parts called fractions, a method known as fractionated delivery. Hyperfractionated delivery is a form of fractionated radiation therapy in which smaller-than-usual doses are administered more frequently, typically two or three times per day instead of once. In contrast, hypofractionated delivery uses larger doses per session and completes treatment over a shorter overall period. Another approach, called accelerated fractionation, involves giving moderate to large doses twice daily to shorten the total treatment time while maintaining effectiveness (ASTRO, 2025).

External beam radiation therapy includes 3D conformal radiation therapy, intensity-modulated radiation therapy, and proton beam radiation therapy. External radiation is the most common type of radiation therapy used for cancer treatment. A machine is used to aim high-energy rays or particles from outside the body into the tumor (American Cancer Society, 2025).

Image-guided radiation therapy involves the use of images of individuals to localize and reposition the individual or delivery system prior to treatment to ensure that the therapeutic beam is correctly directed toward the target (McCullough et al., 2021).

Hypofractionated radiotherapy is the delivery of fewer and larger [> 200 centigray (cGy)] doses of radiation. Hypofractionation is defined in this guideline as external beam radiation therapy with a fraction size between 240 cGy and 340 cGy (Morgan et al., 2018; Smith et al., 2018).

A special treatment procedure covers additional physician effort and work and the technical resources that are involved during complex radiation treatment procedures (ASTRO, 2025).

A special medical physics consultation is used when the complexity of the treatment plan is of such magnitude that a written analysis is necessary to address a specific problem and when the service performed requires the expertise of a qualified medical physicist (ASTRO, 2025).

Clinical Evidence

Bone Metastases

Skelly et al. (2023) conducted an evidence-based report for the Agency for Healthcare Research and Quality (AHRQ) regarding the effectiveness and harms of external beam radiation therapy (EBRT) for palliative treatment of metastatic bone disease. The American Society for Radiation Oncology (ASTRO) was a partner in this review. The study compared dose-fractionation schemes and techniques of delivery for both initial radiation and reirradiation; EBRT alone and in combination with additional therapies was also assessed. Most studies were noted to be of fair quality, and the review included 53 randomized controlled trials (RCTs) and 31 nonrandomized studies of interventions. In those receiving initial radiation for metastatic bone disease, there was a small increase in the likelihood of overall pain response with multiple-fraction EBRT vs single-fraction EBRT up to 4 weeks post radiation therapy [RT; strength of evidence (SOE): moderate] and with higher-dose (6 or 8 Gy) single-fraction EBRT vs lower-dose (4 Gy) single-fraction EBRT up to 52 weeks post RT (SOE: low). Single-fraction and multiple-fraction EBRT did not differ at the later follow-up (SOE: moderate) nor did comparisons of multiple-fraction EBRT dose/fractions (SOE: moderate ≤ 12 weeks; low > 12 weeks). Reirradiation was more common with single- vs multiple-fraction EBRT. Stereotactic body radiation therapy (SBRT; single or multiple fraction) was associated with a slightly higher (up to 20 weeks; SOE: low) and moderately higher (30 weeks; SOE: moderate) likelihood of overall pain response vs multiple-fraction EBRT. For reirradiation, single-fraction and multiple-fraction SBRT had a similar likelihood of overall pain response, as did single-fraction vs multiple-fraction EBRT (SOE: low for all). Harms may have been similar across dose/fraction schemes and techniques; serious harms were rare. Comparative effectiveness evidence for EBRT was sparse. According to the authors, single-fraction and multiple-fraction EBRT likely have similar overall pain response for initial and reirradiation of palliative RT in symptomatic metastatic bone disease; single-fraction EBRT resulted in a higher frequency of reirradiation. The authors noted that although evidence is limited, SBRT, either single or multiple fractions, may have a slightly greater likelihood of overall pain response compared with multiple-fraction EBRT. Limitations include the various definitions of pain response used in the studies and the fact that primary tumor type, location of bone metastasis, and individuals' characteristics also differed across the studies. The authors recommended performing future high-quality studies that compare SBRT with EBRT in those receiving reirradiation and noted that research that evaluates the effectiveness of EBRT compared with that of other treatments is needed.

Migliorini et al. (2021) conducted a meta-analysis that compared the most commonly used radiotherapy regimens for palliative management in individuals with skeletal metastases. In October 2020, the main databases were accessed, and all RCTs that evaluated irradiation of bone metastases were included. Irradiation patterns of 8 Gy and 10 Gy/single fraction, 20 Gy/five fractions, and 30 Gy/10 fractions were included in the meta-analysis. Data from 3,595 individuals were analyzed. The mean follow-up was 9.5 (1-28) months. The cumulative mean age was 63.3 ±2.9 years. Overall, 40.61% (1,461 of 3,595 individuals) were female. The 8-Gy/single-fraction protocol detected a reduced rate of no pain response [log odds ratio (LOR), 3.39], greater rate of pain response (LOR, -5.88), and complete pain remission (LOR, -7.05) compared with the other dose patterns. The 8-Gy group detected a lower rate of pathological fractures (LOR, 1.16), spinal cord compression (LOR, 1.31), and reirradiation (LOR, 2.97) compared with the other dose patterns. The authors concluded that for skeletal metastases, palliative 8-Gy/single-fraction radiotherapy produced outstanding results in terms of pain control, reirradiations, pathological fractures, and spinal cord compression. No differences in terms of survivorship were observed compared with the other multiple-dose patterns.

Chow et al. (2014) conducted a multicenter nonblinded RCT to assess two dose fractionation schedules in participants with painful bone metastases who needed repeat RT. Participants were aged 18 years or older and had radiologically confirmed, painful (i.e., pain measured as ≥ 2 points using the Brief Pain Inventory) bone metastases, had received previous RT, and were taking a stable dose and schedule of pain-relieving drugs (if prescribed). Participants were randomly assigned (1:1) to receive either 8 Gy in a single fraction or 20 Gy in multiple fractions. The primary end point was overall pain response at 2 months, which was defined as the sum of complete and partial pain responses to treatment, and was assessed using both Brief Pain Inventory scores and changes in analgesic consumption. A total of 425 participants were enrolled; however, 19 participants (4%) in the 8-Gy group and 12 (3%) in the 20-Gy group were ineligible after randomization, and 140 (33%) and 132 participants (31%), respectively, were not assessable at 2 months and counted as missing data in the intention-to-treat analysis. The intention-to-treat population, comprising 118 participants (28%) who were allocated to 8-Gy treatment and 135 (32%) who were allocated to 20-Gy treatment, had an overall pain response to treatment [p = 0.21; response difference, 4.00% (upper limit of the 95% CI, 9.2, less than the prespecified noninferiority margin of 10%)]. In the per-protocol population, 116 participants (45%) and 134 participants (51%), respectively, had an overall pain response to treatment [p = 0.17; response difference, 6.00% (upper limit of the 95% CI, 13.2, greater than the prespecified noninferiority margin of 10%)]. The most frequently reported acute radiation-related toxicities at 14 days were lack of appetite [201 (56%) assessable participants who received 8 Gy vs 229 (66%) assessable participants who received 20 Gy; p = 0.011] and diarrhea [81 participants (23%) vs 108 participants (31%); p = 0.018]. Pathological fractures occurred in 30 participants (7%) who were assigned to 8 Gy and 20 (5%) who were assigned to 20 Gy [odds ratio (OR), 1.54; 95% CI, 0.85-2.75; p = 0.15], and spinal cord or cauda equina compressions were reported in seven participants (2%) vs two participants (< 1%), respectively (OR, 3.54; 95% CI, 0.73-17.15; p = 0.094). The authors concluded that in participants with painful bone metastases that required repeat RT, treatment with 8 Gy in a single fraction seemed to be noninferior and less toxic than 20 Gy in multiple fractions; however, as findings were not robust in a per-protocol analysis, trade-offs between efficacy and toxicity may exist.

Huisman et al. (2012) conducted a systematic review and meta-analysis to quantify the effectiveness of reirradiation to achieve pain control in individuals with painful bone metastases. A search was performed to identify eligible studies using the MEDLINE, Embase, and Cochrane Collaboration Library electronic databases. Studies that met the following criteria were eligible: a portion of the individuals received reirradiation at the site of initial RT for radiation-refractory metastatic bone pain; both the initial treatment and the retreatment consisted of localized EBRT; the reported outcomes included (at least) pain response after reirradiation; and the original research data were reported. The search identified 707 titles, of which 10 articles were selected for the systematic review, and seven were included in the meta-analysis (three articles were excluded because results could not be extracted on a per-individual level, the sample size was considered too small, or all individuals received second reirradiation). Of the 10 studies, six were randomized trials, two were cohort studies, and two were case series. A pooled estimate was calculated for overall pain response after reirradiation for metastatic bone pain. A total of 2,694 individuals were initially treated for metastatic bone pain, and 527 individuals (20%) underwent reirradiation. With reirradiation, the number of fractions that were administered ranged from a single fraction to 13 fractions. Overall, a pain response after reirradiation was achieved in 58% of individuals (pooled overall response rate, 0.58; 95% CI, 0.49-0.67). Significant between-study heterogeneity (I^2 = 63.3%; p = 0.01) was observed because of the clinical and methodological differences between the studies. The authors concluded that reirradiation of radiation-refractory bone pain was effective, but approximately 40% of individuals did not seem to benefit from reirradiation, and more research is needed to provide optimal palliative care.

Hartsell et al. (2005) conducted a multicenter, phase 3, randomized trial to investigate whether 8 Gy delivered in a single treatment fraction provides pain and narcotic relief that is equivalent to that of the standard treatment course of 30 Gy delivered in 10 treatment fractions over 2 weeks. Participants with breast or prostate cancer, who had one to three sites of painful bone metastases and moderate to severe pain, were eligible for participation. Participants were randomly assigned to 8 Gy in one treatment fraction (8-Gy arm) or to 30 Gy in 10 treatment fractions (30-Gy arm). Pain relief at 3 months

after randomization was evaluated by the Brief Pain Inventory. A total of 455 participants were allocated to the 8-Gy arm and 443 participants to the 30-Gy arm; pretreatment characteristics were equally balanced between arms. Grade 2 to 4 acute toxicity was more frequent in the 30-Gy arm (17%) than in the 8-Gy arm (10%) (difference, 7%; 95% CI, 3%-12%; p = 0.002). Late toxicity was rare (4%) in both arms. The overall response rate was 66%. The complete and partial response rates were 15% and 50%, respectively, in the 8-Gy arm compared with 18% and 48% in the 30-Gy arm (p = 0.6). At 3 months, 33% of all participants no longer required narcotic medications. The incidence of subsequent pathological fracture was 5% in the 8-Gy arm and 4% in the 30-Gy arm. The retreatment rate was statistically significantly higher in the 8-Gy arm (18%) than in the 30-Gy arm (9%) (p < 0.001). The authors concluded that both regimens were equivalent in terms of pain and narcotic relief at 3 months and were well tolerated, with few adverse effects. The 8-Gy arm had a higher rate of retreatment but had less acute toxicity than the 30-Gy arm.

Clinical Practice Guidelines

American College of Radiology (ACR)

The ACR's special report, Appropriateness Criteria Spinal Bone Metastases, states that randomized trials have proven that equivalent pain relief can be achieved with varied fractionation schemes, including a single 8-Gy fraction, 20 Gy in five fractions, 24 Gy in six fractions, and 30 Gy in 10 fractions (Lo et al., 2013).

American Society for Radiation Oncology (ASTRO)

ASTRO's guideline on palliative RT for symptomatic bone metastases (Alcorn et al., 2024) provides recommendations using consensus-building methodology that is based on a systematic review by the AHRQ. The authors noted that developing the most favorable RT regimen requires an assessment, including prognosis, any previous RT doses, normal tissue risks, quality of life, and patient values and goals. Per the guideline:

- In patients with symptomatic bone metastases treated with conventional palliative RT, 800 centigray (cGy) in one fraction, 2,000 cGy in five fractions, 2,400 cGy in six fractions, or 3,000 cGy in 10 fractions is recommended (strength of recommendation: strong; quality of evidence: high).
- In patients with spine bone metastases that are causing compression of the spinal cord or cauda equina, who are not eligible for initial surgical decompression and are treated with conventional palliative RT, 800 cGy in one fraction, 1,600 cGy in two fractions, 2,000 cGy in five fractions, or 3,000 cGy in 10 fractions is recommended (strength of recommendation: strong; quality of evidence: high).
- In patients with spine bone metastases who would benefit from reirradiation to the same site, conventional palliative RT regimens of 800 cGy in one fraction, 2,000 cGy in five fractions, 2,400 cGy in six fractions, or 2,000 cGy in eight fractions is recommended (strength of recommendation: strong; quality of evidence: moderate).
- In patients with symptomatic, nonspine bone metastases who would benefit from reirradiation to the same site, single-fraction (800 cGy in one fraction) or multifraction conventional palliative RT (2,000 cGy in five fractions or 2,400 cGy in six fractions) is recommended (strength of recommendation: strong; quality of evidence: moderate).

European Society for Therapeutic Radiology and Oncology (ESTRO)

The ESTRO Advisory Committee for Radiation Oncology Practice, regarding EBRT for complicated bone metastases, recommends that in the absence of high-level comparative data, a dose of 30 Gy in 10 fractions should be used post operation; in the absence of comparative data, a single dose of 8 Gy or a fractionated schedule, such as 20 Gy in five fractions or 30 Gy in 10 fractions, may be used to prevent pathological fracture. Where recalcification is the aim of treatment, ESTRO recommends a single dose of 8 Gy or fractionated schedules such as 20 Gy in five fractions or 30 Gy in 10 fractions. Additionally, surgery and postoperative irradiation or primary reirradiation should be considered for previously irradiated bone with threatened or actual fracture using single-dose 8 Gy or fractionated schedules, such as 20 Gy in five fractions or 30 Gy in 10 fractions. Lastly, bone metastases with extraosseous extension may be treated with palliative radiotherapy that encompasses the entire tumor mass, using, for example, a single dose of 8 Gy, 20 Gy in five fractions, or 30 Gy in 10 fractions (Oldenburger et al., 2022).

The ESTRO Advisory Committee for Radiation Oncology Practice guidelines for uncomplicated bone metastases developed by van der Velden et al. (2022) note that treatment for bone metastases should prioritize alleviating current symptoms and minimizing the risk of future complications. Radiotherapy remains the standard approach for symptomatic cases, offering lasting pain relief with low toxicity. The guidelines' recommendations are as follows (not all inclusive):

- Conventional RT is appropriate for treating uncomplicated, painful bone metastases, particularly when pain is not adequately managed with medication or when reducing reliance on pain medication is desired. For widespread pain due to multiple bone metastases, single-fraction hemibody or wide-field irradiation may be considered as a treatment option.
- Patients with uncomplicated, painful bone metastases should receive a single 8-Gy fraction of RT.

- Those who experience inadequate pain relief, no response, or a recurrence of pain after initial RT should be considered for retreatment with a single 8-Gy fraction.

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines support the use of single-fraction palliative radiotherapy to manage pain from bone metastases. Evidence from one study showed that approximately 40% of patients (122 of 298) treated with a single 8-Gy dose experienced pain relief and improved quality of life within 10 days, and this may be appropriate for those with a life expectancy of multiple weeks (or longer) (NCCN, 2025).

Breast Adenocarcinoma

Shumway et al. (2023) conducted an AHRQ systematic review to compare the effectiveness and harms of partial-breast irradiation (PBI) with whole-breast irradiation (WBI) for early-stage breast cancer, which is defined as a small tumor that is ≤ 3 cm and has minimal or no lymph node involvement, and how the individual's tumor and treatment factors may influence the differences in effectiveness and harms. The review included 23 studies, 14 RCTs, six comparative observational studies, and three single-arm observational studies, comprising a total of 17,510 adult women with early-stage breast cancer who received one of the following PBI modalities: multicatheter interstitial brachytherapy, intracavitary brachytherapy, 3D conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), proton beam RT, or intraoperative radiotherapy. PBI was not significantly different from WBI in terms of ipsilateral breast recurrence (IBR), overall survival (OS), or cancer-free survival at 5 and 10 years (high SOE). Evidence for cosmetic outcomes was insufficient. Results were generally consistent when PBI modalities were compared with WBI, whether compared individually or combined. These PBI approaches included 3D-CRT, IMRT, and multicatheter interstitial brachytherapy. Compared with WBI, 3D-CRT showed no difference in IBR, OS, and cancer-free survival at 5 and 10 years (moderate to high SOE); IMRT showed no difference in IBR and OS at 5 and 10 years (low SOE); and multicatheter interstitial brachytherapy showed no difference in IBR, OS, and cancer-free survival at 5 years (low SOE). Compared with WBI, intraoperative radiotherapy was associated with a higher IBR rate at 5, 10, and over 10 years (high SOE), with no difference in OS, cancer-free survival, and mastectomy-free survival (low to high SOE). Significantly fewer acute adverse events occurred with PBI than WBI, with no apparent difference in late adverse events (moderate SOE). Data on quality of life were limited. Head-to-head comparisons between the different PBI modalities showed insufficient evidence to estimate an effect on main outcomes. There were no significant differences in IBR or other outcomes according to individual, tumor, and treatment characteristics; however, data for subgroups were insufficient to draw conclusions. The authors concluded that PBI was associated with less adverse effects; no significant difference in the risk with IBR with PBI was observed compared with WBI. According to the authors, the use of PBI is supported in appropriately selected individuals with early-stage breast cancer. Limitations include the fact that outcomes of each radiation modality were insufficiently reported, which may have limited the ability to make comparisons between modalities, and that the comparison of PBI and WBI was not blinded to either the clinicians or individuals. The review recommended further research to evaluate the outcomes with PBI in those with various clinical and tumor characteristics and to define the optimal radiation treatment dose and technique for PBI.

Brunt et al. (2020) performed a phase 3, randomized, multicenter trial to identify a five-fraction schedule of adjuvant RT delivered in 1 week, which was noninferior in terms of local cancer control and as safe as the standard 15-fraction regimen after primary surgery for early breast cancer. Participants who were aged 18 years or older with invasive breast cancer (pT1-3, pN0-1, M0) and had breast conservation surgery or mastectomy were eligible. The study included 97 hospitals and comprised 4,096 participants who were randomly assigned to either 40 Gy in 15 fractions over 3 weeks (n = 1,361), 27 Gy in five fractions over 1 week (n = 1,367), or 26 Gy in five fractions over 1 week (n = 1,368) to the whole breast or chest wall. Ipsilateral breast tumor relapse was the primary end point. The five-fraction schedules required verification imaging for each fraction, with recommendations to correct all measured displacements. At a median follow-up of 71.5 months, the primary end point event occurred in 79 participants (31 in the 40-Gy group, 27 in the 27-Gy group, and 21 in the 26-Gy group); hazard ratios (HRs) vs 40 Gy in 15 fractions were 0.86 for 27 Gy in five fractions and 0.67 for 26 Gy in five fractions. The 5-year incidence of ipsilateral breast tumor relapse after 40 Gy was 2.1%; the estimated absolute differences vs 40 Gy in 15 fractions were -0.3% for 27 Gy in five fractions (probability of incorrectly accepting an inferior five-fraction schedule: p = 0.0022 vs 40 Gy in 15 fractions) and -0.7% for 26 Gy in five fractions (p = 0.00019 vs 40 Gy in 15 fractions). At 5 years, any moderate or marked clinician-assessed normal tissue effects in the breast or chest wall were reported for 98 of 986 (9.9%) 40-Gy participants, 155 of 1,005 (15.4%) 27-Gy participants, and 121 of 1,020 (11.9%) 26-Gy participants. Across all clinician assessments from 1 to 5 years, ORs vs 40 Gy in 15 fractions were 1.55 for 27 Gy in five fractions and 1.12 for 26 Gy in five fractions. Participant and photographic assessments showed a higher normal tissue effect risk for 27 Gy vs 40 Gy but not for 26 Gy vs 40 Gy. The authors concluded that 26 Gy in five fractions over 1 week was noninferior to 40 Gy in 15 fractions over 3 weeks in terms of local tumor control and is as safe for normal tissue effects up to 5 years in this participant population. Limitations to this study include a lack of masking.

Liu et al. (2020) conducted a meta-analysis and systematic review to compare the toxicity and efficacy of hypofractionated radiotherapy with those of conventional fractionated radiotherapy in individuals with postmastectomy breast cancer (n = 3,871). The primary end point was OS, with disease-free survival, locoregional recurrence, distant metastasis, acute skin toxicity, acute lung toxicity, late skin toxicity, lymphedema, shoulder restriction, and late cardiac-related toxicity as the secondary end points. The review included 25 studies: one RCT and 24 retrospective studies. The meta-analysis found no significant differences in the primary or secondary end points between the two groups. The authors concluded that hypofractionated radiotherapy is not significantly different compared with conventional fractionated radiotherapy with respect to efficacy and toxicity in postmastectomy breast cancer. The authors recommended future large-scale RCTs to confirm this conclusion, along with long-term follow-up in individuals who experience late toxicities.

Meattini et al. (2020) conducted a phase 3, single-center, randomized trial (NCT02104895) to assess whether accelerated partial-breast irradiation (APBI) is a safe and effective alternative treatment compared with WBI in selected participants with early breast cancer. A total of 520 participants, more than 90% of whom had characteristics that were associated with a 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 that was delivered by direct external electron beam. The primary end point was 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). OS 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) and late toxicity (p = 0.0001) and improved cosmetic outcomes, 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 that is treated with external APBI using the IMRT technique in five once-daily fractions is low and does not differ from that after WBI. They also stated that acute and late treatment-related toxicity and cosmesis outcomes were significantly in favor of APBI.

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, quality of life, 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 (10%) participants 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 RT 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 and 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 RT, 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 RT, 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% for APBI and 2.8% for 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.

Shaitelman et al. (2015) conducted a multicenter, unblinded, randomized trial to assess acute and 6-month toxicity and quality of life with conventionally fractionated whole-breast irradiation (CF-WBI) vs those with hypofractionated whole-breast irradiation (HF-WBI). Women who were eligible for enrollment were aged ≥ 40 years with pathologically confirmed female DCIS or invasive breast cancer, stage Tis-T2, N0-N1a, M0, and were treated with breast-conserving surgery, with final negative margins (defined as no tumor on ink); additionally, the physician had declared an intent to deliver WBI, without the addition of a third field to cover the regional lymph nodes. Participants were randomized to treatment with either HF-WBI (42.56 Gy in 16 fractions WBI) or CF-WBI (50 Gy in 25 fractions WBI). The tumor bed boost, if the final margins were negative by ≥ 2 mm or if there was a negative re-excision, was 10 Gy in four fractions or 12.5 Gy in five fractions for HF-WBI and CF-WBI, respectively, and was 12.5 Gy in five fractions or 14 Gy in seven fractions if the final margins were < 2 mm for HF-WBI and CF-WBI. The outcomes of interest included physician-reported acute and 6-month toxicities using the National Cancer Institute Common Toxicity Criteria v4.0 and participant-reported quality of life using the Functional Assessment of Cancer Therapy – Breast version 4. A total of 287 participants were randomized and evaluable. Of 149 participants who were randomized to CF-WBI, all (100%) received the allocated WBI and boost doses. Of 138 participants who were randomized to HF-WBI, 137 (99%) received a hypofractionated schedule of WBI (n = 134, 42.56 Gy/16 fractions; n = 2, 42.4 Gy/16 fractions; n = 1, 42.52 Gy/16 fractions), and 136 (99%) received the allocated boost dose. One participant (1%) who was randomized to HF-WBI received conventional fractionation (46 Gy in 23 fractions, followed by a 14-Gy in seven fractions boost). The median number of elapsed days over which radiation was delivered was 36 days for CF-WBI (IQR, 35-36 days) and 22 days for HF-WBI (IQR, 22-23 days). Half the treatment plans (143) involved a maximum dose (D_{max}) of 107% of the prescription dose or higher. The treatment arms were well matched for baseline characteristics, including Functional Assessment of Cancer Therapy – Breast total score (p = 0.46) and individual quality-of-life items, such as lack of energy (p = 0.86) and trouble meeting family needs (p = 0.54). Maximal physician-reported acute dermatitis (p < 0.001), pruritus (p < 0.001), breast pain (p = 0.001), hyperpigmentation (p = 0.002), and fatigue (p = 0.02) during radiation were lower in participants randomized to HF-WBI. Overall grade ≥ 2 acute toxicity was less with HF-WBI vs CF-WBI (47% vs 78%; p < 0.001). Six months after radiation, physicians reported less fatigue in participants randomized to HF-WBI (p = 0.01), and participants randomized to HF-WBI reported less lack of energy (p < 0.001) and less trouble meeting family needs (p = 0.01). Multivariable regression confirmed the superiority of HF-WBI in terms of participant-reported lack of energy (OR, 0.39; 95% CI, 0.24-0.63) and trouble meeting family needs (OR, 0.34; 95% CI, 0.16-0.75). The authors concluded that (1) HF-WBI appears to yield less acute toxicity than CF-WBI as well as less fatigue and trouble meeting family needs 6 months after completing radiation and (2) these findings should be communicated to individuals as part of shared decision-making.

Haviland et al. (2013) conducted a prespecified analysis as a 10-year update to the UK Standardization of Breast Radiotherapy (START) trials (ISRCTN59368779). The START trials (START-A and START-B) were multicenter, randomized, unmasked trials. Participants were recruited after complete excision of primary invasive breast cancer (pT1-3a, pN0-1, M0) and referred for radiotherapy as part of standard treatment. Participants in START-A (n = 2,236) were randomly assigned to either 50 Gy in 25 fractions (control group), 41.6 Gy in 13 fractions, or 39 Gy in 13 fractions over 5 weeks; START-B participants (n = 2,215) were randomly assigned to either 50 Gy in 25 fractions (control group) over 5 weeks or 40 Gy in 15 fractions over 3 weeks. The 5-year results suggested that lower total doses of radiotherapy delivered in fewer, larger doses (fractions) are at least as safe and effective as the historical standard regimen (50 Gy in 25 fractions) for women after primary surgery for early breast cancer. In this follow-up analysis, participants in START-A had a median follow-up of 9.3 years (IQR, 8.0-10.0 years), after which 139 local-regional relapses had occurred. The 10-year rates of local-regional relapse did not differ significantly between the 41.6-Gy and 50-Gy regimen groups (6.3%, 95% CI, 4.7%-8.5% vs 7.4%, 95% CI, 5.5%-10.0%; HR, 0.91; 95% CI, 0.59-1.38; p = 0.65) or the 39-Gy (8.8%; 95% CI, 6.7%-11.4%) and 50-Gy regimen groups (HR, 1.18; 95% CI, 0.79-1.76; p = 0.41). In START-A, moderate or marked breast induration, telangiectasia, and breast edema were normal tissue effects that were significantly less common in the 39-Gy

group than in the 50-Gy group. Normal tissue effects did not differ significantly between the 41.6-Gy and 50-Gy groups. Participants in START-B had a median follow-up of 9.9 years (IQR, 7.5-10.1 years), after which 95 local-regional relapses had occurred. The proportion of participants with local-regional relapse at 10 years did not differ significantly between the 40-Gy group (4.3%; 95% CI, 3.2%-5.9%) and the 50-Gy group (5.5%; 95% CI, 4.2%-7.2%; HR, 0.77; 95% CI, 0.51-1.16; p = 0.21). In START-B, breast shrinkage, telangiectasia, and breast edema were normal tissue effects that were significantly less common in the 40-Gy group than in the 50-Gy group. The authors concluded that long-term follow-up confirmed that appropriately dosed hypofractionated radiotherapy is safe and effective for individuals with early breast cancer and that their results support the continued use of 40 Gy in 15 fractions.

Whelan et al. (2010) conducted a multicenter randomized trial to determine whether a 3-week schedule of HF-WBI is as effective as a 5-week schedule. Women with invasive breast cancer who had undergone breast-conserving surgery and in whom resection margins were clear and axillary lymph nodes were negative were randomly assigned to receive WBI, either at a standard dose of 50.0 Gy in 25 fractions over a period of 35 days (control group) or at a dose of 42.5 Gy in 16 fractions over a period of 22 days (hypofractionated radiation group). After completion of RT, participants were seen every 6 months for 5 years and then yearly. The primary outcome was any local recurrence of invasive cancer in the treated breast. Secondary outcomes were a distant (including regional) recurrence of breast cancer; second cancers, including contralateral breast cancer; breast cosmesis; late toxic effects of radiation; and death. A total of 1,234 participants underwent randomization, with 612 assigned to the control group and 622 to the hypofractionated radiation group. The two groups were similar at baseline. The risk of local recurrence at 10 years was 6.7% among the 612 women who were assigned to standard irradiation compared with 6.2% among the 622 women who were assigned to the hypofractionated regimen (absolute difference, 0.5 percentage points; 95% CI, -2.5 to 3.5). At 10 years, 71.3% of women in the control group compared with 69.8% of the women in the hypofractionated radiation group had a good or excellent cosmetic outcome (absolute difference, 1.5 percentage points; 95% CI, -6.9 to 9.8). The authors concluded that 10 years after treatment, accelerated HF-WBI was not inferior to standard radiation treatment in women who had undergone breast-conserving surgery for invasive breast cancer with clear surgical margins and negative axillary nodes.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

Shaitelman et al. (2024) developed an ASTRO guideline of evidence-based recommendations for PBI in patients with early-stage cancer or DCIS. For appropriate PBI dose-fractionation regimens, the guideline recommends the following (not all inclusive):

- In patients with early-stage invasive breast cancer or DCIS who are receiving external beam PBI, 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).
- In patients with early-stage invasive breast cancer or DCIS who are receiving external beam PBI, 4,005 cGy in 15 once-daily fractions, delivered over 3 weeks, is recommended (strength of recommendation: strong; quality of evidence: moderate).

ASTRO's guideline on RT for the whole breast states that for women with invasive breast cancer who are receiving WBI, with or without inclusion of the low axilla, the preferred dose fractionation scheme is HF-WBI to a dose of 4,000 Gy in 15 fractions or 4,250 Gy in 16 fractions. The guideline also states that in the presence of strong risk factors for local recurrence (e.g., the single risk factor of positive margins or a combination of risk factors such as young age and close margins), a boost dose of 1,250 Gy in five fractions or 1,400 to 1,600 Gy in seven to eight fractions may be used. Additionally, ASTRO strongly recommends that the decision to offer HF-WBI should be independent of breast size (including central axis separation), provided that dose homogeneity goals can be achieved (Smith et al., 2018).

National Comprehensive Cancer Network (NCCN)

The NCCN's guidelines for breast cancer state that the whole breast should receive a hypofractionated dose of 40 to 42.5 Gy in 15 to 16 fractions; in selected cases, 45 to 50.4 Gy in 25 to 28 fractions may be considered. A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10 to 16 Gy in four to eight fractions. Per the NCCN's guidelines, the preferred RT dosing for APBI is 30 Gy in five fractions. Additionally, the NCCN recommends a minimum of weekly imaging to verify treatment setup, noting that more frequent imaging may be appropriate in cases with inconsistent reproducibility. Deep inspiration breath-hold (DIBH) is a technique that may be used with image-guided radiation therapy (IGRT) to reduce exposure to organs at risk (OARs), and dose-volume histograms should be used to evaluate dose and constraints to normal tissues (e.g., heart, lung) and planning target volumes (PTVs) (NCCN, 2025).

National Institute for Health and Care Excellence (NICE)

The NICE guideline (2018; updated 2025) for the diagnosis and management of breast cancer states:

- The DIBH radiotherapy technique for people with left-sided breast cancer should be used to reduce the dose to the heart.
- Consider 40 Gy in 15 fractions over 3 weeks for people with invasive breast cancer who (1) are having partial-breast, whole-breast, or chest wall radiotherapy, without regional lymph node irradiation, after breast-conserving surgery or mastectomy and have a diagnosis that increases sensitivity to RT or (2) have had implant-based reconstruction or have any other factor that could mean that undergoing RT over 3 weeks is more acceptable [such as a high body mass index (BMI) or fibromyalgia].
- Offer 26 Gy in five fractions over 1 week for people with invasive breast cancer who are having partial-breast, whole-breast, or chest wall radiotherapy, without regional lymph node irradiation, after breast-conserving surgery or mastectomy.
- Offer 40 Gy in 15 fractions over 3 weeks for people with invasive breast cancer who are having regional lymph node irradiation, with or without whole-breast or chest wall radiotherapy, after breast-conserving treatment or mastectomy.
- External beam boost to the tumor bed following whole-breast radiotherapy for women with invasive breast cancer and a high risk of local recurrence is recommended, and women should be informed of the associated risks.

Locally Advanced Non-Small Cell Lung Cancer

Bradley et al. (2015) conducted a multicenter, open-label, randomized trial to compare OS after standard-dose vs high-dose conformal radiotherapy with concurrent chemotherapy and the addition of cetuximab to concurrent chemoradiation in participants with inoperable, stage III non-small cell lung cancer (NSCLC). Participants (aged ≥ 18 years) with unresectable, stage III NSCLC, a Zubrod performance status of 0 to 1, adequate pulmonary function, and no evidence of supraclavicular or contralateral hilar adenopathy were randomly assigned to receive either 60 Gy (standard dose), 74 Gy (high dose), 60 Gy plus cetuximab, or 74 Gy plus cetuximab. All participants also received concurrent chemotherapy with 45 mg/m^2 paclitaxel and carboplatin once a week; 2 weeks after chemoradiation, two cycles of consolidation chemotherapy, separated by 3 weeks, were given and consisted of paclitaxel (200 mg/m^2) and carboplatin. The radiation dose was prescribed at the PTV and was given in two Gy daily fractions, with either IMRT or 3D-CRT. The coprimary objectives were to (1) compare OS in participants who were given 74 Gy with that in participants who were given 60 Gy conformal RT with concurrent chemotherapy and (2) compare OS in participants who were given cetuximab with that in participants who were not given cetuximab. There were several secondary objectives: (1) comparison of progression-free survival and local-regional tumor control; (2) comparison of toxic effects between 74 Gy vs 60 Gy and between cetuximab vs without cetuximab; (3) assessment of participant-reported quality of life in each group of the trial; and (4) exploration of biological markers that might predict clinical outcome. Overall, 166 participants were randomly assigned to receive standard-dose chemoradiotherapy; additionally, 121 were randomly assigned to high-dose chemoradiotherapy, 147 to standard-dose chemoradiotherapy and cetuximab, and 110 to high-dose chemoradiotherapy and cetuximab. The median follow-up for the radiotherapy comparison was 22.9 months (IQR, 27.5-33.3 months). The median OS was 28.7 months (95% CI, 24.1-36.9 months) in participants who received standard-dose radiotherapy and 20.3 months (95% CI, 17.7-25.0 months) in those who received high-dose radiotherapy (HR, 1.38; 95% CI, 1.09-1.76; p = 0.004). The median follow-up for the cetuximab comparison was 21.3 months (IQR, 23.5-29.8 months). The median OS in participants who received cetuximab was 25.0 months (95% CI, 20.2-30.5 months) compared with 24.0 months (95% CI, 19.8-28.6 months) in those who did not (HR, 1.07; 95% CI, 0.84-1.35; p = 0.29). Both the radiation dose and cetuximab results crossed protocol-specified futility boundaries. No statistical differences in grade 3 or worse toxic effects were observed between radiotherapy groups. By contrast, the use of cetuximab was associated with a higher rate of grade 3 or worse toxic effects [205 (86%) of 237 vs 160 (70%) of 228 participants; p < 0.0001]. More treatment-related deaths occurred in the high-dose chemoradiotherapy and cetuximab groups (radiotherapy comparison: eight vs three participants; cetuximab comparison: 10 vs five participants). No differences in severe pulmonary events were observed between the treatment groups. Severe esophagitis was more common in participants who received high-dose chemoradiotherapy than in those who received standard-dose treatment [43 (21%) of 207 participants vs 16 (7%) of 217 participants; p < 0.0001]. The authors concluded that 74-Gy radiation given in two Gy fractions with concurrent chemotherapy was not better than 60 Gy given in two Gy fractions plus concurrent chemotherapy in participants with stage III NSCLC and might be potentially harmful. The authors also reported that the addition of cetuximab to concurrent chemoradiation and consolidation treatment provided no benefit in OS for these participants.

Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)

Daly et al. (2022) developed an ASCO guideline for the management of stage III NSCLC that recommended that neoadjuvant RT can be considered alongside chemotherapy in select surgical candidates, particularly those with N2 nodal involvement or superior sulcus tumors. For patients with stage III NSCLC who are not surgical candidates but have good

performance status, the guideline strongly recommends concurrent chemotherapy and radiation rather than sequential treatment. The recommended regimen combines a platinum-based chemotherapy doublet with RT delivered in a total dose of 60 Gy, with some patients receiving up to 70 Gy, while carefully limiting exposure to the heart, lungs, and esophagus.

National Comprehensive Cancer Network (NCCN)

The NCCN's guideline states that the most commonly prescribed doses for definitive radiotherapy for locally advanced NSCLC are 60- to 70-Gy fractions, with a treatment duration of 6 to 7 weeks. Doses of at least 60 Gy should be given. Additionally, IGRT is appropriate when needed to deliver curative RT safely and is also recommended when using 3D-CRT/IMRT when OARs are in close proximity to high-dose regions or when using complex motion management techniques (NCCN, 2026).

Prostate Adenocarcinoma

Murthy et al. (2021) conducted a phase 3 RCT that compared prophylactic, whole pelvic nodal radiotherapy with prostate-only radiotherapy (PORT) in men with high-risk prostate cancer. Participants (n = 224) who were undergoing radical radiotherapy for node-negative prostate adenocarcinoma, with an estimated nodal risk of ≥ 20%, were randomized to PORT (68 Gy/25# to prostate) or whole pelvic radiotherapy (WPRT; 68 Gy/25# to prostate; 50 Gy/25# to pelvic nodes, including common iliac). IMRT, IGRT, and a minimum of 2 years of androgen deprivation therapy (ADT) were received by all participants. Biochemical failure–free survival (BFFS) for 5 years was the primary end point. Disease-free survival and OS were secondary end points. At a median follow-up of 68 months, 36 biochemical failures (PORT = 25; WPRT = 7) and 24 deaths (PORT = 13; WPRT = 11) were recorded. The 5-year BFFS was 95.0% with WPRT vs 81.2% with PORT. WPRT also showed higher 5-year disease-free survival (89.5% vs 77.2%), but 5-year OS did not appear to differ (92.5% vs 90.8%). Distant metastasis–free survival was also higher with WPRT (95.9% vs 89.2%). The authors concluded that prophylactic WPRT using a contemporary dose and technique, along with long-term ADT, for high-risk or very high-risk prostate cancer resulted in a large and significantly improved BFFS and disease-free survival compared with PORT but did not impact OS. The authors recommended that prophylactic pelvic radiotherapy should be routinely considered for these individuals until the long-term outcomes of ongoing trials are reported.

In a Cochrane systematic review, Hickey et al. (2019) compared hypofractionated EBRT and conventionally fractionated EBRT in men with clinically localized prostate cancer. Selection criteria included randomized controlled comparisons from 1946 to 2019, in which men with localized prostate adenocarcinoma who underwent hypofractionated RT (> 2 Gy per fraction) were compared with men who had conventional RT using standard fractionation (1.8-2 Gy per fraction). Ten studies were included in the review, for a total of 8,278 men. The study found that hypofractionation resulted in little to no difference in prostate cancer–specific survival, little to no difference in late RT genitourinary (GU) toxicity, and uncertainty regarding the effect of hypofractionation on late RT gastrointestinal (GI) toxicity. Secondary outcomes included little to no difference in acute GI radiation toxicity; little to no difference in metastasis-free survival; and a small reduction in recurrence-free survival. The authors concluded that moderate hypofractionation (up to a fraction size of 3.4 Gy) resulted in similar outcomes in terms of disease-specific survival, metastasis-free survival, and OS, with little to no increase in toxicity. Lee et al. (2016), previously cited in this policy, is included in this systematic review.

Catton et al. (2017) conducted a multicenter, randomized noninferiority trial to determine whether hypofractionation vs conventional fractionation is similar in efficacy without increased toxicity. Participants with intermediate-risk prostate cancer [T1-2a, Gleason score ≤ 6, and prostate-specific antigen (PSA) 10.1-20 ng/mL; T2b-2c, Gleason score ≤ 6, and PSA ≤ 20 ng/mL; or T1-2, Gleason score of 7, and PSA ≤ 20 ng/mL] were eligible to participate. Participants were randomized to conventional RT of 78 Gy in 39 fractions over 8 weeks or to hypofractionated RT of 60 Gy in 20 fractions over 4 weeks. Androgen deprivation was not permitted with therapy. The primary outcome was biochemical-clinical failure, defined by any of the following: PSA failure (nadir + 2), hormonal intervention, clinical local or distant failure, or death as a result of prostate cancer. The noninferiority margin was 7.5% (HR, < 1.32). A total of 1,206 participants were randomized, with 608 participants allocated to the hypofractionated RT group (short arm) and 598 participants to the control RT group (standard arm). The median follow-up was 6.0 years. Most of the events were PSA failures. The 5-year biochemical-clinical failure disease-free survival was 85% in both arms (HR, 0.96; 90% CI, 0.77-1.2). Ten deaths due to prostate cancer occurred in the short arm, and 12 occurred in the standard arm. No significant differences were detected between arms for grade ≥ 3 late GU and GI toxicity. The authors concluded that the hypofractionated RT regimen that was used in this trial was not inferior to conventional RT and not associated with increased late toxicity. Furthermore, the authors stated that hypofractionated RT is a more convenient option for individuals and should be considered for intermediate-risk prostate cancer.

Dearnaley et al. (2016) conducted a multicenter, randomized, noninferiority trial that compared a conventionally fractionated schedule with two experimental hypofractionated schedules in men with localized prostate cancer. Men who

were older than 16 years and had histologically confirmed T1b to T3aN0M0 prostate cancer and a World Health Organization performance status of 0 or 1 were eligible. Participants were randomly assigned to conventional (74 Gy delivered in 37 fractions over 7.4 weeks) or one of two hypofractionated schedules (60 Gy in 20 fractions over 4 weeks or 57 Gy in 19 fractions over 3.8 weeks), which were all delivered with intensity-modulated techniques. Most participants were given radiotherapy with 3 to 6 months of neoadjuvant and concurrent androgen suppression. The primary end point was time to biochemical or clinical failure; the critical HR for noninferiority was 1.208. A total of 3,216 men were enrolled and randomly assigned (74-Gy group, 1,065 participants; 60-Gy group, 1,074 participants; 57-Gy group, 1,077 participants). The median follow-up was 62.4 months (IQR, 53.9-77.0 months). The proportion of participants who were biochemical or clinical failure free at 5 years was 88.3% (95% CI, 86.0%-90.2%) in the 74-Gy group, 90.6% (95% CI, 88.5%-92.3%) in the 60-Gy group, and 85.9% (95% CI, 83.4%-88.0%) in the 57-Gy group. Overall, 60 Gy was noninferior to 74 Gy (HR, 0.84; 90% CI, 0.68-1.03; p = 0.0018), but noninferiority could not be claimed for 57 Gy compared with 74 Gy (HR, 1.20; 90% CI, 0.99-1.46; p = 0.48). Long-term side effects were similar in the hypofractionated groups compared with the conventional group. There were no significant differences in either the proportion or cumulative incidence of side effects 5 years after treatment using three clinician-reported as well as participant-reported outcome measures. The estimated cumulative 5-year incidence of Radiation Therapy Oncology Group grade 2 or worse bowel and bladder adverse events was 13.7% (111 events) and 9.1% (66 events) in the 74-Gy group, 11.9% (105 events) and 11.7% (88 events) in the 60-Gy group, and 11.3% (95 events) and 6.6% (57 events) in the 57-Gy group, respectively. No treatment-related deaths were reported. The authors concluded that hypofractionated radiotherapy using 60 Gy in 20 fractions is noninferior to conventional fractionation using 74 Gy in 37 fractions and is recommended as a new standard of care for external beam radiotherapy of localized prostate cancer.

The Hypofractionated Irradiation for Prostate Cancer (HYPRO) trial was a multicenter, open-label, randomized trial to investigate whether hypofractionated EBRT improves relapse-free survival, without increasing toxic effects, compared with conventionally fractionated radiotherapy. Participants at an intermediate risk or high risk who were between 44 and 85 years of age, had histologically confirmed stage T1b to T4 NX-0MX-0 prostate cancer, had a PSA concentration of 60 ng/mL or lower and had a World Health Organization performance status of 0 to 2 were eligible to participate. Enrolled participants were randomly assigned to receive either standard fractionation with 39 fractions of 2 Gy in 8 weeks (five fractions per week) or hypofractionation with 19 fractions of 3.4 Gy in 6.5 weeks (three fractions per week). The primary end point was 5-year relapse-free survival, and secondary outcomes included acute and late GU and GI toxicity. Noninferiority of hypofractionation was tested separately for GU and GI acute toxic effects, with a null hypothesis that cumulative incidences of each type of adverse event were not more than 8% higher in the hypofractionation group than in the standard fractionation group. In 2015, Aluwini et al. reported results for a total of 820 participants in the HYPRO study who were randomly assigned to treatment with standard fractionation (n = 410) or hypofractionation (n = 410). The authors concluded that hypofractionated radiotherapy was not noninferior to standard fractionated radiotherapy in terms of acute GU and GI toxicity in men with intermediate-risk or high-risk prostate cancer, and the cumulative incidence of grade 2 or worse acute GI toxicity was significantly higher in participants who were given hypofractionation than in those who were given standard fractionated radiotherapy. However, the authors also stated that before final conclusions can be made about the utility of hypofractionation, efficacy outcomes are needed. In 2016, Incrocci et al. reported 5-year relapse-free survival outcomes. Relapse-free survival at 5 years was 80.5% (95% CI, 75.7%-84.4%) in participants who were assigned hypofractionation and 77.1% (95% CI, 71.9%-81.5%) in those who were allocated conventional fractionation (adjusted HR, 0.86; 95% CI, 0.63-1.16; log-rank p = 0.36). No treatment-related deaths occurred. The authors concluded that based on all the HYPRO trial evidence, hypofractionated radiotherapy (19 fractions of 3.4 Gy) was not superior to conventional radiotherapy, with respect to 5-year relapse-free survival, and that their hypofractionated radiotherapy regimen cannot be regarded as the new standard of care for individuals with intermediate-risk or high-risk prostate cancer.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO's guideline on hypofractionated RT for localized prostate cancer states that based on high-quality evidence, moderate hypofractionated EBRT (defined as 240-340 Gy per fraction) should be recommended to low-risk and intermediate-risk patients who opt for active treatment and patients with high risk when the pelvic nodes will not be treated. Based on moderate-quality evidence, the guideline conditionally recommends regimens of 6,000 Gy delivered in 20 fractions of 300 Gy and 7,000 Gy delivered in 28 fractions of 250 Gy. The guideline also states that men should be counseled about the small increased risk of acute GI toxicity with moderate hypofractionation; however, late GI and GU toxicities were similar with hypofractionated and conventional treatments. A single optimal regimen cannot yet be identified, as studies with head-to-head comparisons of multiple fractionation schemes have not been completed (Morgan et al., 2018).

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

Morgan et al. (2024) developed an evidence-based guideline for the AUA in collaboration with ASTRO and the SUO regarding salvage therapy for prostate cancer, which is intended to assist care decisions for patients with recurrent prostate cancer following prior curative treatment. The guideline is a three-part series; part I is a discussion of treatment decision-making, part II focuses on treatment for nonmetastatic biochemical recurrence (BCR) after primary radical prostatectomy (RP), and part III is for the evaluation and management of recurrence after RT and focal therapy, regional recurrence, and oligometastasis. For treatment decision-making at the time of suspected BCR after primary RP, the guideline recommends the following (not all inclusive):

- For patients with a detectable PSA after RP, in whom salvage RT is being considered, clinicians should provide salvage radiation when the PSA is ≤ 0.5 ng/mL (moderate recommendation; evidence level: grade B).
- For patients with a detectable PSA after RP who are at high risk for clinical progression, clinicians may offer salvage radiation when PSA values are < 0.2 ng/mL (conditional recommendation; evidence level: grade C).

For treatment delivery for nonmetastatic BCR after primary RP, the guideline recommends (not all inclusive):

- For patients with BCR following RP without any high-risk features, clinicians may offer radiation alone (conditional recommendation; evidence level: grade C).
- In patients with BCR following RP who are undergoing salvage RT with ADT, clinicians may use expanded radiation fields that include the regional lymph nodes (conditional recommendation; evidence level: grade B).

For the evaluation and management of suspected nonmetastatic recurrence after RT, the guideline recommends (not all inclusive):

- In patients with biopsy-documented prostate cancer recurrence after primary RT who are candidates for salvage local therapy, clinicians should offer RP, cryoablation, high-intensity focused ultrasound, or reirradiation as part of a shared decision-making approach (moderate recommendation; evidence level: grade C).

For the evaluation and management of regional recurrence, the guideline recommends (not all inclusive):

- In patients with pelvic nodal recurrence following primary RP, clinicians should offer ADT plus salvage RT to the prostate bed and pelvic lymph nodes (expert opinion).
- In patients with pelvic nodal recurrence following primary RT who did not receive prior pelvic nodal RT, clinicians should offer salvage pelvic nodal RT plus ADT (expert opinion).

In an AUA/ASTRO guideline (endorsed by the SUO) on localized prostate cancer, Eastham et al. (2022) stated that target localization, normal tissue avoidance, simulation, advanced treatment planning/delivery, and image-guidance procedures should be used to optimize the therapeutic ratio of EBRT delivery for prostate cancer. When EBRT is the primary treatment for prostate cancer, the guideline recommends dose escalation (strong recommendation; evidence level: grade A). Moderate hypofractionated EBRT should be recommended to low-risk and intermediate-risk patients (strong recommendation; evidence level: grade A), and ultra-hypofractionated EBRT for patients with low- or intermediate-risk prostate cancer may be considered (conditional recommendation; evidence level: grade B). In patients with low-risk or favorable intermediate-risk prostate cancer who elect RT, dose-escalated, hypofractionated EBRT (moderate or ultra), a permanent low-dose rate seed implant, or a temporary high-dose rate prostate implant should be offered as equivalent forms of treatment (strong recommendation; evidence level: grade B). In patients with low- or intermediate-risk prostate cancer, clinicians should not electively radiate the pelvic lymph nodes (strong recommendation; evidence level: grade B). In patients with high-risk prostate cancer, clinicians may offer radiation to the pelvic lymph nodes (conditional recommendation; evidence level: grade B). Additionally, when treating the pelvic lymph nodes with radiation, clinicians should use IMRT with doses between 45 Gy to 52 Gy (strong recommendation; evidence level: grade B).

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for prostate cancer list moderate hypofractionation schedules as 3 Gy in 20 fractions (preferred), 2.7 Gy in 26 fractions, and 2.5 Gy in 28 fractions; for a low metastatic burden, 2.75 Gy in 20 fractions is appropriate. Additionally, the guidelines state that a conventional fractionation regimen consists of 1.8 to 2 Gy in 37 to 45 fractions. Per the NCCN, daily prostate localization using IGRT is essential, with either 3D-CRT or IMRT, for target margin reduction and treatment accuracy (NCCN, 2026).

Image-Guided Radiation Therapy

Wang et al. (2022) conducted a systematic review and meta-analysis to evaluate the impact of IGRT on individual efficacy, toxicity, and second cancers in individuals with prostate cancer. Three RCTs and 15 cohort studies (n = 6,521 men) were included in the review. The median duration of follow-up in the IGRT group was 46.2 months and in the

control, group was 52.7 months. The meta-analysis demonstrated that IGRT significantly reduced acute GU (risk ratio, 0.78; 95% CI, 0.69-0.88; p < 0.001; nine studies) and GI toxicity (risk ratio, 0.49; 95% CI, 0.35-0.68; p < 0.001; four studies) and late GI toxicity (HR, 0.25; 95% CI, 0.07-0.87; p = 0.03; three studies) compared with non-IGRT. Compared with prospective studies, retrospective studies showed that IGRT had a more significant effect in reducing the late GI toxicity. Compared with nondaily IGRT, daily IGRT significantly improved 3-year PSA relapse-free survival (HR, 0.45; 95% CI, 0.28-0.72; p = 0.001; two studies) and BFFS (HR, 0.57; 95% CI, 0.39-0.83; p = 0.003; three studies). Furthermore, high-frequency daily IGRT could lead to a greater 3-year BFFS benefit in individuals with prostate cancer than weekly IGRT. No significant effects of IGRT on acute rectal toxicity, late GU toxicity, 5-year OS, and second cancer mortality were found. The authors concluded that IGRT had a significant association with GI and acute GU toxicity reduction and improved the biochemical tumor control but had no significant effect on 5-year OS and second cancer mortality. Additionally, the authors reported that for protecting acute GU and rectal toxicity, IGRT combined with IMRT might be more effective than 3D-CRT. Limitations include the fact that the majority of the reviews that were included in this study were retrospective. The authors recommended future RCTs to clarify the role of IGRT in prostate cancer.

Bockel et al. (2021) conducted a systematic review to assess the recent literature concerning 3D image-guided brachytherapy for reirradiation in the context of local recurrences in gynecologic malignancies. The authors conducted a large-scale literature research, and 15 original studies that met their research criteria were selected to be included in the review. Local control rates ranged from 44% to 71.4% at 2 to 5 years, and OS rates ranged from 39.5% to 78% at 2 to 5 years. Grade ≥ 3 toxicities ranged from 1.7% to 50%, with only one study reporting a grade 5 event. Results in terms of outcome and toxicities were highly variable, depending on the studies. Several studies suggested that local control could be improved with two Gy equivalent doses of > 40 Gy. The authors concluded that image-guided brachytherapy appears to be a feasible alternative to salvage surgery in inoperable individuals or individuals who refuse surgery, with an acceptable outcome in those who have no other curative therapeutic options; however, this is at a high cost of long-term grade ≥ 3 toxicities in some studies. Due to the heterogeneity and small size of populations that are reported in the studies, no formal conclusions or strict recommendations could be made, especially regarding the doses that are required to offer the best local control and dose constraints that are applicable to the OAR. The authors indicated that centralization of data and large-scale, multicentric, international, prospective trials are warranted.

Yao et al. (2019) conducted a case series analysis to investigate the setup uncertainties and to establish an optimal imaging schedule for prone-positioned whole-breast radiotherapy. Overall, 20 prone-positioned breast patients, who were treated with tangential fields from 2015 to 2017, were retrospectively enrolled in this study. The prescription dose for the whole-breast treatment was 266 Gy × 16 for all the patients, and the treatments were delivered with the source-to-surface distance setup technique. At every fraction of treatment, the patient was set up based on the body localization tattoos. Megavoltage (MV) portal imaging was then taken to confirm the setup; if a discrepancy (> 3 mm) was found between the portal images and corresponding plan images, the patient positioning was adjusted accordingly with couch movement. Based on the information that was acquired from the daily tattoo and portal imaging setup, three sets of data, named as weekly imaging guidance (WIG), no daily imaging guidance (NIG), and initial 3 days then weekly imaging guidance (3 + WIG) were sampled, constructed, and analyzed in reference to the benchmark of the daily imaging guidance (DIG). A comparison of the setup uncertainties, target coverage (D_{95} and D_{max}), V_5 of the ipsilateral lung, the mean dose for the heart, and the mean and max dose for the left anterior descending coronary artery (LAD) among the four imaging guidance (IG) schedules were made. Relative to the daily IG benchmark, the NIG schedule led to the largest residual setup uncertainties; the uncertainties were similar for the WIG and 3 + WIG schedules. Little variations were observed for D_{95} of the target among NIG, DIG, and WIG. The target D_{max} also exhibited little changes among all the IG schedules. While V_5 of the ipsilateral lung changed very little among all four schedules, the percent change of the mean heart dose was more pronounced; however, its absolute values were still within the tolerance. However, for the left-sided breast patients, the LAD dose could be significantly impacted by the imaging schedules and could potentially exceed its tolerance criteria in some patients if NIG, WIG, and 3 + WIG schedules were used. The authors concluded that for left-side whole-breast treatment in the prone position using the source surface distance treatment technique, the DIG can ensure dosimetric coverage of the target as well as prevent critical organs, especially LAD, from receiving unacceptable levels of a dose. For right-sided whole-breast treatment in the prone position, the weekly imaging setup guidance appears to be the optimal choice.

Kilburn et al. (2016) conducted a retrospective cohort analysis to determine if treatment planning based on individualized tumor motion with 4D computed tomography (4D-CT) imaging, followed by daily IGRT with daily kilovoltage cone-beam computed tomography (CBCT), allows more accurate tumor targeting, with improved local control and reduced side effects, compared with weekly 2D MV portal imaging based on bony landmarks. Patients with stage IIB to IIIB NSCLC, who were treated with concurrent chemotherapy and EBRT with curative intent, were included in the study. Patients in both cohorts (IGRT and non-IGRT) were treated with either 3D-CRT or IMRT. Outcomes included failure-free survival for local failure–free survival (LFFS), regional failure–free survival, locoregional failure–free survival, distant failure–free survival disease, progression-free survival, and OS and were estimated using the Kaplan-Meier method. Univariate and

multivariate models were used to assess the association between patient and treatment-related covariates and local failure. A total of 169 patients were treated with definitive radiotherapy and concurrent chemotherapy, with a median follow-up of 48 months in the IGRT cohort and 96 months in the non-IGRT cohort. IGRT was used in 36% (62 patients). OS was similar between cohorts (2-year OS, 47% vs 49%; p = 0.63). The IGRT cohort had improved 2-year LFFS (80% vs 64%; p = 0.013) and locoregional failure-free survival (75% and 62%; p = 0.04). Univariate analysis revealed that IGRT and treatment year improved LFFS, while group stage, dose, and positron emission tomography/CT planning had no impact. IGRT remained significant in the multivariate model, with an adjusted HR of 0.40 (p = 0.01). Distant failure–free survival (58% vs 59%; p = 0.67) did not differ significantly. The authors concluded that IGRT with daily CBCT confers an improvement in the therapeutic ratio compared with no patients treated without IGRT.

Nabavizadeh et al. (2016) conducted a survey of the ASTRO physician membership to identify IGRT practice patterns as well as IGRT's impact on clinical workflow and PTVs. A sample of 5,979 treatment site–specific surveys were emailed to the membership of ASTRO, with questions pertaining to IGRT modality/frequency, PTV expansions, the method of image verification, and the perceived utility/value of IGRT. On-line image verification was defined as images obtained and reviewed by the physician before treatment. Off-line image verification was defined as images that were obtained before treatment and then reviewed by the physician before the next treatment. Of 601 evaluable responses, 95% reported IGRT capabilities other than portal imaging. The majority (92%) used volumetric imaging (CBCT or MV CT), with volumetric imaging being the most commonly used modality for all sites, except breast. The majority of respondents obtained daily CBCTs for head and neck IMRT, lung 3D-CRT or IMRT, anus or pelvis IMRT, prostate IMRT, and prostatic fossa IMRT. For all sites, on-line image verification was most frequently performed during the first few fractions only. No association was seen between IGRT frequency or CBCT use and clinical treatment volume to PTV expansions. Of the 208 academic radiation oncologists who reported working with residents, only 41% reported trainee involvement in IGRT verification processes. The authors concluded that consensus guidelines, further evidence-based approaches for PTV margin selection, and greater resident involvement are needed for the standardized use of IGRT practices.

Wang et al. (2015) assessed late toxicities in participants with extremity soft tissue sarcoma who were treated with preoperative IGRT to a reduced target volume in a multi-institutional, prospective, phase 2 trial. Cohort A (n = 12) received IGRT with chemotherapy, and cohort B (n = 86) received IGRT without chemotherapy, followed by limb-sparing resection. Participant position was adjusted before each treatment after daily pretreatment images were coregistered with digitally reconstructed radiographs. All participants received IGRT to reduced tumor volumes, and late toxicities were assessed at 2 years. Due to poor accrual, cohort A was closed prematurely and was not reported. Overall, 79 eligible participants from cohort B formed the basis of this report. At a median follow-up of 3.6 years, five participants did not have surgery because of disease progression. There were five local treatment failures, all of which were in field. Of the 57 participants who were assessed for late toxicities at 2 years, 10.5% experienced at least one grade ≥ 2 toxicity as compared with 37% of participants in the National Cancer Institute of Canada SR2 (CAN-NCIC-SR2: Phase III Randomized Study of Pre- vs Postoperative Radiotherapy in Curable Extremity Soft Tissue Sarcoma) trial who received preoperative RT without IGRT (p < 0.001). The authors concluded that there was a significant reduction in late toxicities in participants who were treated with preoperative IGRT, and the absence of marginal-field recurrences suggests that the target volumes used in the RTOG-0630 study are appropriate for preoperative IGRT for extremity soft tissue sarcoma. Limitations include the lack of randomization, small study size, and lack of cohort A reporting.

Korreman et al. (2012) conducted a multicenter case series analysis to quantify the effects of 4D-CT, 4D image guidance (4D-IG), and beam gating on calculated treatment field margins in a population of individuals with lung cancer. A total of 46 individuals with NSCLC participated in four separate motion management protocols. Respiration-correlated imaging was performed for treatment planning purposes in all individuals; nine individuals were imaged with 4D-CT scans, seven individuals were imaged using fluoroscopy (with gold seeds in tumors), and 30 individuals were imaged using 4D-CT (five individuals had an implanted fiducial marker). The magnitude of respiratory tumor motion was measured. The required treatment field margins were calculated using a statistical recipe (van Herk 2000), with magnitudes of all uncertainties, except respiratory peak-to-peak displacement, being the same for all individuals. Required margins for respiratory motion management were calculated using the residual respiratory tumor motion for each individual for various motion management strategies. Margin reductions for respiration management were calculated using 4D-CT, 4D-IG, and gated beam delivery. The median tumor motion magnitude was 4.4 mm in the 46 individuals (range, 0 to 29.3 mm). This value corresponded to the required treatment field margins of 13.7 to 36.3 mm (median, 14.4 mm). The use of 4D-CT, 4D-IG, and beam gating required margins that were reduced by 0 to 13.9 mm (median, 0.5 mm), 3 to 5.2 mm (median, 5.1 mm), and 0 to 7 mm (median, 0.2 mm), respectively, to a total of 8.5 to 12.4 mm (median, 8.6 mm). The authors concluded that a respiratory management strategy for lung cancer radiotherapy, including planning on 4D-CT scans and daily image guidance, provides a potential reduction of 37% to 47% in treatment field margins; therefore, the 4D-IG strategy was the most effective strategy for > 85% of the individuals in their study.

Lin et al. (2012) conducted a single-center, retrospective case series analysis to determine the impact of BMI on daily setup variations and frequency of imaging that are necessary for patients with endometrial cancer who are treated with adjuvant IMRT with daily image guidance. BMI mean daily shifts and random and systematic errors in each translational and rotational direction were calculated for each patient. Margin recipes were generated based on BMI. Linear regression and Spearman rank correlation analysis were performed. To simulate a less-than-daily IGRT protocol, the average shift of the first five fractions was applied to subsequent setups without IGRT for assessing the impact on setup error and margin requirements. A total of 30 patients were included in the analysis. All patients underwent surgery for endometrial cancer, including a total hysterectomy, bilateral salpingo-oophorectomy, and pelvic/para-aortic lymph node dissection for endometrial cancer. Stages ranged from IB to IIIC. Of the patients, six had uterine sarcoma, 21 had endometrioid adenocarcinoma, and three had papillary serous carcinoma. One patient received pelvic radiation for a recurrence of endometrial cancer. The median patient age was 59 years (range, 45 to 82 years). The median BMI was 32.9 kg/m^2 (range, 23 to 62 kg/m^2). Of the 30 patients, 16.7% (n = 5) were of normal weight (BMI < 25 kg/m^2); 23.3% (n = 7) were overweight (BMI ≥ 25 to < 30 kg/m^2); 26.7% (n = 8) were mildly obese (BMI ≥ 30 to < 35 kg/m^2); and 33.3% (n = 10) were moderately to severely obese (BMI ≥ 35 kg/m^2). On linear regression, mean absolute vertical, longitudinal, and lateral shifts positively correlated with BMI ($p = 0.0127$, $p = 0.0037$, and $p < 0.0001$, respectively). Systematic errors in the longitudinal and vertical directions were found to be positively correlated with BMI category ($p < 0.0001$ for both). IGRT for the first five fractions, followed by correction of the mean error for all subsequent fractions, led to a substantial reduction in setup error and resultant margin requirement overall compared with no IGRT. The authors concluded that daily shifts, systematic errors, and margin requirements were highest in patients who were obese, and as such, tailored use of image-guided IMRT in women with a high BMI who are receiving pelvic radiotherapy is thus appropriate.

Chen et al. (2007) conducted a retrospective case series analysis to determine the optimal definition of target margins for patients with esophageal carcinoma who have been treated with conformal RT. Pretreatment MV CT scans were used to evaluate setup variations in anterior-posterior (AP), lateral, and superior-inferior (SI) directions and rotational variations, including pitch, roll, and yaw, in patients with pathologically confirmed esophageal carcinoma who were treated with helical tomotherapy. A total of 10 patients were included in the analysis; eight had adenocarcinoma, and two had squamous cell carcinoma. After patients were positioned using their skin tattoos/marks, MV CT scans were performed before every treatment and automatically registered to planning kilovoltage CT scans according to bony landmarks. Image registration data were used to adjust patient setups before treatment. A total of 250 MV CT scans were analyzed. Correlations between setup variations and body habitus, including height, weight, relative weight change, body surface area, and patient age, were evaluated. The SDs for systematic setup corrections in AP, lateral, and SI directions and pitch, roll, and yaw rotations were 1.5, 3.7, and 4.8 mm and 0.5°, 1.2°, and 0.8°, respectively. The appropriate averages of random setup variations in AP, lateral, and SI directions and pitch, roll, and yaw rotations were 2.9, 5.2, and 4.4 mm and 1.0°, 1.2°, and 1.1°, respectively. Setup variations were stable throughout the entire course of radiotherapy in all three translational and three rotational displacements, with little change in magnitude. No significant correlations were found between setup variations and body habitus variables. The authors concluded that daily MV CT scans before each treatment can effectively detect setup errors and thus reduce PTV margins. This will reduce the radiation dose to critical organs and may lower treatment-related toxicities.

Kotte et al. (2007) conducted a case series analysis to evaluate the intrafraction motion of the prostate during EBRT in individuals with prostate cancer. A total of 427 individuals with stage T3Nx/0Mx/0 prostate carcinoma who received IMRT treatment combined with position verification with fiducial gold markers were included in the analysis. For a total of 11,426 treatment fractions (average, 27 per individual), portal images were taken of the first segment of all five beams. The irradiation time of the technique varied between 5 and 7 minutes. From these data, the location of gold markers could be established in every treatment beam, under the assumption of minimal marker movement. In 66% of treatment fractions, a motion outside a range of 2 mm was observed, with 28% outside a range of 3 mm. The intrafraction marker movements showed that motion directions were often reversed. However, the effect was small. Even with perfect online position correction at the start of irradiation, intrafraction motion caused position uncertainty, but systematic errors were limited to < 0.6 mm and random errors to < 0.9 mm. This would result in a lower limit of 2 mm for margins in the absence of any other uncertainties. The authors concluded that intrafraction motion of the prostate occurs frequently during external beam irradiation on a time scale of 5 to 7 minutes. Margins of 2 mm account for these intrafraction motions. However, larger margins are required, in practice, to accommodate other uncertainties in the treatment.

Clinical Practice Guidelines

American Association of Physicists in Medicine (AAPM)

The AAPM's report, Quality Assurance for Image-Guided Radiation Therapy Utilizing CT-Based Technologies, states that CT-based image guidance systems have the potential to profoundly change how RT is delivered. Quality control protocols used for these devices are highly dependent on their intended use. The primary aim of image guidance is to detect and correct positional uncertainties, and as such, attention should be given to the geometric accuracy assessment. As PTV

margins become tighter, the geometric accuracy of RT delivery systems becomes as important as the dosimetric accuracy, meriting implementation of daily quality control procedures (Bissonnette et al., 2012).

American College of Radiology (ACR)/American Society for Radiation Oncology (ASTRO)

ACR-ASTRO's Practice Parameter for Image-Guided Radiation Therapy states that IGRT has led to substantially greater accuracy and precision of radiation delivery. The need for accuracy and precision has been increased by research, which shows that the accuracy of targeting using IGRT significantly affects OS. This need for accuracy is potentially being met by ongoing advances in radiation planning and delivery that allow for much more conformal dose distributions, sharper dose gradients, and higher doses per fraction. Thus, IGRT is particularly applicable to highly conformal treatment modalities, such as 3D-CRT, IMRT, and heavy particle therapy. Patient positioning prior to simulation is determined by the radiation oncologist and is based on patient comfort, reproducibility, and the effect on the location of anatomical structures (i.e., prone vs supine). Some immobilization devices that are used to improve accuracy and reproducibility in patient positioning devices are vacuum-formable cushions, head rests, prone belly boards, and abdominal compression devices. Techniques that are used to account for intrafraction and interfraction target movement and possible residuals from onboard image registration, localization, and correction procedures for targets significantly affected by motion, as related to the IGRT approach, include respiratory gating, tumor tracking, abdominal compression, full bladder, and DIBH. Common indications for IGRT include any target volume that is located near or within critical structures and/or in tissue with inherent setup variation; any target volume in close proximity to critical structures that must be protected; any volume of interest that must be covered with narrow margins to adequately protect immediately adjacent structures; any target volume that is subject to daily variation that is due to internal motion; any target for which the adjacent area has been previously irradiated, with precise abutting fields; or any scenario in which dose escalation is planned beyond the usual doses for similar tumors (Luh et al., 2020).

American Society for Radiation Oncology (ASTRO)

ASTRO's Coding Resource states that IGRT can be considered when using 3D-CRT, IMRT, proton beam RT, and or external beam–based accelerated PBI. Any time that a target volume is located in or near critical structures, IGRT may be indicated to improve the therapeutic ration. Common clinical indications include the following, when the target volume is subject to daily variation due to internal motion: (1) the immediately adjacent area has been previously irradiated and (2) the volume of interest must be covered with narrow margins to protect immediately adjacent structures and when dose escalation is planned. Additionally, IGRT is not indicated but not limited to the superficial treatment of skin cancer or to the alignment of bony landmarks without implanted fiducials (ASTRO, 2025).

ASTRO's guideline for the treatment of primary liver cancer states that for patients with hepatocellular carcinoma or intrahepatic cholangiocarcinoma who are receiving dose-escalated ultra- or moderately hypofractionated EBRT, respiratory motion management and daily image guidance are recommended (Apisarnthanarax et al., 2022).

ASTRO's guideline for the treatment of oligometastatic NSCLC states that for patients receiving highly conformal RT using inverse dose planning, appropriate motion management strategies and image-guided RT delivery are recommended (Iyengar et al., 2023).

ASTRO's guideline for pancreatic cancer RT states that for patients receiving conventionally fractionated RT, daily image guidance is strongly recommended (Palta et al., 2019).

ASTRO's guideline regarding soft tissue sarcoma strongly recommends daily IGRT, with at least weekly volumetric image guidance, for patients with primary localized extremity and truncal soft tissue sarcomas and for primary localized retroperitoneal sarcomas when preoperative RT is planned (Salerno et al., 2021).

ASTRO's white paper on safety considerations for IGRT states that it is a powerful tool that enables radiation oncologists to further increase the conformality of radiation delivery, with higher-dose prescriptions and shorter fractionation schedules. However, IGRT is time and resource intensive and increases the need for process-oriented thinking and interprofessional communication. The white paper recommends that practitioners work together as a team to address environmental and technical concerns; additionally, documented standard operating procedures should be followed for planning to ensure that PTVs are properly constructed and that team members allow adequate time for quality assurance checks and to investigate any problems (Jaffray et al., 2013). ASTRO released an updated report on IGRT regarding quality and safety considerations. The report builds on the previous version and notes that IGRT requires an interdisciplinary team–based approach, staffed with trained specialists, significant personnel resources, specialized technology, and implementation time. The paper recommends the development of a comprehensive quality assurance program to ensure that IGRT is performed safely and effectively (Qi et al., 2023).

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for biliary tract cancer state that IGRT is strongly recommended when using RT, IMRT, and SBRT to improve treatment accuracy and reduce treatment-related toxicity (NCCN, 2025).

The NCCN guidelines for gastric cancer state that image guidance may be used appropriately to enhance clinical targeting (NCCN, 2025).

The NCCN's head and neck cancers guidelines state that image guidance is required to provide assurance of accurate daily delivery. Anatomical changes, including rapidly shrinking tumors, changes in air cavities, and or significant weight loss, may necessitate repeat diagnostic imaging and replanning (NCCN, 2025).

The NCCN's hepatocellular cancer guidelines state that IGRT is strongly recommended when using EBRT to reduce treatment-related toxicity and improve treatment accuracy (NCCN, 2025).

The NCCN guideline for NSCLC states that IGRT, including (but not limited to) orthogonal pair planar imaging and/or volumetric imaging, is recommended when using stereotactic ablative radiotherapy, 3D-CRT/IMRT, and proton therapy, with steep dose gradients around the target, when OARs are in close proximity to high-dose regions, and when using complex motion management techniques (NCCN, 2026).

The NCCN's guideline for soft tissue sarcoma states that when EBRT is used, treatment planning for retroperitoneal/intra-abdominal sarcoma with IGRT can be used to improve the therapeutic ratio (NCCN, 2025).

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.

Radiation therapy is a procedure and, therefore, is not subject to FDA regulation. However, the FDA has approved the accelerators and other equipment used to generate and deliver proton beam radiation therapy. Refer to the following website for more information (use product code LHN): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 11, 2025)

The FDA has approved a number of devices for use in intensity-modulated radiation therapy, stereotactic body radiation therapy, and stereotactic radiosurgery. 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.
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Policy History/Revision Information

Date	Summary of Changes

03/01/2026	**Coverage Rationale**
	Radiation Therapy Fractionation
	Breast Adenocarcinoma
	• Revised coverage criteria:
	  ○ Added criterion requiring "delivery of up to 10 fractions for accelerated partial-breast irradiation with 3D technique"
	  ○ Replaced criterion requiring "delivery of up to 33 fractions (inclusive of a boost to the tumor bed) when the individual has a connective tissue disorder such as lupus or scleroderma" with "delivery of up to 33 fractions (inclusive of a boost to the tumor bed) when the individual has a connective tissue disorder such as *systemic* lupus *erythematosus* or scleroderma"
	Image-Guided Radiation Therapy
	• Added instruction to refer to the coding clarifications in the *Applicable Codes* section of the policy
	• Removed language indicating image-guided radiation therapy (IGRT) is not medically necessary for superficial treatment of skin cancer including superficial radiation therapy or electronic brachytherapy when the [listed] criteria are not met
	Definitions
	• Updated definition of "Definitive Treatment"
	Coding Clarifications
	CPT Codes 77402, 77407, and 77412
	• Added notation to indicate:
	  ○ Radiation treatment delivery should be reported using the appropriate level of complexity
	  ▪ Conventional single electron field, multiple electron fields, or 2D photons should be reported under CPT code 77402 (Level 1)
	  ▪ Standard single-isocenter 3D or intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) treatments should be reported under CPT code 77407 (Level 2)
	  ▪ CPT code 77412 should be used only when delivery requires multiple isocenters with photon therapy, single-isocenter treatment with active motion-management techniques, total-skin electrons, or mixed electron/photon fields (Level 3); when CPT code 77412 is reported, documentation must clearly describe the circumstances that justify Level 3 rather than Level 2 treatment delivery
	  ○ When image-guided radiation therapy is used with 2D, 3D, IMRT techniques, the technical component is included under CPT codes 77402, 77407, and 77412 and should not be reported separately; the professional component of IGRT should be reported as 77387-26
	CPT Codes 77436, 77437, 77438, and 77439
	• Updated notation to indicate megavoltage planning, imaging, and treatment delivery codes should not be reported during superficial, surface, or orthovoltage radiation therapy regardless of the number of treatment sites; CPT codes 77436, 77437, 77438, and 77439 should be reported for superficial, surface, or orthovoltage radiation therapy
	CPT Code 77331
	• Updated notation to indicate special dosimetry (CPT code 77331) should be used to document the measurement of radiation dose at a specific point within a treatment area using specialized devices such as thermoluminescent dosimeters, optically simulated dosimeters, diode probes, special dosimetry probes, film dosimetry, and implanted markers
	  ○ CPT code 77331 is used when radiation dose measurements are needed in treatment areas that fall outside the standard parameters of the treatment planning system or equipment calibration
	  ○ When special dosimetry is requested, the number of measurements typically ranges from one to six, depending on the clinical need; any requests beyond this standard range must be supported with documentation and will be considered on a case-by-case basis

Date	Summary of Changes
	○ IMRT planning (CPT code 77301) includes special dosimetry CPT Code 77301 • Removed notation indicating CPT code 77301 is considered for coverage only when the primary radiation procedure is proven and medically necessary **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version 2026T0613K

Instructions for Use

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

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

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