Optum

Radiation therapy: Fractionation, image-guidance and special services

Clinical guidelines

Effective January 1, 2023

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Indications

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 is medically necessary for the following:
  - 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) is medically necessary for any of the following:
  - Treatment of supraclavicular and/or internal mammary lymph nodes
  - Postmastectomy radiation therapy
  - Individual has received previous thoracic radiation therapy
  - Individual has a connective tissue disorder such as lupus or scleroderma

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 for any of the following:
  - Individual with high-risk prostate cancer is undergoing radiation treatment to pelvic lymph nodes
  - Radiation therapy is delivered post-prostatectomy
  - Individual has a history of inflammatory bowel disease such as ulcerative colitis or Crohn's disease
  - 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 for any of the following:

- When used with intensity-modulated radiation therapy (IMRT)
- When used with proton beam radiation therapy (PBRT)
- When the target has received prior radiation therapy or abuts a previously irradiated area
- When the implanted fiducial markers are being used for target localization
- During definitive treatment with radiation therapy 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 over 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 the prone position
  - During boost treatment of rectal and bladder cancer
  - Esophageal cancer
  - Gastric cancer
  - Head and neck cancer
  - Hepatobiliary cancer
  - Lung cancer
  - Pancreatic cancer
  - Sarcoma

IGRT is considered not medically necessary for all other indications including but not limited to the following:

- Brachytherapy*
- Stereotactic body radiation therapy (SBRT)**
- Stereotactic radiosurgery (SRS)**
- Superficial treatment of skin cancer including superficial radiation therapy or electronic brachytherapy
- To align bony landmarks without implanted fiducials

Special services

Special services include the need for special dosimetry, special medical physics consultation, and special treatment procedures. Refer to Coding Notes for additional details.

Definitions

Limited metastatic disease: Absence of visceral metastasis and less than four bone metastases with no metastasis outside the vertebral bodies or pelvis (Parker et al., 2018).

General information

A course of radiation therapy involves a sequence of distinct activities including consultation, treatment planning, technical preparation and special services, treatment delivery, treatment management and follow-up care management. The team, led by a radiation oncologist, includes a medical radiation physicist, dosimetrist, radiation therapist, oncology nurses and ancillary staff working together to coordinate the patient's clinical treatment plan (ASTRO 2022).

External beam radiation therapy (EBRT) includes the following: three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), proton beam radiation therapy (PBRT), stereotactic body radiation therapy (SBRT) and stereotactic radiation surgery (SRS). External beam radiation, which aims high-energy rays or particles from outside the body into the tumor, is the most common type of radiation therapy used for cancer treatment (American Cancer Society, 2022).

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 et al., 2018; Smith et al., 2018).

Special treatment procedures cover additional physician effort, work and technical resources involved during complex radiation treatment procedures such as brachytherapy, concurrent use of intravenous chemotherapy (except Herceptin use in breast cancer), reconstruction and analysis of previous radiation therapy plans, hyperthermia, total and hemi-body irradiation, per oral or endocavitary irradiation, and pediatric patients requiring anesthesia (ASTRO 2022).

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, such as with brachytherapy, use of radioisotopes, implanted pacemakers or defibrillator devices, reconstruction of previous radiation therapy plans, pregnant patients 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 2022).

Documentation requirements

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

Radiation therapy fractionation

Medical notes documenting the following, when applicable:

- Diagnosis
- History of present illness
- Prior irradiated areas and their prescriptions
- Proposed radiation prescription:
  - Number of fractions
  - Dose per fraction
  - Total dose

Image-guided radiation therapy (IGRT)

Medical notes documenting the following, when applicable:

- Diagnosis
- History of present illness
- Current and prior treatments such as:
  - 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

Clinical evidence

Fractionation

Bone metastasis

Migliorini et al. (2021) conducted a meta-analysis comparing the most commonly used radiotherapy regimens for palliative management in patients with skeletal metastases. 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% (1,461 of 3,595 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 8Gy 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. 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. 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 authors identified 707 titles, of which 10 articles were selected for the systematic review and 7 were included in the meta-analysis. Of the 10 studies, 6 were randomized trials, 2 were cohort studies, and 2 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 study suggests reirradiation of radiation-refractory bone pain is effective, but approximately 40% of patients do not seem to benefit from reirradiation. More research is needed to identify optimal palliative care.

Clinical practice guidelines and specialty society statements

American College of Radiology (ACR)

An ACR 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, 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, 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 30 Gy in 10 fractions should be used postoperatively, and in the absence of comparative data, a single dose of 8 Gy or a fractionated schedule such as 20 Gy in 5 fractions or 30 Gy in 10 fractions may be used to prevent pathological fracture. ESTRO recommends where recalcification is the treatment objective, 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 or 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. Finally, 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 radiation therapy may be used to address pain associated with bone metastases. Study data suggest 40% of patients (122/298) who received a single 8 Gy dose for painful bone metastases experienced pain reduction and improved quality of life within 10 days (NCCN, 2022).

Breast adenocarcinoma

A meta-analysis and systematic review was conducted by Lui et al. (2020) 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, distant 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 study suggests hypofractionated radiotherapy is not significantly different compared to conventional fractionated radiotherapy with respect to efficacy or toxicity in postmastectomy breast cancer. Future large-scale RCTs are needed to confirm these results along with long-term follow-up of patients who experience late toxicities.

Shaitelman et al. (2015) conducted a multi-center, unblinded, randomized trial to assess acute and six-month toxicity and quality of life (QoL) with conventionally fractionated WBI (CF-WBI) versus HF-WBI. Women eligible for enrollment were age ≥ 40 years with pathologically confirmed 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 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 ≥2 mm 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 <2 mm 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 QoL 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 Dmax 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 QoL 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 5 weeks and START-B patients (n=2,215) to either 50 Gy in 25 fractions (control group) over 5 weeks or 40 Gy in 15 fractions over 3 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.

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 study suggests 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 and specialty society statements

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 hypofractionated-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 (Smith 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, 2022).

National Institute for Health and Care Excellence (NICE)

The NICE guideline (2018) for the 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 disease after breast-conserving surgery or mastectomy. Additionally, external beam boost to the tumor bed following whole-breast radiotherapy for women with invasive breast cancer and a high risk for local recurrence is recommended.

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-smallcell lung cancer. Patients (aged ≥ 18 years) with unresectable stage III non-smallcell 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; 2 weeks after chemoradiation, two cycles of consolidation chemotherapy separated by 3 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 intensity-modulated radiation therapy or three-dimensional conformal radiation therapy. The coprimary objectives were to compare the OS of patients given 74 Gy with those given 60 Gy conformal radiation therapy with concurrent chemotherapy and to compare the OS 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: 8 vs. 3 patients; cetuximab comparison: 10 vs. 5 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 and specialty society statements

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 6 weeks (Rodrigues 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 60–70 Gy fractions administered over a course of 6–7 weeks. Doses of at least 60 Gy should be given (NCCN, 2022).

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 ≥ 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 androgen deprivation therapy were received by all patients. Biochemical failure-free survival (BFFS) for 5 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 vs. 81.2% with PORT. WPRT also showed higher 5-year DFS (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 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 DFS as compared with PORT but did not impact OS. The authors recommend prophylactic pelvic radiotherapy should be routinely considered for these patients until the long-term outcomes of ongoing trials are reported.

In Cochrane systematic review, Hickey et al. (2019) compared hypofractionated EBRT and conventionally fractionated EBRT for men with clinically localized prostate cancer. 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 OS with little to no increase in toxicity.

Roach et al. (2018) provided a long-term update of the RTOG 9413 study that demonstrated WPRT plus neoadjuvant hormonal therapy improved PFS in patients with intermediate-risk or high-risk localized prostate cancer compared with PORT plus neoadjuvant hormonal therapy, WPRT plus adjuvant hormonal therapy, and PORT plus adjuvant hormonal therapy.

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 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 (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 RT group (short arm) and 598 patients to the control RT 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 ≥ 3 late genitourinary and GI toxicity. The authors concluded that the hypofractionated RT regimen used in this trial was not inferior to conventional RT and was not associated with increased late toxicity. Furthermore, the study suggests that hypofractionated RT is more convenient for patients and may be considered for intermediate-risk prostate cancer.

Dearnaley et al. (2016) conducted a multi-center, randomized noninferiority 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 4 weeks or 57 Gy in 19 fractions over 3.8 weeks) all delivered with intensity-modulated techniques. Most patients were given radiotherapy with 3 to 6 months of neoadjuvant and concurrent androgen suppression. The primary endpoint 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 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 5 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 noninferior to 74 Gy (HR 0.84, 90% CI 0.68 to 1.03; p=0.0018) but noninferiority 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 5 years after treatment using three clinician-reported as well as patient-reported outcome measures. The estimated cumulative 5-year incidence of 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 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 multi-center, open label, randomized trial to investigate whether hypofractionated external beam radiotherapy 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 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 endpoint was 5-year relapse-free survival and secondary outcomes included acute and late genitourinary and gastrointestinal toxicity. Noninferiority of hypofractionation was tested separately for genitourinary and gastrointestinal 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 genitourinary and gastrointestinal toxicity for men with intermediate-risk and high-risk prostate cancer, and the cumulative incidence of grade 2 or worse acute gastrointestinal 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 and specialty society statements

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 external beam radiation therapy (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 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 gastrointestinal (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 2018).

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

The AUA/ASTRO guideline (Eastham et al., 2022) on localized prostate cancer states that target localization, normal tissue avoidance, simulation, advanced treatment planning/delivery and image-guidance procedures to optimize the therapeutic ration of EBRT delivery for prostate cancer should be used. When EBRT is the primary treatment for prostate cancer, the guideline recommends dose escalation. Moderate hypofractionated EBRT should be recommended to low-risk and intermediate risk patients, and ultra hypofractionated EBRT for patients with low- or intermediate-risk prostate cancer may be considered. 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. In patients with low- or intermediate-risk prostate cancer, clinicians should not electively radiate pelvic lymph nodes. In patients with high-risk prostate cancer, clinicians may offer radiation to the pelvic lymph nodes. Finally, when treating the pelvic lymph nodes, clinicians should use IMRT with doses between 45 and 52 Gy.

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, 2022).

Image-guided radiation therapy (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. Fifteen studies met the author's search criteria and 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 organs at risk.

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×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, set up was 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 (D95, Dmax), V5 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 D95 of the target among NIG, DIG and WIG. The target Dmax also exhibited little changes among all the IG schedules. While V5 of the ipsilateral lung changed very little among all 4 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 ConeBeam 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 external beam radiation therapy with curative intent were included in the study. Patients in both cohorts (IGRT and non-IGRT) were treated with either three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT). Outcomes included failure-free survival (FFS) for local (LFFS), regional (RFFS), locoregional (LRFFS), distant (DFFS) disease, progression-free survival (PFS), and overall survival (OS) 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. OS was similar between cohorts (2-year OS, 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.

Nabavizadeh et al. (2016) conducted a 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 was emailed to the membership of the American Society for Radiation Oncology (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 intensity modulated radiation therapy (IMRT), lung three-dimensional conformal radiation therapy 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.

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; 9 patients were imaged with 4DCT scans, 7 patients were imaged using fluoroscopy (with gold seeds in tumors), and 30 patients were imaged using 4DCT (5 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 body mass index (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, 6 had uterine sarcoma, 21 had endometrioid adenocarcinoma, and 3 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 RT. Pretreatment megavoltage computed tomography (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; 8 had adenocarcinoma, and 2 had squamous cell carcinoma. After patients were positioned using their skin tattoos/marks, megavoltage computed tomography (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 study suggests that daily MVCT scans before each treatment can effectively detect setup errors and thus reduce planning target volume (PTV) 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 (Σ) were limited to <0.6 mm, and random errors (Σ) 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 and specialty society statements

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'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-D conformal radiation therapy (CRT), intensity-modulated radiation therapy (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 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, 2013).

Applicable codes

CPT® Code	Description
77014	Computed tomography guidance for placement of radiation therapy fields
77331	Special dosimetry (e.g., TLD, microdosimetry) (specify), only when prescribed by the treating physician. * See coding clarification below
77370	Special medical radiation physics consultation * See coding clarification below
77385	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
77386	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex
77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services * See coding clarification below
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	Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation) * See coding clarification below
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

Coding clarification

- Special dosimetry (CPT 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. Note that IMRT planning (77301) includes special dosimetry (ASTRO, 2022).
- Special medical radiation physics consultation (CPT 77370) should be reported once under the following circumstances: brachytherapy, SRS, SBRT, use of radioisotopes, patient has implanted cardiac device, reconstruction of previous radiation therapy plan, pregnant patient undergoing radiation therapy or fusion of three-dimensional image sets such as PET or MRI scans. Note that IMRT planning (77301) includes fusion of three-dimensional image sets such as PET or MRI (ASTRO, 2022).
- 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, 2022).
- Special treatment procedure (CPT 77470) should be reported once under the following circumstances: 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 2022).

*IGRT codes should not be used to report imaging during brachytherapy. Verification of applicator position should be reported using CPT 77280; simple simulation (ASTRO, 2022).

**IGRT cannot be reported separately with SBRT or SRS (ASTRO, 2022).

HCPCS Code	Description
G6001	Ultrasonic guidance for placement of radiation therapy fields
G6002	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	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

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Review and approval history

Version	Description of activity
1.0	New guideline effective January 1, 2023.

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