Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 1/1/25**
(See policy history boxes for previous effective dates)

Title: Intensity-Modulated Radiation Therapy (IMRT) of the Prostate

Description/Background

Prostate cancer is the second leading cause of cancer-related death among men in the U.S.[6] According to the most recent incidence data available from 2020, there were 201,082 reported new cases of prostate cancer among men in the United States. From 2016 to 2020, localized, regional, distant, and unknown stage prostate cancer accounted for 69.9%, 13.4%, 7.9%, and 8.8% of new cases, respectively. In 2020, the incidence of prostate cancer was highest for men 70 to 74 years of age and Black men. White (non-Hispanic) men had lower percentages of distant (7.7%) and unstaged prostate cancer (7.2%) than did any other race/ethnicity. With regard to survival for distant stage disease, 5-year survival was highest among Asian-Pacific islanders (45.4%), followed by Hispanics (38.8%), American Indian/Alaska natives (32.6%), Black (34.9%), and White (32.5%) men . Five-year survival for all stages combined was higher for Black men as compared to White or Hispanic men.

Prostate Cancer Treatment

For localized prostate cancer, radiotherapy (RT) is an accepted option for primary (definitive) treatment. Other options include surgery (radical prostatectomy), hormonal treatment, or active surveillance.

In the postoperative setting, radiotherapy to the prostate bed is an accepted procedure for patients with an increased risk of local recurrence, based on 3 randomized controlled trials that showed a significant increase in biochemical recurrence-free survival.[7,8,9] Professional society guidelines have recommended adjuvant radiotherapy for patients with adverse pathologic findings at the time of prostatectomy and salvage radiotherapy for patients with prostate-specific antigen recurrence or local recurrence after prostatectomy in the absence of metastatic disease.[10,5]

Radiotherapy Techniques

Radiation therapy may be administered externally (ie, a beam of radiation is directed into the body) or internally (ie, a radioactive source is placed inside the body, near a tumor).[11] External radiotherapy techniques include "conventional" or 2-dimensional (2D) RT, 3-dimensional (3D) conformal RT, and intensity-modulated radiation therapy (IMRT).

Conventional External Beam Radiotherapy

Methods to plan and deliver RT have evolved that permit more precise targeting of tumors with complex geometries. Conventional 2D treatment planning utilizes X-ray films to guide and position radiation beams.[11] Bony landmarks visualized on X-ray are used to locate a tumor and direct the radiation beams. The radiation is typically of uniform intensity.

Three-Dimensional Conformal Radiation

Radiation treatment planning has evolved to use 3D images, usually from computed tomography (CT) scans, to more precisely delineate the boundaries of the tumor and to discriminate tumor tissue from adjacent normal tissue and nearby organs at risk for radiation damage. Three-dimensional conformal RT (3D-CRT) involves initially scanning the patient in the position that will be used for the radiation treatment.[11] The tumor target and surrounding normal organs are then outlined in 3D on the scan. Computer software assists in determining the orientation of radiation beams and the amount of radiation the tumor and normal tissues receive to ensure coverage of the entire tumor in order to minimize radiation exposure for at risk normal tissue and nearby organs. Other imaging techniques and devices such as multileaf collimators (MLCs) may be used to "shape" the radiation beams. Methods have also been developed to position the patient and the radiation portal reproducibly for each fraction and to immobilize the patient, thus maintaining consistent beam axes across treatment sessions.

Intensity-Modulated Radiotherapy

Intensity-modulated radiation therapy is the more recent development in external radiation. Treatment planning and delivery are more complex, time-consuming, and labor-intensive for IMRT than for 3D-CRT. Similar to 3D-CRT, the tumor and surrounding normal organs are outlined in 3D by a scan and multiple radiation beams are positioned around the patient for radiation delivery.[11] In IMRT, radiation beams are divided into a grid-like pattern, separating a single beam into many smaller "beamlets". Specialized computer software allows for “inverse” treatment planning. The radiation oncologist delineates the target on each slice of a CT scan and specifies the target's prescribed radiation dose, acceptable limits of dose heterogeneity within the target volume, adjacent normal tissue volumes to avoid, and acceptable dose limits within the normal tissues. Based on these parameters and a digitally reconstructed radiographic image of the tumor, surrounding tissues, and organs at risk, computer software optimizes the location, shape, and intensities of the beam ports to achieve the treatment plan's goals.

Increased conformality may permit escalated tumor doses without increasing normal tissue toxicity and is proposed to improve local tumor control, with decreased exposure to surrounding normal tissues, potentially reducing acute and late radiation toxicities. Better dose homogeneity within the target may also improve local tumor control by avoiding underdosing within the tumor and may decrease toxicity by avoiding overdosing.

Other advanced techniques may further improve radiotherapy treatment by improving dose distribution. These techniques are considered variations of IMRT. Volumetric modulated arc therapy delivers radiation from a continuous rotation of the radiation source. The principal advantage of volumetric modulated arc therapy is greater efficiency in treatment delivery time,

reducing radiation exposure and improving target radiation delivery due to less patient motion. Image-guided RT involves the incorporation of imaging before and/or during treatment to more precisely deliver RT to the target volume.

Regulatory Status

In general, IMRT systems include intensity modulators, which control, block, or filter the intensity of radiation; and, RT planning systems which plan the radiation dose to be delivered.

A number of intensity modulators have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. Intensity modulators include the Innocure Intensity Modulating Radiation Therapy Compensators (Innocure) and Decimal Tissue Compensator (Southeastern Radiation Products), cleared in 2006 and 2004, respectively. FDA product code: IXI. Intensity modulators may be added to standard linear accelerators to deliver IMRT when used with proper treatment planning systems.

Radiotherapy planning systems have also been cleared for marketing by FDA through the 510(k) process. They include the Prowess Panther (Prowess), TiGRT (LinaTech), Ray Dose (Ray Search Laboratories), and the eIMRT Calculator (Standard Imaging). FDA product code: MUJ.

Fully integrated IMRT systems also are available. These devices are customizable, and support all stages of IMRT delivery, including planning, treatment delivery, and health record management. One such device to have been cleared for marketing by FDA through the 510(k) process is the Varian IMRT system (Varian Medical Systems). FDA product code: IYE.

Medical Policy Statement

Intensity-modulated radiotherapy (IMRT) may be considered established for the treatment of prostate cancer based on the analysis of dosimetric data including comparative models if necessary.

Inclusionary and Exclusionary Guidelines

Refer to Medical Policy Statement.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

77301	77338	77385	77386	77387	G6015
G6016					

Other codes (investigational, not medically necessary, etc.):

NA

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Multiple-dose planning studies have generated 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) treatment plans from the same scans, and then compared predicted dose distributions within the target and adjacent organs at risk. Results of such studies have shown that IMRT improves on 3D-CRT on conformality to, and dose homogeneity within, the target. Dosimetry using stationary targets generally confirms these predictions. Thus, radiation oncologists have hypothesized that IMRT may provide better treatment outcomes than 3D-CRT. However, these types of studies offer indirect evidence for IMRT treatment benefit, and it is difficult to relate dosing study results to actual effects on health outcomes.

Comparative studies of radiation-induced adverse effects from IMRT vs alternative radiation delivery are probably the most important evidence for establishing the benefit of IMRT. Single-arm series of IMRT can give insights into the potential for benefit, particularly if an adverse event that is expected to occur at high rates is shown to decrease by a large amount. Studies of treatment benefit are also important to establish whether IMRT is at least as good as other types of delivery, but, absent such comparative trials, it is likely that benefit from IMRT is at least as good as with other types of delivery.

In general, when the indication for IMRT is to avoid radiation to sensitive areas, dosimetry studies have been considered sufficient evidence to demonstrate that harm would be avoided using IMRT. For other indications, such as using IMRT to provide better tumor control, comparative studies of health outcomes are needed to demonstrate such a benefit.

Intensity-Modulated Radiotherapy for Primary (Definitive) Therapy for Localized Prostate Cancer

Clinical Context and Test Purpose

The purpose of IMRT in individuals who have localized prostate cancer and undergoing definitive radiotherapy (RT) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who have localized prostate cancer and are undergoing definitive therapy.

Interventions

The test being considered is IMRT.

Radiotherapy is an integral component of prostate cancer treatment. Intensity-modulated radiotherapy has been proposed as a method of external-beam RT that delivers adequate radiation to the tumor volume while minimizing the radiation dose to surrounding normal tissues and structures.

Comparators

The following test is currently being used to treat localized prostate cancer: 3D-CRT.

Outcomes

The general outcomes of interest are overall survival (OS), locoregional recurrence, quality of life, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

A meta-analysis by Yu et al (2016) included 23 studies (N=9556 patients) that compared IMRT with 3D-CRT for gastrointestinal (GI), genitourinary (GU), and rectal toxicity, biochemical control, and OS[12] Reviewers included 16 retrospective comparisons and 5 prospective cohort studies published before July 2015. The relative risk (RR) for the pooled analysis was considered significant if the 95% confidence interval did not overlap at 1 at the $p<0.05$ level. Intensity-modulated radiotherapy resulted in less acute and late GI toxicity, less rectal bleeding, and improved biochemical control (Table 1). There was a modest increase in acute GU toxicity, and no significant differences between the two treatments in acute rectal toxicity, late GU toxicity, and OS.

Table 1. Outcomes for IMRT Compared With 3D-CRT

Comparison	No. of Studies	No. of Patients	RR for IMRT vs 3D-CRT	95% CI
Acute GI toxicity	12	4142	0.59	0.44 to 0.78
Late GI toxicity	13	6519	0.54	0.38 to 0.78
Acute rectal toxicity	4	2188	1.03	0.45 to 2.36
Late rectal bleeding	5	1972	0.48	0.27 to 0.85
Acute GU toxicity	14	4603	1.08	1.00 to 1.17
Late GU toxicity	12	5608	1.03	0.82 to 1.30
Biochemical control	6	2416	1.17	1.08 to 1.27
Overall survival	3	924	1.07	0.96 to 1.19

3D-CRT: 3-dimensional conformal radiotherapy; CI: confidence interval; GI: gastrointestinal, grade 2-4 toxicity; GU: genitourinary, grade 2-4 toxicity; IMRT: intensity-modulated radiotherapy; RR: relative risk.

Bauman et al (2012) published a systematic review that assessed IMRT in the treatment of prostate cancer to quantify its potential benefits and to make recommendations for RT programs considering adopting this technique within Ontario, Canada.[13] Based on a review of 11 published reports through March 2009 (9 retrospective cohort studies, 2 RCTs) including 4559 patients, reviewers recommended IMRT over 3D-CRT for aggressive treatment of localized prostate cancer where an escalated radiation (>70 gray [Gy]) dose would be required. Four studies (3 retrospective cohort studies, 1 RCT) reported differences in adverse effects between IMRT and 3D-CRT. The RCT (N=78) reported significantly less frequent acute GI toxicity in the IMRT group than in the 3D-CRT group. This was true for grade 2, 3 or 4 toxicity (20% vs. 61%, p=.001), grade 3 or 4 toxicity (0% vs. 13%, p=.001), and for acute proctitis (15% vs. 38%, p=.03). A second RCT included in this systematic review reported no differences in toxicity between IMRT and 3D-CRT. For late GI toxicity, 4 of 9 studies, all retrospective cohort studies (N=3333), reported differences between IMRT and 3D-CRT. One RCT, reporting on late GI toxicity, did not find any differences between IMRT and 3D-CRT. Five of 9 studies reported on late GU effects: only 1 reported a difference in late GU effects in favor of 3D-CRT. Two retrospective cohort studies reported mixed findings on quality of life outcomes.[13]

A systematic review by Hummell et al (2012) conducted for the Health Technology Assessment Programme evaluated the clinical effectiveness of IMRT for the radical treatment of prostate cancer.[14] The literature search through May 2009 identified 8 nonrandomized studies comparing IMRT with 3D-CRT. Clinical outcomes were OS, biochemical (prostate-specific antigen [PSA]) relapse-free survival, toxicity, and health-related quality of life. The biochemical relapse-free survival was not affected by treatment received, except when doses differed between groups; in those cases, a higher dose with IMRT was favored over lower doses with 3D-CRT. There was some indication that GU toxicity was worse for patients treated with dose-escalated IMRT. However, any group difference resolved by 6 months after treatment. Data comparing IMRT and 3D-CRT supported the theory that higher doses (up to 81 Gy) can improve biochemical survival for patients with localized prostate cancer. Most studies reported an advantage for IMRT in GI toxicity, particularly for the volume of the rectum treated, because toxicity can be reduced by increasing conformality of treatment.

Randomized Controlled Trials

Studies not included in the Yu et al (2016) meta-analysis[12] are summarized below.

Viani et al (2016) reported a pseudorandomized trial (sequential allocation) that compared toxicity between IMRT and 3D-CRT in 215 men who had localized prostate cancer.[15] Treatment consisted of hypofractionated RT at a total dose of 70 Gy at 2.8 Gy per fraction using either IMRT or 3D-CRT. The primary endpoint of the trial was toxicity, defined as any symptoms up to 6 months after treatment (acute) or that started 6 months after treatment (late). Quality of life was assessed with a prostate-specific module. The study was adequately powered, and the groups were comparable at baseline. However, blinding of patients and outcome assessors were not reported. As shown in Table 2, the 3D-CRT group reported significantly higher incidence of acute and late GI and GU toxicity, with similar rates of biochemical control (PSA nadir + 2 ng/mL). The combined incidence of acute GI and GU toxicity was 28% for the 3D-CRT group compared with 11% for the IMRT group. Prostate-specific quality of life was reported to be worse in the 3D-CRT group at 6, 12, and 24 months, but not at 36 months posttreatment.

Table 2. Acute and Late Toxicity Rates With 3D-CRT and IMRT

Comparison	3D-CRT (n=109), %	IMRT (n=106), %	p
Acute GI toxicity, grade ≥2	24	7	0.001
Acute GU toxicity, grade ≥2	27	9	0.001
Late GI toxicity, grade ≥2	21.7	6.4	0.001
Late GU toxicity, grade ≥2	12.3	3.7	0.02
Biochemical control	94.3	95.4	0.678

GI: gastrointestinal; GU: genitourinary; IMRT: intensity-modulated radiotherapy; 3D-CRT: 3-dimensional conformal radiotherapy.

Nonrandomized Studies

Sujenthiran et al (2017) published a retrospective cohort study evaluating 23,222 men who were treated for localized prostate cancer with IMRT (n=6,933) or 3D-CRT (n=16,289) between January 2010 and December 2013 and whose data were available in various databases within the English National Health Service.[16] Dosage was similar between treatment types: patients in both groups received a median of 2 Gy per fraction for a median total dose of 74 Gy. Gastrointestinal and GU toxicities were categorized as grade 3 or above using National Cancer Institute Common Terminology Criteria. On average, patients in the IMRT group experienced fewer GI toxic events per 100 person-years (adjusted hazard ratio [HR], 0.66; 95% CI, 0.61 to 0.72; p<0.01). The rate of GU toxicity events was similar between treatment groups (IMRT, 2.3 GU events per 100 person-years vs 3D-CRT, 2.4 GU events per 100 person-years; HR, 0.94; 95% CI, 0.84 to 1.06; p=0.31). The most commonly diagnosed GI toxicity event was radiation proctitis (n=5,962 [68.5%] of 8701 diagnoses). Of 4061 GU toxicity diagnoses, the most common was hematuria (1265 [31.1%]). Study limitations included therapeutic differences and baseline GI and GU symptoms unaccounted for in the analysis, as well as limited follow-up on GI and GU toxicity. Reviewers concluded that IMRT showed a significant reduction in GI toxicity severity over 3D-CRT and similar levels of GU toxicity severity.

Michalski et al (2013) reported comparative data for IMRT and 3D-CRT from the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial.[17] In this trial, the initial protocol only included 3D-CRT, but during the trial, the protocol was amended to include IMRT. As a result, 491 patients were treated with 3D-CRT and 257 were treated with IMRT.

Patients treated with 3D-CRT received 55.8 Gy to the prostate and seminal vesicles and then 23.4 Gy to the prostate only. All IMRT patients received 79.2 Gy to the prostate and seminal vesicles. Radiation exposure for the bladder and rectum were significantly reduced with IMRT. There was a significant decrease in the incidence of grades 2, 3 and 4 late GI toxicity for IMRT on univariate analysis (p=.039). On multivariate analysis, there was a 26% reduction in grade 2, 3, and 4 GI toxicity for the IMRT group, but this difference was not statistically significant (p=.099). There were no differences in early or late GU toxicity between groups.

Vora et al (2013) reported on 9-year tumor control and chronic toxicities observed in 302 patients treated with IMRT for clinically localized prostate cancer at a single institution.[18] Median dose delivered was 76 Gy (range, 70 to 77 Gy), and 35% of patients received androgen deprivation therapy. Local and distant recurrence rates were 5% and 8.6%, respectively. At 9 years, biochemical control rates were 77% for low-risk, 70% for intermediate-risk, and 53% for high-risk patients (p=0.05). At last follow-up, none had persistent GI and only 0.7% had persistent GU toxicities of grade 3 or 4. The high-risk group was associated with a higher distant metastasis rate (p=0.02) and death from prostate cancer (p=.001).

Wong et al (2009) reported on a retrospective study of radiation dose escalation in 853 patients with localized (T1c-T3N0M0) prostate cancer.[19] Radiotherapies used included conventional dose (71 Gy) 3D-CRT (n=270), high-dose (75.6 Gy) IMRT (n=314), permanent transperineal brachytherapy (n=225), and external-beam RT plus brachytherapy boost (n=44). All patients were followed for a median of 58 months (range, 3 to 121 months). The 5-year OS rate for the entire group was 97%. The 5-year biochemical no evidence of disease rates, local control rates, and distant control rates were 74%, 93%, and 96%, respectively, for 3D-CRT; 87%, 99%, and 97%, respectively, for IMRT; 94%, 100%, and 99%, respectively, for BRT alone; and 94%, 100%, and 97%, respectively, for external-beam RT plus brachytherapy.

Dosing for Low-Risk versus Intermediate- to High-Risk Prostate Cancer
The National Comprehensive Cancer Network (NCCN) has recommended the use of RT for patients with prostate cancer, based on risk stratification by clinical and pathologic findings. These recommendations are based on some studies that did and did not include IMRT as the mode of RT.

In 1993, a U.S. cancer research center initiated an RCT comparing toxicity levels with outcomes after 3D-CRT (at 78 Gy) and 2-dimensional RT (at 70 Gy) in patients with localized prostate cancer. The long-term results of this study were reported by Kuban et al (2008).[2] The trial included 301 patients with stage T1b to T3 disease who received 70 Gy (n=150) or 78 Gy (n=151). Median follow-up was 8.7 years. Patient risk levels in the 70 and 78 Gy groups were low risk (n=31 and n=30), intermediate risk (n=71 and n=68), and high risk (n=48 and n=53), respectively. When analyzed by risk group, patients with low-risk disease treated to 78 Gy versus 70 Gy, had a freedom from biochemical or clinical failure of 88% and 63%, respectively (p=.042). The intermediate-risk patients showed no statistically significant difference in freedom from biochemical or clinical failure based on dose level (p=.36). Patients with high-risk disease showed a significant difference in freedom from biochemical or clinical failure based on dose (63% vs. 26%, p=.004), although when these high-risk patients were stratified by PSA level, only those patients with a PSA level greater than 10 ng/mL showed a difference in freedom from biochemical or clinical failure.

The NCCN guideline also cites the Kuban et al (2008) study[2], in addition to Kalbasi et al (2015)[20] as evidence for a dose of 75.6 to 79.2 Gy (with or without inclusion of the seminal

vesicles) as appropriate for patients with low-risk cancers and that the conventional dose of 70 Gy is no longer considered adequate.

For patients with intermediate- and high-risk prostate cancer, the NCCN has cited the following studies. Xu et al (2011) reported on a toxicity analysis of dose escalation from 75.6 to 81.0 Gy in 189 patients receiving definitive RT for prostate cancer.[4] Patients were at high, intermediate, and low risk according to NCCN definitions, and were dosed at physician discretion. A total of 119 patients received 75.6 Gy and 70 received 81.0 Gy. Patients were followed at intervals of 3 to 6 months for 5 years and yearly thereafter (median follow-up, 3 years). The 81.0 Gy group had higher rates of grade 2 acute GU toxicity (p<.001), late GU toxicity (p=.001), and late GI toxicity (p=.082), but a lower rate of acute GI toxicity (p=.002). There were no notable differences in final GU (p=.551) or final GI (p=.194) toxicity when compared with the 75.6 Gy group.

Eade et al (2007) reported on the results of 1530 consecutive patients treated for localized prostate cancer with 3D-CRT between 1989 and 2002.[3] Patients were grouped by dose level: less than 70 Gy (n=43), 70 to 74.9 Gy (n=552), 75 to 79.9 Gy (n=568), and 80 Gy or more (n=367). Median follow-up ranged from 46 to 86 months. Adjusted 5-year estimates of freedom from biochemical failure for the 4 groups were 60%, 68%, 76%, and 84% using American Society for Radiation Oncology criteria and 70%, 81%, 83%, and 89% using Phoenix criteria, respectively. The authors concluded that a pronounced RT dose-response by freedom from biochemical failure was seen after adjusting for pretreatment PSA level, Gleason score, and tumor stage and that the vast majority of patients should receive 80 Gy or more, although a subgroup of patients might be adequately treated with a lower dose of radiation.

Section Summary: IMRT for Primary (Definitive) RT for Localized Prostate Cancer
The evidence on IMRT for definitive treatment of localized prostate cancer includes several prospective comparative studies, retrospective comparative studies, and systematic reviews. Results generally showed that IMRT consistently reduced the risk of GI and GU toxicities with similar survival outcomes as compared to 3D-CRT. A reduction in clinically significant complications of RT is likely to improve quality of life for treated patients.

Intensity-Modulated Radiotherapy for Prostate Cancer After Prostatectomy

Clinical Context and Test Purpose
The purpose of IMRT in individuals who have prostate cancer and are undergoing RT after prostatectomy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who have prostate cancer and are undergoing RT after prostatectomy.

Interventions
The test being considered is IMRT.

Comparators

The following tool is currently being used treat localized prostate cancer after prostatectomy: 3D-CRT.

Outcomes
The general outcomes of interest are OS, locoregional recurrence, quality of life, and treatment-related morbidity.

Study Selection Criteria
See information under the first indication.

REVIEW OF EVIDENCE

Systematic Reviews
The joint American Urological Association and the American Society for Radiation Oncology (2013) guidelines on the use of adjuvant and salvage RT after prostatectomy was based on a systematic review conducted by Thompson et al (2013) who searched the literature from 1990 to 2012, and selected 294 articles.[10] Reviewers attempted to determine which RT technique and doses produced optimal outcomes, but found it impossible to answer these questions because most available data came from observational studies and approximately one-third treated patients with conventional (2D) external-beam modalities. Of the literature assessed in the review, less than 5% of studies reported using IMRT. Reviewers stated that 64 to 65 Gy is the minimum dose that should be delivered after prostatectomy, but that dosage should be individualized to the patient. A 2019 amendment to the guidelines, incorporating 155 references published between January 1990 and December 2017, affirmed that determining which RT techniques and doses produced optimal outcomes in the adjuvant and salvage RT contexts was "not possible".[5]

Nonrandomized Comparative Studies
Massaccesi et al (2013) reported preliminary results of acute toxicities from a phase 2 trial of hypofractionated IMRT with simultaneous integrated boost to the pelvic nodes and prostate bed after prostatectomy.[21] Between 2008 and 2012, 49 patients considered to be at high-risk of relapse after radical prostatectomy, or who had biochemical relapse, received 45 GY in 1.8-Gy fractions to the whole pelvis and 62.5 Gy in 2.5-Gy fractions (equivalent dose, 68.75) to the prostate bed. The toxicity findings were compared with those of 52 consecutive patients selected from an electronic database who underwent adjuvant or salvage 3D-CRT with standard 2-Gy fractionation to the prostatic bed and regional pelvic nodes. Grade 1, 2, 3, and 4 acute GU toxicity occurred in 71.2% of all patients without a significant difference between the groups (hypofractionated IMRT vs conventionally fractionated 3D-CRT) (p=0.51). Grade 2 acute GU toxicity, reported in 19.8% of all patients, was less frequent in patients in the IMRT group (9.6% vs 28.8%, p=.02). There were no cases of grade 3 acute GU toxicity. Thirty (29.7%) patients developed grade 2 acute GI toxicity; the difference between groups was not significant. No cases of grade 3 acute GI toxicity were reported. The study concluded that the acute toxicity profile for hypofractionated high-dose simultaneous integrated boost-IMRT after prostatectomy compared favorably with that of conventionally fractionated high-dose 3D-CRT.

Alongi et al (2009) reported on acute toxicity results of whole-pelvis irradiation for 172 consecutive patients with clinically localized prostate cancer treated with IMRT or 3D-CRT as adjuvant (n=100) or salvage (n=72) therapy after radical prostatectomy and pelvic lymph node dissection.[22] Whole pelvis radiation was considered in patients with a limited lymphadenectomy and/or in the presence of a high-risk of nodal involvement, in patients with

positive lymph nodes and/or in the presence of adverse prognostic factors (Gleason score >7 and/or preoperative PSA level >10 ng/mL). Eighty-one patients underwent 3D-CRT, and 91 underwent IMRT. No grade 3 or 4 acute GU or lower GI side effects were observed. Acute grade 2 GU and acute lower GI grade 2 events did not differ significantly between treatment groups (Table 3). There was a higher incidence of acute upper GI grade 2, 3, and 4 toxicity in the 3D-CRT group. The authors concluded that acute toxicity following postoperative whole pelvis irradiation was reduced with IMRT compared with 3D-CRT; this effect was most significant for upper GI symptoms, owing mainly to better bowel sparing with IMRT.

Table 3. Acute and Late Toxicity Rates With 3D-CRT and IMRT

Comparison	3D-CRT, n (%)	IMRT, n (%)	p
Acute lower GI toxicity, grade ≥2	7 (8.6)	3 (3.3)	0.14
Acute upper GI toxicity, grade ≥2	18 (22.2)	6 (6.6)	0.004
Acute GU toxicity	10 (12.3)	6 (6.6)	0.19

3D-CRT: 3-dimensional conformal radiotherapy; GI: gastrointestinal; GU: genitourinary; IMRT: intensity-modulated radiotherapy.

Single-Arm Studies

Several prospective single-arm phase 2 studies have evaluated the safety and efficacy of different methods of delivering IMRT (eg, integrated boost, hypofractionation) in this clinical context.

Leite et al (2021) conducted a single-arm, phase 2 study that evaluated the safety and feasibility of postoperative hypofractionated RT with intensity-modulated and image-guided RT to the prostate bed in 61 patients who had undergone radical prostatectomy.[23] Of these patients, 57 received salvage RT and 4 received adjuvant RT. The dose prescribed to the prostate bed was 51 Gy in 3.4 Gy daily fractions using IMRT and imaging guidance; all patients were treated with IMRT with volumetric arch therapy. After a median follow-up of 16 months, results revealed that 11.5% of patients experienced acute grade ≥2 GU symptoms and 13.1% experienced acute grade ≥2 GI symptoms. Late grade ≥2 GU and GI toxicity occurred at a rate of 8.2% and 11.5%, respectively. Three patients experienced a biochemical recurrence and the median time to the PSA nadir was 9 months. The actutimes biochemical failure-free survival was 95.1%.

PLATIN 3 Trial

Initial results of the phase 2 Prostate and Lymph Node Irradiation With Integrated Boost-IMRT After Neoadjuvant Antihormonal Treatment (PLATIN) trial were published by Katayama et al (2014).[24] This trial evaluated the safety and feasibility of irradiating the pelvic lymph nodes simultaneously with a boost to the prostate bed in 40 patients with high-risk features or inadequate lymphadenectomy after radical prostatectomy. Treatment consisted of 2 months of antihormonal treatment before IMRT of the pelvic lymph nodes (51.0 Gy) with a simultaneous integrated boost to the prostate bed (68.0 Gy). No incidence of acute grade 3 or 4 toxicity occurred. Nearly 23% of patients experienced acute grade 2 GI and GU toxicity, 10% late grade 2 GI toxicity, and 5% late grade 2 GU toxicity. One patient developed late grade 3 proctitis and enteritis. At a median of 24 months, 89% of patients were free of a PSA recurrence.

PRIAMOS1 Trial

Acute toxicity results from the Hypofractionated RT of the Prostate Bed With or Without the Pelvic Lymph Nodes trial were reported by Katayama et al (2014).[25] This prospective phase 2 trial assessed the safety and toxicity of hypofractionated RT of the prostate bed with IMRT as a basis for further prospective trials. Forty patients with indications for adjuvant or salvage therapy (pathologic stage T3 and/or R1/2 or with a PSA recurrence after prostatectomy) were enrolled from February to September 2012; 39 were evaluated. All patients received a total dose of 54.0 Gy to the prostate bed, 28 for salvage and 11 in the adjuvant setting. Based on preoperative staging, patients were risk stratified as low (n=2), intermediate (n=27), or high (n=10). Ten weeks after completion of therapy, there were no adverse events exceeded grade 3. Acute GI toxicity rates were 56.4% and 17.9% for grade 1 and 2, respectively, and acute grade 1 GU toxicity was recorded in 35.9% of patients.

Corbin et al (2013) reported on the adverse effects in men at high-risk of recurrence 2 years after prostatectomy and IMRT.[26] Between 2007 and 2010, 78 consecutive men received adjuvant RT (n=17 [22%]) or salvage RT (n=61 [78%]). The median IMRT dose was 66.6 Gy (range, 60 to 72 Gy). Quality of life data were collected prospectively at 2, 6, 12, 18, and 24 months, and included urinary incontinence, irritation or obstruction, bowel or rectal function, and sexual function. No significant changes were observed from baseline through 2-year follow-up, with global urinary irritation or obstruction scores unchanged or improved over time from baseline, global urinary incontinence improved from baseline to 24 months in the subset of patients receiving adjuvant therapy, and global bowel and sexual domain scores improved or were unaffected over follow-up (though initially lower at 2 months).

Section Summary: IMRT for Prostate Cancer After Prostatectomy

The evidence on the use of IMRT for prostate cancer after prostatectomy includes nonrandomized comparative studies, single-arm phase 2 trials, and systematic reviews. Although the comparative studies are primarily retrospective, the evidence has generally shown that IMRT compared favorably to 3D-CRT with regard to GI and GU toxicity. Notably, a retrospective comparative study found a significant reduction in acute GI toxicity with IMRT compared with 3D-CRT, mainly due to better bowel sparing with IMRT. Another retrospective comparative study found a reduction in GU toxicity. A reduction in clinically significant complications of RT is likely to improve the quality of life for treated patients.

Summary of Evidence

For individuals who have localized prostate cancer and are undergoing definitive RT who received IMRT, the evidence includes several prospective comparative studies, retrospective studies, and systematic reviews. Relevant outcomes are overall survival (OS), disease-free survival (DFS), quality of life, and treatment-related morbidity. Although there are few prospective comparative trials, the evidence has generally shown that IMRT provides survival outcomes similar to 3-dimensional conformal radiotherapy (3D-CRT) while reducing gastrointestinal (GI) and genitourinary (GU) toxicity. These findings are supported by treatment planning studies, which have predicted that IMRT improves target volume coverage and sparing of adjacent organs compared with 3D-CRT. A reduction in clinically significant complications of RT is likely to improve the quality of life for treated patients. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have prostate cancer and are undergoing RT after prostatectomy who receive IMRT, the evidence includes retrospective comparative studies, single-arm phase 2 trials, and systematic reviews. Relevant outcomes are overall survival, disease-free survival, quality of life, and treatment-related morbidity. Although the comparative studies are primarily retrospective, the evidence has generally shown that IMRT compared favorably to 3D-CRT with regard to GI and GU toxicity. Notably, a retrospective comparative study found a significant reduction in acute upper GI toxicity with IMRT compared with 3D-CRT, mainly due to better bowel sparing with IMRT. Another retrospective comparative study found a reduction in GU toxicity. A reduction in clinically significant complications of RT is likely to improve the quality of life for treated patients. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Radiology

The American College of Radiology Appropriateness Criteria (2017)state, "the available comparative data suggest that higher EBRT [external beam radiation therapy] doses are more effective at achieving prostate specific antigen failure-free survival for localized prostate cancer and that safe dose escalation can be more readily achieved with the increased conformity of IMRT [intensity-modulated radiation therapy] relative to 3D-CRT [3-dimensional conformal radiation therapy]."[27]

American Society for Radiation Oncology et al.

The American Society for Radiation Oncology, American Society of Clinical Oncology, and American Urological Association (2019) published guidelines on hypofractionated external beam RT in localized prostate cancer with the following recommendations:[28]

Table 4. Recommendations on Hypofractionated External Beam Radiation Therapy in Localized Prostate Cancer

Statement	RS	QOE	consensus
"In men with low-risk PC who decline active surveillance and receive EBRT to the prostate with or without radiation to the seminal vesicles, moderate hypofractionation should be offered."	Strong	High	100%
"In men with intermediate-risk PC receiving EBRT to the prostate with or without radiation to the seminal vesicles, moderate hypofractionation should be offered."	Strong	High	100%

“In men with high-risk PC receiving EBRT to the prostate, but not including pelvic lymph nodes, moderate hypofractionation should be offered.”	Strong	High	94%
“In patients who are candidates for EBRT, moderate hypofractionation should be offered regardless of patient age, comorbidity, anatomy, or urinary function. However, physicians should discuss the limited follow-up beyond 5 years for most existing RCTs evaluating moderate hypofractionation.”	Strong	High	94%
“Men should be counseled about the small increased risk of acute gastrointestinal toxicity with moderate hypofractionation.”	Strong	High	100%
“Regimens of 6000 cGy delivered in 20 fractions of 300 cGy and 7000 cGy delivered in 28 fractions of 250 cGy are suggested since they are supported by the largest evidentiary base.”	Conditional	Moderate	100%

cGY: centigray; EBRT: external beam radiation therapy; RS: recommendation strength; QOE: quality of evidence; PC: prostate cancer; RCT: randomized controlled trial.

In 2019, the American Society for Radiation Oncology and American Urological Association published an amendment to their 2013 guideline on adjuvant and salvage radiation therapy after prostatectomy.[5,10] The guideline contains statements (Table 5) that provide direction to clinicians and patients regarding the use of RT in this setting. The amendment included an additional statement (Statement 9) on the use of hormone therapy with salvage RT and long-term data were used to update an existing statement (Statement 2) on adjuvant RT.[5]

Table 5. Recommendations for Adjuvant and Salvage Radiotherapy after Prostatectomy

Statement	Evidence Strength
Statement 1: "Patients who are being considered for management of localized prostate cancer with radical prostatectomy should be informed of the potential for adverse pathologic findings that portend a higher risk of cancer recurrence and that these findings may suggest a potential benefit of additional therapy after surgery."	Clinical principle
Statement 2: "Patients with adverse pathologic findings including seminal vesicle invasion, positive surgical margins, and extraprostatic extension should be informed that adjuvant radiotherapy, compared to radical prostatectomy only, reduces the risk of biochemical recurrence, local recurrence, and clinical progression of cancer. They should also be informed that the impact of adjuvant radiotherapy on subsequent metastases and overall survival is less clear; one of three randomized controlled trials that addressed these outcomes indicated a benefit but the other two trials did not demonstrate a benefit. However, these two trials were not designed to identify a significant reduction in metastasis or death with adjuvant radiotherapy."	Clinical principle
Statement 3: "Physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy including seminal vesicle invasion, positive surgical margins, or extraprostatic extension because of demonstrated reductions in biochemical recurrence, local recurrence, and clinical progression."	Grade A
Statement 4: "Patients should be informed that the development of a PSA recurrence after surgery is associated with a higher risk of development of metastatic prostate cancer or death from the disease. Congruent with this clinical principle, physicians should regularly monitor PSA after radical prostatectomy to enable early administration of salvage therapies if appropriate."	Clinical principle
Statement 5: "Clinicians should define biochemical recurrence as a detectable or rising PSA value after surgery that is ≥ 0.2 ng/ml with a second confirmatory level ≥ 0.2 ng/ml."	Grade C
Statement 6: "A restaging evaluation in the patient with a PSA recurrence may be considered."	Grade C

Statement 7: "Physicians should offer salvage radiotherapy to patients with PSA or local recurrence after radical prostatectomy in whom there is no evidence of distant metastatic disease."	Grade C
Statement 8: "Patients should be informed that the effectiveness of radiotherapy for PSA recurrence is greatest when given at lower levels of PSA."	Clinical principle
Statement 9: "Clinicians should offer hormone therapy to patients treated with salvage radiotherapy (postoperative PSA ≥0.20 ng/mL) Ongoing research may someday allow personalized selection of hormone or other therapies within patient subsets."	Grade A
Statement 10: "Patients should be informed of the possible short-term and long-term urinary, bowel, and sexual side effects of radiotherapy as well as of the potential benefits of controlling disease recurrence."	Clinical principle

PSA: prostate specific antigen.
Grade A: well-conducted and highly generalizable RCTs or exceptionally strong observational studies with consistent findings.
Grade B: RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings.
Grade C: observational studies that are inconsistent, have small sample sizes or have other problems that potentially confound interpretation of data.
Clinical principle: statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the
medical literature.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines (v.4.2024) on prostate cancer indicate that highly conformal radiotherapy (RT) should be used in conventional fraction doses of 75.6 to 79.2 gray (Gy) for low-risk prostate cancer and up to 81 Gy for intermediate- and high-risk prostate cancer.[1] For adjuvant/salvage external-beam RT, the recommended dose ranged from 64 to 72 Gy in standard fractionation. The guideline also indicates that intensity-modulated radiotherapy is used increasingly in clinical practice and states that IMRT "reduced the risk of gastrointestinal toxicities and rates of salvage therapy compared to 3D-CRT [3-dimensional conformal radiotherapy] in some but not all older retrospective and population-based studies, although treatment cost is increased." The NCCN also notes that more recent data have revealed that "moderately hypofractionated image-guided IMRT regimens (2.4 to 4 Gy per fraction over 4 to 6 weeks) have been tested in randomized trials, and their efficacy has been similar or non-inferior to conventionally fractionated IMRT. Overall, the panel believes that hypofractionated IMRT techniques, which are more convenient for patients, can be considered as an alternative to conventionally fractionated regimens when clinically indicated."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might affect this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT03526510	Randomized Trial of Concomitant Hypofractionated IMRT Boost Versus Conventional Fractionated IMRT Boost for Localized High Risk Prostate Cancer	178	Dec 2024
Unpublished			
NCT00326638	Randomized Phase III Trial of 3D Conformal Radiotherapy Versus Helical Tomotherapy IMRT in High-Risk Prostate Cancer	72	Jun 2020

NCT: national clinical trial

Government Regulations

National:

There is no national coverage determination on this topic.

Local:

Wisconsin Physicians Service Insurance Corporation – LCD Radiation Oncology Including Intensity Modulated Radiation Therapy (IMRT) (L34652)
Original Effective Date 10/01/2015
Retirement Date 04/01/16

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds
- Charged Particle (Proton or Helium Ion) Radiation Therapy
- Intensity Modulated Radiation Therapy (IMRT): Central Nervous System Tumors
- Intensity-Modulated Radiation Therapy (IMRT): Head and Neck Cancers
- Intensity Modulated Radiation Therapy (IMRT) of the Abdomen, Pelvis and Chest
- Intensity Modulated Radiation Therapy (IMRT) of the Breast and Lung
- Perirectal Spacer for Radiation Therapy Treatment of Prostate Cancer (SPACEOAR®)

References

1. National Comprehensive Cancer Network. Prostate Cancer. Version 4.2024 May 17, 2024 prostate.pdf (nccn.org). Accessed 8/6/24
2. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys. Jan 01 2008; 70(1): 67-74. PMID 17765406
3. Eade TN, Hanlon AL, Horwitz EM, et al. What dose of external-beam radiation is high enough for prostate cancer?. Int J Radiat Oncol Biol Phys. Jul 01 2007; 68(3): 682-9. PMID 17398026

4. Xu N, Rossi PJ, Jani AB. Toxicity analysis of dose escalation from 75.6 gy to 81.0 gy in prostate cancer. Am J Clin Oncol. Feb 2011; 34(1): 11-5. PMID 20101167
5. Pisansky TM, Thompson IM, Valicenti RK, et al. Adjuvant and Salvage Radiation Therapy After Prostatectomy: ASTRO/AUA Guideline Amendment, Executive Summary 2018. Pract Radiat Oncol. 2019; 9(4): 208-213. PMID 31051281
6. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in November 2022.
7. Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet. Aug 2005; 366(9485): 572-8. PMID 16099293
8. Thompson IM, Jr., Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA. Nov 15 2006;296(19):2329-2335. PMID 17105795
9. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol. Jun 20 2009;27(18):2924-2930. PMID 19433689
10. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol. Aug 2013;190(2):441-449. PMID 23707439.
11. Misher C. Radiation therapy: which type is right for me? Last reviewed: March 15,2024. Radiation Therapy: Which type is right for me? | OncoLink. Accessed 8/6/24.
12. Yu T, Zhang Q, Zheng T, et al. The Effectiveness of Intensity Modulated Radiation Therapy versus Three-Dimensional Radiation Therapy in Prostate Cancer: A Meta-Analysis of the Literatures. PLoS One. 2016; 11(5): e0154499. PMID 27171271
13. Bauman G, Rumble RB, Chen J, et al. Intensity-modulated radiotherapy in the treatment of prostate cancer. Clin Oncol (R Coll Radiol). Sep 2012; 24(7): 461-73. PMID 22673744
14. Hummel S, Simpson EL, Hemingway P, et al. Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation. Health Technol Assess. Oct 2010; 14(47): 1-108, iii-iv. PMID 21029717
15. Viani GA, Viana BS, Martin JE, et al. Intensity-modulated radiotherapy reduces toxicity with similar biochemical control compared with 3-dimensional conformal radiotherapy for prostate cancer: A randomized clinical trial. Cancer. Jul 01 2016;122(13):2004-2011. PMID 27028170
16. Sujenthiran A, Nossiter J, Charman SC, et al. National Population-Based Study Comparing Treatment-Related Toxicity in Men Who Received Intensity Modulated Versus 3-Dimensional Conformal Radical Radiation Therapy for Prostate Cancer. Int J Radiat Oncol Biol Phys. Dec 01 2017; 99(5): 1253-1260. PMID 28974414
17. Michalski JM, Yan Y, Watkins-Bruner D et al. Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial. Int J Radiat Oncol Biol Phys. Dec 01 2013; 87(5):932-8. PMID 24113055
18. Vora SA, WW, Schild SE et al. Nine-Year Outcome and Toxicity in Patients treated with IMRT for Localized Prostate Cancer. J Urol. Aug 2013;190(2):521-6. PMID 23415964
19. Wong WW, Vora SA, Schild SE et al. Radiation dose escalation for localized prostate cancer: intensity-modulated radiotherapy versus permanent transperineal brachytherapy. Cancer. Dec 01 2009; 115(23):5596-606. PMID 19670452

20. Kalbasi A, Li J, Berman A, et al. Dose-Escalated Irradiation and Overall Survival in Men With Nonmetastatic Prostate Cancer. JAMA Oncol. Oct 2015; 1(7): 897-906. PMID 26181727
21. Massaccesi M, Cilla S, Deodato F, et al. Hypofractionated intensity-modulated radiotherapy with simultaneous integrated boost after radical prostatectomy: preliminary results of a phase II trial. Anticancer Res. Jun 2013;33(6):2785-2789. PMID 23749942
22. Alongi F, Fiorino C, Cozzarini C, et al. IMRT significantly reduces acute toxicity of whole-pelvis irradiation in patients treated with post-operative adjuvant or salvage radiotherapy after radical prostatectomy. Radiother Oncol. Nov 2009; 93(2): 207-12. PMID 19766338
23. Leite ETT, Ramos CCA, Ribeiro VAB, et al. Hypofractionated Radiation Therapy to the Prostate Bed With Intensity-Modulated Radiation Therapy (IMRT): A Phase 2 Trial. Int J Radiat Oncol Biol Phys. Apr 01 2021; 109(5): 1263-1270. PMID 33346091
24. Katayama S, Habl G, Kessel K, et al. Helical intensity-modulated radiotherapy of the pelvic lymph nodes with integrated boost to the prostate bed - initial results of the PLATIN 3 Trial. BMC Cancer. Jan 14 2014; 14: 20. PMID 24422782
25. Katayama S, Striecker T, Kessel K, et al. Hypofractionated IMRT of the prostate bed after radical prostatectomy: acute toxicity in the PRIAMOS-1 trial. Int J Radiat Oncol Biol Phys. Nov 15 2014; 90(4): 926-33. PMID 25216858
26. Corbin KS, Kunnavakkam R, Eggener SE, et al. Intensity modulated radiation therapy after radical prostatectomy: Early results show no decline in urinary continence, gastrointestinal, or sexual quality of life. Pract Radiat Oncol. 2013; 3(2): 138-44. PMID 24674317
27. Zaorsky NG, Showalter TN, Ezzell GA, et al. ACR Appropriateness Criteria for external beam radiation therapy treatment planning for clinically localized prostate cancer, part II of II. Adv Radiat Oncol. 2017; 2(3): 437-454. PMID 29114613
28. Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: Executive Summary of an ASTRO, ASCO and AUA Evidence-Based Guideline. J Urol. Mar 2019; 201(3): 528-534. PMID 30759696

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 8/6/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/13	8/20/13	9/10/13	Joint policy established
1/1/15	10/21/14	11/3/14	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine maintenance HCPCS G codes added to policy Revised medical policy statement and criteria. Added IMRT after radical prostatectomy as a covered indication.
3/1/17	12/13/16	12/13/16	Routine Maintenance Added procedure code 0438T (not covered); updated exclusions and rationale

11/1/17	8/15/17	8/15/17	Routine maintenance Rationale and references updated
3/1/18	12/12/17	12/12/17	Code update. Procedure code 0438T deleted; replaced with code 55874; added perirectal spacer information.
7/1/18	4/17/18	4/17/18	Perirectal spacer (SpaceOAR) (55874) to be considered established with radiotherapy for prostate cancer.
1/1/19	10/16/18	10/16/18	Routine maintenance: revised MPS to be more general, no exclusions; diverge from BCBSA with broader scope. Deleted sections related to SpaceOAR.
1/1/20	10/15/19		Routine maintenance
1/1/21	10/20/20		Routine maintenance
1/1/22	10/19/21		Routine maintenance Ref 21 added
1/1/23	10/18/22		Routine maintenance (ls) Ref 1 added
1/1/24	10/17/23		Routine maintenance (jf) Vendor Managed: eviCore Ref 6 added
1/1/25	10/15/24		Routine maintenance (jf) Vendor Managed: eviCore Added Ref: 27, 28

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: INTENSITY-MODULATED RADIATION THERAPY (IMRT) OF THE PROSTATE

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria applies
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.