

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

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Community Plan Policy

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Medicare Advantage Coverage Summary

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Application

UnitedHealthcare Commercial

This Medical Policy applies to all UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

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

Coverage Rationale

Radiation Therapy Fractionation

Bone Metastases

When providing palliative external beam radiation therapy (EBRT) for the treatment of a bone metastasis 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 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
 - Post-mastectomy radiation therapy; or
 - Individual has received previous thoracic radiation therapy; or

- Individual has a connective tissue disorder such as lupus 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 medical 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's 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 (IGRT)

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 previously irradiated area; or
- When implanted fiducial markers are being used for target localization; or
- During definitive treatment using 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
 - Left breast cancer and deep inspiration breath hold (DIBH) technique is being used
 - Patient is being treated in prone position
 - 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

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

- Superficial treatment of skin cancer including superficial radiation therapy or electronic brachytherapy
- To align bony landmarks without implanted fiducials (e.g. during palliative radiation therapy)

Note: Refer to the [Coding Clarification](#) section for special services and use of IGRT with brachytherapy, SRS, and SBRT.

Documentation Requirements

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 documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

CPT/HCPCS Code	Required Clinical Information
Radiation Therapy: Fractionation, Image-Guidance, and Special Services	
Refer to the Applicable Codes section for a complete list of codes and their descriptions.	<p>Radiation Therapy Fractionation</p> <p>Medical notes documenting the following, when applicable:</p> <ul style="list-style-type: none">• Diagnosis• History of present illness• Prior irradiated areas and their prescriptions• Proposed radiation prescription:<ul style="list-style-type: none">○ Number of fractions○ Dose per fraction○ Total dose <p>Image-Guided Radiation Therapy (IGRT)</p> <p>Medical notes documenting the following, when applicable:</p> <ul style="list-style-type: none">• Diagnosis• History of present illness• Current and previous treatments such as:<ul style="list-style-type: none">○ Will you be radiating a previously irradiated area or an area directly adjacent to a previously irradiated area○ Will IGRT be used in conjunction with another radiation therapy modality○ Treatment modality• Patient BMI• Proposed treatment plan

Definitions

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:

- IGRT cannot be reported separately with stereotactic body radiation therapy (SBRT) or stereotactic radiosurgery (SRS) (ASTRO, 2023)
- IGRT codes should not be used for imaging performed during brachytherapy. Verification of applicator position should be reported using simple simulation CPT code 77280 (ASTRO, 2023)
- **Special dosimetry** CPT code [77331](#) should be used to document the measurement of radiation dose using special radiation equipment such as thermoluminescent dosimeters (TLD), solid state diode probes, or special dosimetry probes

When special dosimetry is requested, the usual frequency will vary from one to six measurements. Any additional request will be evaluated on a case-by-case basis. IMRT planning (77301) includes special dosimetry (ASTRO, 2023)

- **Special medical radiation physics consultation** CPT code [77370](#) should be reported once under the following circumstances: brachytherapy, stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT), use of radioisotopes, patient has an implanted cardiac devices, reconstruction of previous radiation therapy plan, pregnant patient undergoing radiation therapy, or fusion of three-dimensional image sets such as positron emission tomography (PET) scan or magnetic resonance imaging (MRI) scan. IMRT planning (77301) includes fusion of three-dimensional image sets such as PET scan or MRI scan. (ASTRO, 2023)
- **Special treatment procedure** CPT code [77470](#) should be reported once under the following circumstances: brachytherapy, concurrent use of chemotherapy (except Herceptin use in breast cancer), reconstruction and analysis of previous radiation therapy plan, hyperthermia, total and hemi-body irradiation, per oral or endocavitary irradiation, and pediatric patient requiring anesthesia (ASTRO, 2023)
- **Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services** CPT code [77399](#) should only be reported if no other code adequately describes the procedure or service in question (ASTRO, 2023)

Note: CPT codes 77331, 77301, 77370, 77470, 77399 are considered for coverage only when the primary radiation procedure is proven and medically necessary.

CPT Code	Description
77014 See coding clarification	Computed tomography guidance for placement of radiation therapy fields
77331 See coding clarification	Special dosimetry (e.g., TLD, microdosimetry) (specify), only when prescribed by the treating physician
77370 See coding clarification	Special medical radiation physics consultation
77385	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
77386	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex
77387 See coding clarification	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
77399 See coding clarification	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
77401	Radiation treatment delivery, superficial and/or ortho voltage, per day
77402	Radiation treatment delivery, => 1 MeV; simple
77407	Radiation treatment delivery, => 1 MeV; intermediate
77412	Radiation treatment delivery, => 1 MeV; complex
77470 See coding clarification	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

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HCPCS Code	Description
G6001 See coding clarification	Ultrasonic guidance for placement of radiation therapy fields
G6002 See coding clarification	Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy
G6003	Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple blocks or no blocks: up to 5 mev
G6004	Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple blocks or no blocks: 6-10 mev
G6005	Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple blocks or no blocks: 11-19 mev
G6006	Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple blocks or no blocks: 20 mev or greater
G6007	Radiation treatment delivery, two separate treatment areas, three or more ports on a single treatment area, use of multiple blocks: up to 5 mev
G6008	Radiation treatment delivery, two separate treatment areas, three or more ports on a single treatment area, use of multiple blocks: 6-10 mev
G6009	Radiation treatment delivery, two separate treatment areas, three or more ports on a single treatment area, use of multiple blocks: 11-19 mev
G6010	Radiation treatment delivery, two separate treatment areas, three or more ports on a single treatment area, use of multiple blocks: 20 mev or greater
G6011	Radiation treatment delivery, three or more separate treatment areas, custom blocking, tangential ports, wedges, rotational beam, compensators, electron beam; up to 5 mev
G6012	Radiation treatment delivery, three or more separate treatment areas, custom blocking, tangential ports, wedges, rotational beam, compensators, electron beam; 6-10 mev
G6013	Radiation treatment delivery, three or more separate treatment areas, custom blocking, tangential ports, wedges, rotational beam, compensators, electron beam; 11-19 mev
G6014	Radiation treatment delivery, three or more separate treatment areas, custom blocking, tangential ports, wedges, rotational beam, compensators, electron beam; 20 mev or greater
G6015	Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session
G6016	Compensator-based beam modulation treatment delivery of inverse planned treatment using three or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session
G6017 See coding clarification	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

Description of Services

A course of radiation therapy is comprised of a series of distinct activities which includes 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, through the patient's course of treatment. The team works together to coordinate the patient's clinical treatment plan including consultations and evaluations, developing the appropriate dosimetry calculations and isodose plan, building treatment devices to refine treatment delivery, as needed, delivering the radiation therapy, and performing any other special services required to ensure safe and precise delivery of radiation therapy (ASTRO 2023).

External beam radiation therapy (EBRT) includes the following: three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), and proton beam radiation therapy (PBRT). 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, 2023).

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

Hypofractionated radiotherapy is the delivery of fewer and larger (> 200 cGy) doses of radiation. Hypofractionation is defined in this guideline as EBRT with a fraction size between 240 cGy and 340 cGy (Morgan 2018, Smith 2018).

Special treatment procedure covers additional physician effort, work, and technical resources involved during complex radiation treatment procedures e.g., brachytherapy, concurrent use of intravenous chemotherapy (except Herceptin use in breast cancer), reconstruction and analysis of previous radiation therapy plan, hyperthermia, total and hemi-body irradiation, per oral or endocavitary irradiation, and pediatric patient requiring anesthesia (ASTRO 2023).

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 qualified medical physicist e.g., brachytherapy, use of radioisotopes, patient has an implanted pacemaker or defibrillator device, reconstruction of previous radiation therapy plan, pregnant patient undergoing radiation therapy or fusion of three-dimensional image sets such as PET scan or MRI scan (not separately reportable with IMRT planning code 77301) (ASTRO 2023).

Clinical Evidence

Bone Metastases

Migliorini et al. (2021) conducted a meta-analysis comparing the most commonly used radiotherapy regimens for palliative management in patients with skeletal metastases. In October 2020, the main databases were accessed and all randomized clinical trials (RCTs) evaluating irradiation of bone metastases were included. Irradiation patterns of 8 Gy- and 10 Gy/single fraction, 20 Gy/5 fractions, 30 Gy/10 fractions were included in the meta-analysis. Data from 3595 patients were analyzed. The mean follow-up was 9.5 (1 to 28) months. The cumulative mean age was 63.3 ±2.9. 40.61% (1461 of 3595 patients) were female. The 8Gy/single fraction protocol detected reduced rate of "no pain response" (LOR 3.39), greater rate of "pain response" (LOR-5.88) and complete pain remission (LOR-7.05) compared to 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 re-irradiation (LOR 2.97) compared to 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, re-irradiations, pathological fractures, and spinal cord compression. There were no differences in terms of survivorship compared to the other multiple dose patterns.

Chow et al. (2014) conducted a multi-center, non-blinded, randomized, controlled trial to assess two dose fractionation schedules in patients with painful bone metastases needing repeat radiation therapy. Patients 18 years or older who had radiologically confirmed, painful (i.e., pain measured as ≥ 2 points using the Brief Pain Inventory) bone metastases, had received previous radiation therapy, and were taking a stable dose and schedule of pain-relieving drugs (if prescribed). Patients were randomly assigned (1:1) to receive either 8 Gy in a single fraction or 20 Gy in multiple fractions. The primary endpoint was overall pain response at 2 months, which was defined as the sum of complete and partial pain responses to treatment, assessed using both Brief Pain Inventory scores and changes in analgesic consumption. A total of 425 patients were enrolled however, 19 (4%) patients in the 8 Gy group and 12 (3%) in the 20 Gy group were found to be ineligible after randomization, and 140 (33%) and 132 (31%) patients, respectively, were not assessable at 2 months and were counted as missing data in the intention-to-treat analysis (ITT). The ITT population comprised 118 (28%) patients allocated to 8 Gy treatment and 135 (32%) allocated to 20 Gy treatment had an overall pain response to treatment ($p = 0.21$; response difference of 4.00% [upper limit of the 95% CI 9.2, less than the prespecified non-inferiority margin of 10%]). In the per-protocol population, 116 (45%) patients and 134 (51%) patients, 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 non-inferiority margin of 10%]). The most frequently reported acute radiation-related toxicities at 14 days were lack of appetite (201 [56%] assessable patients who received 8 Gy vs. 229 [66%] assessable patients who received 20 Gy; $p = 0.011$) and diarrhea (81 [23%] patients vs. 108 [31%] patients; $p = 0.018$). Pathological fractures occurred in 30 (7%) patients assigned to 8 Gy and 20 (5%) patients 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 (2%) patients versus two (< 1%) patients, respectively (OR 3.54, 95% CI 0.73–17.15; $p = 0.094$). The authors concluded that in patients with painful bone metastases requiring repeat radiation therapy, treatment with 8 Gy in a single fraction seems to be non-inferior 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 patients with painful bone metastases. A search was performed to identify eligible studies using the MEDLINE, EMBASE, and the Cochrane Collaboration library electronic databases. Studies that met the following criteria were eligible: a portion of the participants received reirradiation at the site of initial radiation therapy for radiation-refractory metastatic bone pain; both the initial treatment and the retreatment consisted of localized EBRT; reported outcomes included (at least) pain response after reirradiation; and 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-patient level, the sample size was considered too small, or all patients 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 patients were initially treated for metastatic bone pain, 527 (20%) patients underwent reirradiation. With reirradiation, the number of fractions administered ranged from a single fraction to 13 fractions. Overall, a pain response after reirradiation was achieved in 58% of patients (pooled overall response rate 0.58, 95% CI 0.49 to 0.67). There was a significant between-study heterogeneity ($I^2 = 63.3\%$, $p = 0.01$) because of the clinical and methodological differences between the studies. The authors concluded that reirradiation of radiation-refractory bone pain is effective, but approximately 40% of patients do not seem to benefit from reirradiation, and more research is needed to provide optimal palliative care.

Hartsell et al. (2005) conducted multi-center, phase III, 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 two weeks. Patients with breast or prostate cancer who had one to three sites of painful bone metastases and moderate to severe pain were eligible for participation. Patients 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 three months after randomization was evaluated with the Brief Pain Inventory. A total of 455 patients were allocated to the 8 Gy arm and 443 patients to the 30 Gy arm; pretreatment characteristics were equally balanced between arms. Grade 2–4 acute toxicity was more frequent in the 30 Gy arm (17%) than in the 8 Gy arm (10%) (difference = 7%, 95% CI = 3% to 12%; $p = 0.002$). Late toxicity was rare (4%) in both arms. The overall response rate was 66%. 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 three months, 33% of all patients no longer required narcotic medications. The incidence of subsequent pathologic fracture was 5% for the 8 Gy arm and 4% for 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 Three months and were well tolerated with few adverse effects. The 8 Gy arm had a higher rate of re-treatment but had less acute toxicity than the 30 Gy arm.

Clinical Practice Guidelines

American College of Radiology (ACR)

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 5 fractions, 24 Gy in 6 fractions, or 30 Gy in 10 fractions (Lo et al., 2013).

American Society for Radiation Oncology (ASTRO)

ASTRO's guideline on palliative radiation therapy for bone metastases states that up to 10 Gy fractions have been shown to be effective for the treatment of pain and/or prevention of morbidity from peripheral bone metastases (Lutz et al., 2017).

European Society for Therapeutic Radiology and Oncology (ESTRO)

The ESTRO Advisory Committee for Radiation Oncology Practice (ACROP) regarding EBRT for complicated bone metastases recommends that in the absence of high level comparative data, a dose of 30Gy in 10 fractions should be used postoperatively, and in the absence of comparative data, a single dose of 8 Gy, or fractionated schedule such as 20 Gy in 5 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 5 fractions, or 30 Gy in 10 fractions are recommended. Additionally, surgery and post-operative 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 5 fractions, or 30 Gy in 10 fractions. Lastly, bone metastases with extra-osseous extension may be treated with palliative radiotherapy encompassing the entire tumor mass, using for example, a single dose of 8 Gy, 20 Gy in 5 fractions, or 30 Gy in 10 fractions (Oldenburger et al., 2022).

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for palliative care states single-fraction palliative RT may be used to address pain associated with bone metastases. Study data suggest that 40% of patients (122/298) who received a single 8 Gy RT dose for painful bone metastases experienced pain reduction and improved quality of life within 10 days (NCCN, 2023).

Breast Adenocarcinoma

Brunt et al. (2020) performed a phase 3, randomized, multicenter trial to identify a five-fraction schedule of adjuvant RT delivered in one week that is non-inferior in terms of local cancer control, and as safe as the standard 15 fraction regimen after primary surgery for early breast cancer. Patients that were 18 years or older with invasive breast cancer (pT1–3, pN0–1, M0) who had breast conservation surgery or mastectomy were eligible. The study included 97 hospitals, 4096 patients, who were randomly assigned to either 40 Gy in 15 fractions over 3 weeks (n = 1361), 27 Gy in five fractions over one week (n = 1367), or 26 Gy in five fractions over one week (n = 1368) to the whole breast or chest wall. Ipsilateral breast tumor relapse was the primary endpoint. 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 endpoint event occurred in 79 patients (31 in the 40 Gy group, 27 in the 27 Gy group, and 21 in the 26 Gy group); hazard ratios versus 40 Gy in 15 fractions were 0.86 for 27 Gy in five fractions, and 0.67 for 26 Gy in five fractions. Five-year incidence of ipsilateral breast tumor relapse after 40 Gy was 2.1%; estimated absolute differences versus 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 was reported for 98 of 986 (9.9%) 40 Gy patients, 155 (15.4%) of 1005 27 Gy patients, and 121 of 1020 (11.9%) 26 Gy patients. Across all clinician assessments from 1–5 years, odds ratios versus 40 Gy in 15 fractions were 1.55 for 27 Gy in five fractions, and 1.12 for 26 Gy in five fractions. Patient and photographic assessments showed higher normal tissue effect risk for 27 Gy versus 40 Gy but not for 26 Gy versus 40 Gy. The authors concluded that 26 Gy in five fractions over one week was non-inferior to 40 Gy in 15 fractions over three weeks in terms of local tumor control, and is as safe for normal tissue effects up to five years for this patient population. Limitations to this study include lack of masking.

Liu et al. (2020) conducted a meta-analysis and systemic review to compare the toxicity and efficacy of hypofractionated radiotherapy with conventional fractionated radiotherapy in postmastectomy breast cancer patients (n = 3871). The primary endpoint was overall survival with disease-free survival, locoregional recurrence, distance metastasis, acute skin toxicity, acute lung toxicity, late skin toxicity, lymphedema, shoulder restriction, and late cardiac related toxicity as the secondary endpoints. The review included 25 studies, one RCT and 24 retrospective studies. The meta-analysis found no significant differences in the primary or secondary endpoints between the two groups. The authors concluded hypofractionated radiotherapy is not significantly different compared to conventional fractionated radiotherapy with respect to efficacy or toxicity in postmastectomy breast cancer. The authors recommended future large-scale RCTs to confirm this conclusion along with long-term follow-up of patients who experience late toxicities.

Shaitelman et al. (2015) conducted multi-center, unblinded, randomized trial to assess acute and six-month toxicity and quality of life with conventionally fractionated WBI (CF-WBI) versus HF-WBI. Women eligible for enrollment were age ≥ 40 years with pathologically-confirmed female carcinoma in situ (DCIS) or invasive breast cancer, stage Tis-T2, N0-N1a, M0, treated with breast conserving surgery with final negative margins (defined as no tumor on ink), with the physician-declared intent to deliver whole-breast irradiation (WBI) without addition of a third field to cover the regional lymph nodes. Patients 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 final margins were negative by ≥ 2mm or if there was a negative re-excision was 10 Gy in 4 fractions or 12.5 Gy in 5 fractions for HF-WBI and CF-WBI, respectively, and 12.5 Gy in 5 fractions or 14 Gy in 7 fractions if final margins were < 2mm for HF-WBI and CF-WBI, respectively. Outcomes of interest included physician-reported acute and six-month toxicities using National Cancer Institute Common Toxicity Criteria (NCICTC) v4.0 and patient-reported quality of life using the Functional Assessment of Cancer Therapy – Breast (FACT-B) version 4. A total of 287 patients were randomized and evaluable. Of 149 patients randomized to CF-

WBI, all (100%) received the allocated WBI and boost doses. Of 138 patients 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 (1%) patient randomized to HF-WBI received conventional fractionation (46 Gy in 23 fractions followed by a 14 Gy in 7 fraction boost). Median number of elapsed days over which radiation was delivered was 36 days for CF-WBI (IQR 35–36) and 22 days for HF-WBI (IQR 22–23). Half of the treatment plans (143) involved a D_{max} of 107% of prescription dose or higher. Treatment arms were well-matched for baseline characteristics including FACT-B 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 patients 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 patients randomized to HF-WBI (p = 0.01), and patients 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 patient-reported lack of energy (OR 0.39, 95% CI 0.24 to 0.63) and trouble meeting family needs (OR 0.34, 95% CI 0.16 to 0.75). The authors concluded that HF-WBI appears to yield less acute toxicity than CF-WBI, as well as less fatigue and trouble meeting family needs six months after completing radiation, and that these findings should be communicated to patients as part of shared decision-making.

Haviland et al. (2013) conducted a prespecified analysis as a 10-year update to the UK Standardisation of Breast Radiotherapy (START) trials (ISRCTN59368779). The START trials (START-A and START-B) were multi-center, randomized, unmasked trials. Patients were recruited after complete excision of primary invasive breast cancer (pT1–3a, pN0–1, M0) and referred for radiotherapy as part of standard treatment. Patients in START-A (n = 2,236) were randomly assigned to either 50 Gy in 25 fractions (control group) or 41.6 Gy in 13 fractions or 39 Gy in 13 fractions over five weeks and START-B patients (n = 2,215) to either 50 Gy in 25 fractions (control group) over five weeks or 40 Gy in 15 fractions over three weeks. Five-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, patients in START-A had a median follow-up of 9.3 years (IQR 8.0 to 10.0), after which 139 local-regional relapses had occurred. Ten-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 to 8.5 vs. 7.4%, 5.5 to 10.0; Hazard Ratio [HR] 0.91, 95% CI 0.59 to 1.38; p = 0.65) or the 39 Gy (8.8%, 95% CI 6.7 to 11.4) and 50 Gy regimen groups (HR 1.18, 95% CI 0.79 to 1.76; p = 0.41). In START-A, moderate or marked breast induration, telangiectasia, and breast edema were significantly less common normal tissue effects in the 39 Gy group than in the 50 Gy group. Normal tissue effects did not differ significantly between 41.6 Gy and 50 Gy groups. Patients in START-B had a median follow-up of 9.9 years (IQR 7.5 to 10.1), after which 95 local-regional relapses had occurred. The proportion of patients with local-regional relapse at 10 years did not differ significantly between the 40 Gy group (4.3%, 95% CI 3.2 to 5.9) and the 50 Gy group (5.5%, 95% CI 4.2 to 7.2; HR 0.77, 95% CI 0.51 to 1.16; p = 0.21). In START-B, breast shrinkage, telangiectasia, and breast edema were significantly less common normal tissue effects in the 40 Gy group than in the 50 Gy group. The authors concluded that long-term follow-up confirms that appropriately dosed hypofractionated radiotherapy is safe and effective for patients with early breast cancer, and that their results support the continued use of 40 Gy in 15 fractions.

Whelan et al. (2010) conducted a multi-center, randomized trial to determine whether a hypofractionated 3-week schedule of whole-breast irradiation 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 whole-breast irradiation either at a standard dose of 50.0 Gy in 25 fractions over a period of 35 days (the control group) or at a dose of 42.5 Gy in 16 fractions over a period of 22 days (the hypofractionated-radiation group). After completion of radiation therapy, patients were seen every six months for five 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 patients 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 assigned to standard irradiation as compared with 6.2% among the 622 women 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 as 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 ten years after treatment, accelerated, hypofractionated whole-breast irradiation 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)

ASTRO's guideline on radiation therapy for the whole breast states that for women with invasive breast cancer receiving WBI with or without inclusion of the low axilla, the preferred dose-fractionation scheme is HF-WBI to a dose of 4000 Gy in 15 fractions or 4250 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 1250 Gy in 5 fractions or 1400 to 1600 Gy in 7 to 8 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)

NCCN's guideline for breast cancer states the whole breast should receive a hypofractionated dose of 40–42.5 Gy in 15–16 fractions; in selected cases 45–50.4 Gy in 25–28 fractions may be considered. A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–8 fractions (NCCN, 2023).

National Institute for Health and Care Excellence (NICE)

The NICE guideline (2018; updated 2023) for diagnosis and management of breast cancer states:

- Deep inspiratory breath-hold radiotherapy technique for people with left-sided breast cancer should be used to reduce the dose to the heart
- The standard dose fractionation recommended for use with EBRT is 40 Gy in 15 fractions for women with invasive breast cancer after breast-conserving surgery or mastectomy
- Offer 26 Gy in 5 fractions over one week for people with invasive breast cancer 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 three weeks for people with invasive breast cancer 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 multi-center, open-label randomized trial to compare overall survival after standard-dose versus high-dose conformal radiotherapy with concurrent chemotherapy and the addition of cetuximab to concurrent chemoradiation for patients with inoperable stage III non-small-cell lung cancer. Patients (aged ≥ 18 years) with unresectable stage III non-small-cell lung cancer, a Zubrod performance status of 0-1, 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 patients also received concurrent chemotherapy with 45 mg/m² paclitaxel and carboplatin once a week; two weeks after chemoradiation, two cycles of consolidation chemotherapy separated by three weeks were given consisting of paclitaxel (200 mg/m²) and carboplatin. The radiation dose was prescribed to the planning target volume and was given in 2 Gy daily fractions with either IMRT or 3D-CRT. The coprimary objectives were to compare the overall survival of patients given 74 Gy with those given 60 Gy conformal radiation therapy with concurrent chemotherapy and to compare the overall survival of patients given cetuximab with those not given cetuximab. There were several secondary objectives including a comparison of progression-free survival and local regional tumor control, comparison of toxic effects between 74 Gy versus 60 Gy, and between cetuximab versus without cetuximab, to assess patient-reported quality of life in each group of the trial and to explore biological markers that might predict clinical outcome. One hundred and sixty-six patients were randomly assigned to receive standard-dose chemoradiotherapy, 121 to high-dose chemoradiotherapy, 147 to standard-dose chemoradiotherapy and cetuximab, and 110 to high-dose chemoradiotherapy and cetuximab. Median follow-up for the radiotherapy comparison was 22.9 months (IQR 27.5 to 33.3). Median overall survival was 28.7 months (95% CI 24.1 to 36.9) for patients who received standard-dose radiotherapy and 20.3 months (17.7 to 25.0) for those who received high-dose radiotherapy (HR 1.38, 95% CI 1.09 to 1.76; $p = 0.004$). Median follow-up for the cetuximab comparison was 21.3 months (IQR 23.5 to 29.8). Median overall survival in patients who received cetuximab was 25.0 months (95% CI 20.2 to 30.5) compared with 24.0 months (19.8 to 28.6) in those who did not (HR 1.07, 95% CI 0.84 to 1.35; $p = 0.29$). Both the radiation-dose and cetuximab results crossed protocol-specified futility boundaries. There were no statistical differences in grade 3 or worse toxic effects 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 patients; $p < 0.0001$). There were more treatment-related deaths in the high-

dose chemoradiotherapy and cetuximab groups (radiotherapy comparison: eight vs. three patients; cetuximab comparison: ten vs. five patients). There were no differences in severe pulmonary events between treatment groups. Severe esophagitis was more common in patients who received high-dose chemoradiotherapy than in those who received standard-dose treatment (43 [21%] of 207 patients vs. 16 [7%] of 217 patients; $p < 0.0001$). The authors concluded that 74 Gy radiation given in 2 Gy fractions with concurrent chemotherapy was not better than 60 Gy given in 2 Gy fractions plus concurrent chemotherapy for patients 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 overall survival for these patients.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO's guideline, Definitive Radiation Therapy in Locally Advanced Non-Small Cell Lung Cancer, states that the ideal dose fractionation for curative intent chemoradiation therapy is 60 Gy given in 2 Gy once daily fractions over six weeks (Rodrigues et al., 2015).

National Comprehensive Cancer Network (NCCN)

NCCN's guideline states the most commonly prescribed doses for definitive radiotherapy for locally advanced non-small cell lung cancer is 60 to 70 Gy fractions with a treatment duration of 6-7 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 organs at risk (OARs) are in close proximity to high dose regions, or when using complex motion management techniques (NCCN, 2023).

Prostate Adenocarcinoma

Murthy et al. (2021) conducted a phase III RCT comparing prophylactic whole-pelvic nodal radiotherapy to prostate only radiotherapy (PORT) in men with high-risk prostate cancer. Patients ($n = 224$) undergoing radical radiotherapy for node-negative prostate adenocarcinoma, with estimated nodal risk $\geq 20\%$ 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 two years androgen deprivation therapy were received by all patients. Biochemical failure-free survival (BFFS) for five years was the primary endpoint. Disease-free survival and overall survival were secondary endpoints. At a median follow-up of 68 months, 36 biochemical failures (PORT = 25, WPRT = 7) and 24 deaths (PORT = 13, WPRT = 11) were recorded. Five-year BFFS was 95.0% with WPRT versus 81.2% with PORT. WPRT also showed higher 5-year disease-free survival (89.5% v 77.2%), but 5-year overall survival did not appear to differ (92.5% v 90.8%). Distant metastasis-free survival was also higher with WPRT (95.9% v 89.2%). The authors concluded prophylactic WPRT using a contemporary dose and technique along with long-term androgen deprivation therapy for high-risk and very high-risk prostate cancer resulted in a large and significantly improved BFFS and disease-free survival as compared with PORT, but did not impact overall survival. The authors recommend prophylactic pelvic radiotherapy should be routinely considered for these patients 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 for 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 radiation therapy (> 2 Gy per fraction) were compared with men who had conventional radiation therapy using standard fractionation (1.8 Gy to 2 Gy per fraction). Ten studies were included in the review for a total of 8,278 men. The study found hypofractionation resulted in little to no difference in prostate cancer-specific survival, little to no difference in late radiation therapy genitourinary (GU) toxicity, and uncertainty regarding the effect of hypofractionation on late radiation therapy gastrointestinal (GI) toxicity. Secondary outcomes included little to no difference in acute GI radiation toxicity and little to no difference in metastasis-free survival, and a small reduction in recurrence-free survival. The authors concluded moderate hypofractionation (up to a fraction size of 3.4 Gy) resulted in similar outcomes in terms of disease-specific, metastasis-free, and overall survival with little to no increase in toxicity. Lee et al. (2016) which was previously cited in this policy, is included in this systematic review.

Catton et al. (2017) conducted a multi-center, randomized noninferiority trial to determine whether hypofractionation versus conventional fractionation is similar in efficacy without increased toxicity. Patients with intermediate-risk prostate cancer (T1 to 2a, Gleason score ≤ 6 , and prostate-specific antigen [PSA] 10.1 to 20 ng/mL; T2b to 2c, Gleason ≤ 6 , and PSA ≤ 20 ng/mL; or T1 to 2, Gleason = 7, and PSA ≤ 20 ng/mL) were eligible to participate. Patients were randomized to conventional radiation

therapy of 78 Gy in 39 fractions over eight weeks or to hypofractionated radiation therapy of 60 Gy in 20 fractions over four weeks. Androgen deprivation was not permitted with therapy. The primary outcome was biochemical-clinical failure (BCF) 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 patients were randomized, with 608 patients allocated to the hypofractionated radiation therapy group (short arm) and 598 patients to the control radiation therapy group (standard arm). Median follow-up was 6.0 years. Most of the events were PSA failures. The 5-year BCF disease-free survival was 85% in both arms (HR 0.96; 90% CI, 0.77 to 1.2). Ten deaths as a result of prostate cancer occurred in the short arm and 12 in the standard arm. No significant differences were detected between arms for grade \geq 3 late genitourinary and GI toxicity. The authors concluded that the hypofractionated radiation therapy regimen used in this trial was not inferior to conventional radiation therapy and was not associated with increased late toxicity. Furthermore, that authors state that hypofractionated radiation therapy is more convenient for patients and should be considered for intermediate-risk prostate cancer.

Dearnaley et al. (2016) conducted a multi-center, randomized non-inferiority trial comparing a conventionally fractionated schedule with two experimental hypofractionated schedules in men with localized prostate cancer. Men older than 16 years who had histologically confirmed T1b–T3aN0M0 prostate cancer and a WHO performance status of 0 or 1 were eligible. Patients 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 four weeks or 57 Gy in 19 fractions over 3.8 weeks) all delivered with intensity-modulated techniques. Most patients were given radiotherapy with three to six months of neoadjuvant and concurrent androgen suppression. The primary endpoint was time to biochemical or clinical failure; the critical HR for non-inferiority was 1.208. A total of 3,216 men were enrolled and randomly assigned (74 Gy group, 1,065 patients; 60 Gy group, 1,074 patients; 57 Gy group, 1,077 patients). The median follow-up was 62.4 months (IQR 53.9 to 77.0). The proportion of patients who were biochemical or clinical failure free at five years was 88.3% (95% CI 86.0 to 90.2) in the 74 Gy group, 90.6% (88.5 to 92.3) in the 60 Gy group, and 85.9% (83.4 to 88.0) in the 57 Gy group. Sixty Gy was non-inferior to 74 Gy (HR 0.84, 90% CI 0.68 to 1.03; $p = 0.0018$) but non-inferiority could not be claimed for 57 Gy compared with 74 Gy (HR 1.20, 0.99 to 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 five years after treatment using three clinician-reported as well as patient-reported outcome measures. The estimated cumulative five year incidence of Radiation Therapy Oncology Group (RTOG) 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, 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 non-inferior 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 multi-center, open label, randomized trial to investigate whether hypofractionated EBRT improves relapse-free survival without increasing toxic effects, compared with conventionally fractionated radiotherapy. Patients at intermediate- risk or high-risk, between 44 and 85 years of age with histologically confirmed stage T1b–T4 NX-0MX-0 prostate cancer, a prostate-specific antigen concentration of 60 ng/mL or lower, and a WHO performance status of 0–2 were eligible to participate. Enrolled participants were randomly assigned to receive either standard fractionation with 39 fractions of 2 Gy in eight weeks (five fractions per week) or hypofractionation with 19 fractions of 3.4 Gy in 6.5 weeks (three fractions per week). The primary endpoint was 5-year relapse-free survival and secondary outcomes included acute and late GU and GI toxicity. Non-inferiority 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 non-inferior to standard fractionated radiotherapy in terms of acute GU and GI toxicity for men with intermediate-risk and high-risk prostate cancer, and the cumulative incidence of grade 2 or worse acute GI toxicity was significantly higher in patients given hypofractionation than in those given standard fractionated radiotherapy. However, the authors also stated that before final conclusions can be made about the utility of hypofractionation, efficacy outcomes were 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 to 84.4) for patients assigned hypofractionation and 77.1% (71.9 to 81.5) for those allocated conventional fractionation (adjusted HR 0.86, 95% CI 0.63 to 1.16; log-rank $p = 0.36$). There were no treatment-related deaths. The authors concluded that based on all of 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 patients with intermediate-risk or high-risk prostate cancer.

Clinical Practice Guidelines

American Society for Radiation Oncology (ASTRO)

ASTRO's guideline on hypofractionated radiation therapy for the localized prostate cancer states that based on high-quality evidence, moderate hypofractionated EBRT (defined as 240 to 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 6000 Gy delivered in 20 fractions of 300 Gy and 7000 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 in hypofractionated and conventional treatments, and that 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 of Clinical Oncology (ASTRO)

In an AUA/ASTRO guideline on localized prostate cancer, Eastham et al. (2022) states that target localization, normal tissue avoidance, simulation, advanced treatment planning/delivery, and image-guidance procedures to optimize the therapeutic ratio of EBRT delivery for prostate cancer should be utilized. 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- or favorable intermediate-risk prostate cancer electing radiation therapy, dose-escalated hypofractionated EBRT (moderate or ultra), permanent low-dose rate (LDR) seed implant, or temporary high-dose rate (HDR) 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 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 utilize IMRT with doses between 45 Gy to 52 Gy. (Strong Recommendation; Evidence Level: Grade B)

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for prostate cancer states that a conventional fractionation regimen consists of 1.8 to 2.0 Gy in 37 to 45 fractions (NCCN 2023).

IGRT

Bockel et al. (2021) conducted a systematic review to assess the recent literature concerning three-dimensional image-guided brachytherapy (3D-IGBT) for reirradiation in the context of local recurrences from gynecological 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 2-5 years, and overall survival rates ranged from 39.5% to 78% at 2-5 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 studies. Several studies suggested that local control could be improved with 2 Gy equivalent doses > 40 Gy. The authors concluded that IGBT appears to be a feasible alternative to salvage surgery in inoperable patients or patients refusing surgery, with an acceptable outcome for patients who have no other curative therapeutic options, however at a high cost of long-term grade ≥ 3 toxicities in some studies. Due to the heterogeneity and the small size of populations reported in the studies, no formal conclusions or strict recommendations could be made, especially regarding the doses required to offer the best local control and the dose constraints applicable to the organ-at-risk. 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 the prone-positioned whole breast radiotherapy. Twenty prone-positioned breast patients 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 \times 16 for all of the patients and the treatments were delivered with the source to surface distance (SSD) setup technique. At every fraction of treatment, the patient was set up based on the body localization tattoos. Mega-voltage (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 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} , D_{max}), V_5 of the ipsilateral lung, the mean dose of heart, the mean and max dose of the left-anterior-descending coronary artery (LAD) among the four-imaging guidance (IG) schedules were made. Relative to the daily imaging guidance (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; but 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 SSD treatment technique, the daily imaging guidance can ensure dosimetric coverage of the target as well as preventing critical organs, especially LAD, from receiving unacceptable levels of 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 four-dimensional CT imaging, followed by daily IGRT with daily kilo-voltage Cone-beam computed tomography (kV CBCT) allows more accurate tumor targeting with improved local control and reduced side effects compared to weekly two-dimensional 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 3DCRT or IMRT. Outcomes included failure-free survival (FFS) for local (LFFS), regional (RFFS), locoregional (LRFFS), distant (DFFS) disease, progression-free survival, and overall survival and were estimated using 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 utilized in 36% (62 patients) of patients. Overall survival was similar between cohorts (2-year overall survival, 47% vs. 49%, $p = 0.63$). The IGRT cohort had improved two-year LFFS (80% vs. 64%, $p = 0.013$) and LRFS (75% and 62%, $p = 0.04$). Univariate analysis revealed that IGRT and treatment year improved LFFS while group stage, dose, and PET/CT planning had no impact. IGRT remained significant in the multivariate model with an adjusted HR of 0.40 ($p = 0.01$). DFFS (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 patients treated without IGRT.

Nabavizadeh et al. (2016) conducted a survey of the American Society for Radiation Oncology (ASTRO) physician membership to identify IGRT practice patterns, as well as IGRT's impact on clinical workflow and planning treatment volumes (PTVs). A sample of 5,979 treatment site-specific surveys were emailed to the membership of the ASTRO, with questions pertaining to IGRT modality/frequency, PTV expansions, method of image verification, and 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 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 megavoltage computed tomography [MVCT]), 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 utilization 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 standardized use of IGRT practices.

Wang et al. (2015) assessed late toxicities in patients with extremity soft tissue sarcoma treated with preoperative IGRT to a reduced target volume in a multi-institutional prospective phase II trial. Cohort A ($n = 12$) received IGRT with chemotherapy and cohort B ($n = 86$) received IGRT without chemotherapy, followed by limb-sparing resection. Patient position was adjusted before each treatment after daily pretreatment images were coregistered with digitally reconstructed radiographs. All patients received IGRT to reduced tumor volumes and late toxicities were assessed at two years. Due to poor accrual, cohort A was closed prematurely and was not reported. Seventy-nine eligible patients from cohort B formed the basis of this report. At a median follow-up of 3.6 years, five patients did not have surgery because of disease progression. There were five local treatment failures, all of which were in field. Of the 57 patients assessed for late toxicities at two years, 10.5% experienced at

least one grade ≥ 2 toxicity as compared with 37% of patients 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 receiving preoperative radiation therapy without IGRT ($p < .001$). The authors concluded there was a significant reduction of late toxicities in patients who were treated with preoperative IGRT and absence of marginal-field recurrences suggest that the target volumes used in the Radiation Therapy Oncology Group RTOG-0630 study are appropriate for preoperative IGRT for extremity soft tissue sarcoma. Limitations include lack of randomization, small study size, and lack of cohort A reporting.

Korreman et al. (2012) conducted a multi-center case series analysis to quantify the effects of four-dimensional computed tomography (4DCT), 4D image guidance (4D-IG), and beam gating on calculated treatment field margins in a lung cancer patient population. A total of 46 patients with non-small-cell lung cancer participated in four separate motion management protocols. Respiration-correlated imaging was performed for treatment planning purposes for all patients; nine patients were imaged with 4DCT scans, seven patients were imaged using fluoroscopy (with gold seeds in tumors), and 30 patients were imaged using 4DCT (five patients 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, the same for all patients. Required margins for respiratory motion management were calculated using the residual respiratory tumor motion for each patient for various motion management strategies. Margin reductions for respiration management were calculated using 4DCT, 4D-IG, and gated beam delivery. The median tumor motion magnitude was 4.4 mm for the 46 patients (range, 0 to 29.3 mm). This value corresponded to required treatment field margins of 13.7 to 36.3 mm (median 14.4 mm). The use of 4DCT, 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 4DCT scans and daily image guidance provides a potential reduction of 37% to 47% in treatment field margins and therefore, the 4D image guidance strategy was the most effective strategy for $> 85\%$ of the patients 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 necessary for patients with endometrial cancer 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 (range, 23 to 62). Of the 30 patients, 16.7% ($n = 5$) were normal weight (BMI < 25); 23.3% ($n = 7$) were overweight (BMI ≥ 25 to < 30); 26.7% ($n = 8$) were mildly obese (BMI ≥ 30 to < 35); and 33.3% ($n = 10$) were moderately to severely obese (BMI ≥ 35). 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 direction 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 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 and treated with conformal radiation therapy. Pretreatment MVCT 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, for patients with pathologically confirmed esophageal carcinoma and 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, MVCT 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 MVCT 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 standard deviations 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 MVCT scans before each treatment can effectively detect setup errors and thus reduce planning target volume margins. This will reduce 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 external-beam radiation therapy of patients with prostate cancer. A total of 427 patients 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 patient), portal images were taken of the first segment of all five beams. The irradiation time of the technique varied between 5–7 min. From these data, the location of gold markers could be established within 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 5–7 min. 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)

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 radiation therapy 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 radiation therapy delivery systems becomes as important as the dosimetric accuracy, meriting implementation of daily quality control procedures (Bissonnette, 2012).

American College of Radiology (ACR)

ACR's Practice Parameter for Image-Guided Radiation Therapy states 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 overall survival. 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 3-DCRT, IMRT, or heavy particle therapy. Common indications for IGRT include any target volume 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 where the adjacent area has been previously irradiated and abutting fields must be precise, or any scenario in which dose escalation is planned beyond the usual doses for similar tumors (ACR, 2019).

American Society for Radiation Oncology (ASTRO)

ASTRO's Coding Resource states IGRT can be considered when using 3-D CRT, IMRT, PBRT and external beam-based accelerated partial breast irradiation. Any time a target volume is located within or near critical structures, IGRT may be indicated to improve the therapeutic ration. Common clinical indications include, when the target volume is subject to daily variation due to internal motion, the immediately adjacent area has been previously irradiated, 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 superficial treatment of skin cancer or to align bony landmarks without implanted fiducials (ASTRO, 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 inter-professional communication. The white paper recommends that practitioners work together as a team to address environmental and technical concerns, documented standard operating procedures should be followed for planning to ensure PTVs are properly constructed, and that team members allow adequate time for quality assurance checks and to investigate any problems (Jaffray et al., 2013).

National Comprehensive Cancer Network (NCCN)

The NCCN guideline for biliary tract cancer states IGRT is strongly recommended when using RT, IMRT, and stereotactic body RT (SBRT) to improve treatment accuracy and reduce treatment-related toxicity (NCCN, 2023)

The NCCN guideline for gastric cancer states image guidance may be used appropriately to enhance clinical targeting (NCCN, 2023).

NCCN's head and neck cancers guideline states image guidance is required to provide assurance of accurate daily delivery. Anatomical changes including rapidly shrinking tumors, changes in air cavities, or significant weight loss may necessitate repeat diagnostic imaging and replanning (NCCN, 2023).

NCCN's hepatocellular cancer guideline states IGRT is strongly recommended when using EBRT to reduce treatment-related toxicity and improve treatment accuracy (NCCN, 2023).

The NCCN guideline for non-small cell lung cancer states IGRT including (but not limited to) orthogonal pair planar imaging and/or volumetric imaging, is recommended when using SABR, 3D-CRT/IMRT, and proton therapy with steep dose gradients around the target, when OARs are in close proximity to high-dose regions, and when using complex motion management techniques (NCCN, 2023).

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, 2023).

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 PBRT. Refer to the following website for more information (use product code LHN): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmnm.cfm>. (Accessed August 18, 2023)

The FDA has approved a number of devices for use in IMRT, SBRT and SRS. Refer to the following website for more information (use product codes MUJ and IYE): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmnm.cfm>. (Accessed August 18, 2023)

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Policy History/Revision Information

Date	Summary of Changes
02/01/2024	<p>Coverage Rationale</p> <p>Image-Guided Radiation Therapy (IGRT)</p> <ul style="list-style-type: none"> Replaced language indicating “IGRT is medically necessary during definitive treatment using 3D-CRT for breast cancer and hypofractionated radiation therapy delivered <i>over</i> five fractions to the whole breast or chest wall” with “IGRT is medically necessary during definitive treatment using 3D-CRT for breast cancer and hypofractionated radiation therapy delivered <i>up to</i> five fractions to the whole breast or chest wall” Revised list of circumstances for which IGRT is not medically necessary; removed: <ul style="list-style-type: none"> Brachytherapy Stereotactic body radiation therapy (SBRT) Stereotactic radiosurgery (SRS) Updated notation; removed list of examples of special services for use of IGRT <p>Applicable Codes</p> <ul style="list-style-type: none"> Added notation to indicate CPT codes 77301, 77331, 77370, 77399, and 77470 are considered for coverage only when the primary radiation procedure is proven and medically necessary Added instruction to refer to the <i>Coding Clarifications</i> section [of the policy] for CPT/HCPCS codes 77014, 77387, G6001, G6002, and G6017 <p>Supporting Information</p> <ul style="list-style-type: none"> Updated <i>Description of Services</i>, <i>Clinical Evidence</i>, and <i>References</i> sections to reflect the most current information Archived previous policy version 2023T0613F

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