8.01.47	Intensity-Modulated Radiotherapy of the Prostate		
Original Policy Date:	March 30, 2015	**Effective Date:**	November 20, 2020
Section:	8.0 Therapy	**Page:**	Page 1 of 24

Policy Statement

Note: The following is a preview of this policy. A final position statement (taking into consideration feedback) will take effect on November 20, 2020.

Intensity-modulated radiotherapy (IMRT)
Intensity modulated radiotherapy, using a moderately hypofractionated regimen, may be considered **medically necessary** for the treatment of localized prostate cancer (see Policy Guidelines).

Treatment of prostate cancer with conventional fractionation (1.8-2.0 Gy x 37-45) may be considered **medically necessary**, but documentation to support the medical necessity for using conventional fractionation must be provided

Intensity-modulated radiotherapy (IMRT) may be considered **medically necessary** after radical prostatectomy as:

I. Adjuvant therapy when there are adverse pathologic findings at prostatectomy or with a persistently detectable prostate-specific antigen level after prostatectomy (see Policy Guidelines section)
II. Salvage therapy when there is evidence of biochemical or local recurrence when there is no evidence of distant metastatic disease (see Policy Guidelines section)

Intensity-modulated radiotherapy (IMRT) is considered **investigational** for the treatment of prostate cancer when the above criteria are not met.

Brachytherapy with Intensity-Modulated Radiotherapy Boost
Intensity-modulated radiotherapy (IMRT) may be considered **medically necessary** in conjunction with permanent transperineal implantation of radioactive seeds or high-dose rate temporary brachytherapy.

Policy Guidelines

IMRT in the treatment of prostate cancer
Multiple studies have confirmed the superiority of IMRT to 3D CRT in the treatment of prostate cancer. Therefore, the use of IMRT for the treatment of prostate cancer is considered medically necessary.

Localized Prostate Cancer: Radiotherapy (RT) as Definitive Treatment
Localized prostate cancer can be defined as cancer confined to the prostate gland T1-T2N0-NXM0 or as locally advanced cancer. Locally advanced cancer is confined to adjacent structures and includes T3a-T3bN0-NXM0. The presence of tumor invasion beyond extracapsular extension or other than seminal vesicles, or with evidence of regional lymph node involvement, in the absence of distant metastases T4N0-N1M0, does not necessarily preclude definitive therapy.

Fractionation in the treatment of Prostate Cancer: In the treatment of prostate cancer across all risk groups, moderate hypofractionation provides important potential advantages in cost and convenience for patients without loss of efficacy. Recommended regimens include 2.5 Gy x 28, 2.7 Gy x 26 or 3 Gy x 20 fractions. Table PG1 outlines regimens that have shown acceptable efficacy and toxicity based on National Comprehensive Cancer Network (NCCN) guidelines.

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The optimal regimen for an individual patient warrants evaluation of comorbid conditions, voiding symptoms, and toxicity therapy.

Additional fractionation schemes may be used as long as sound oncologic principles and appropriate estimate of biologically effective dose (BED) are considered.

Table PG1.

Regimen for Definitive Therapy	NCCN Risk Group (✓ indicates an appropriate regimen option if radiation therapy is given)					
	Very-Low[1]	Low[1]	Favorable or good prognostic[2] intermediate	Unfavorable, or poor prognostic[2], intermediate	High and Very-High[3]	Node Positive
Beam Therapies						
72 Gy to 80 Gy at 2 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
75.6 Gy to 80.0 Gy at 1.8 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
70.2 Gy at 2.7 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
70 Gy at 2.5 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
60 Gy at 3 Gy per fraction	✓	✓	✓	✓ with 4-6 mo ADT	✓ with 2-3 y ADT	✓ with 2-3 y ADT
51.6 Gy at 4.3 Gy per fraction	✓	✓	✓			
37 Gy at 7.4 Gy per fraction	✓	✓	✓			
40 Gy at 8 Gy per fraction	✓	✓	✓			
36.25 Gy at 7.25 Gy per fraction	✓	✓	✓			
Brachytherapy Monotherapy						
Iodine 125 implant at 145 Gy	✓	✓	✓			
Palladium 103 implant at 125 Gy	✓	✓	✓			
Cesium implant at 115 Gy	✓	✓	✓			
HDR 27 Gy at 13.5 Gy in 2 implants	✓	✓	✓			
HDR 28 Gy at 9.5 Gy BID in 2 implants	✓	✓	✓			
Combined EBRT and Brachytherapy (EBRT 45-50.4 Gy at 1.8-2.0 Gy/fx, unless otherwise noted)						
Iodine 125 implant at 110-115 Gy				✓ ± 4 mo ADT	✓ with 1-3 y ADT	✓ with 1-3 y ADT
Palladium 103 implant 90-100 Gy				✓ ± 4 mo ADT	✓ with 1-3 y ADT	✓ with 1-3 y ADT
Cesium implant at 85 Gy				✓ ± 4 mo ADT	✓ with 1-3 y ADT	✓ with 1-3 y ADT
HDR 21.5 Gy at 10.75 Gy x 2				✓ ± 4 mo ADT	✓ with 1-3 y ADT	✓ with 1-3 y ADT

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Regimen for Definitive Therapy	NCCN Risk Group (✓ indicates an appropriate regimen option if radiation therapy is given)					
	Very-Low[1]	Low[1]	Favorable or good prognostic[2] intermediate	Unfavorable, or poor prognostic[2], intermediate	High and Very-High[3]	Node Positive
EBRT 37.5 Gy at 2.5 Gy + 12-15 Gy single HDR				✓ ± 4 mo ADT	✓ with 1-3 y ADT	✓ with 1-3 y ADT

ADT: Androgen Deprivation Therapy; EBRT: External Beam Radiation Therapy; Gy: Gray
[1]Active surveillance should be strongly considered
[2]"Good" or "Poor" prognostic is not strictly defined. Predictive nomograms and/or molecular testing can be used to prognosticate prostate-specific antigen (PSA) persistence/ recurrence, prostate cancer specific mortality and metastasis free survival after definitive external beam radiation therapy. Although the prognostic value has been established, the predictive value of these tests remain unknown.
[3]Prophylactic nodal radiation maybe considered if estimate of nodal metastasis is high.

Allowable codes and frequencies for IMRT:

Description	Code	Maximum per course of treatment	Notes
Treatment Planning	77261, 77262 or 77263	1	
Respiratory motion management	77293	0	Only for breast and lung cancer; otherwise documentation of medical necessity is required
IMRT radiotherapy plan	77301	1	If comparison 3D plan is generated, it is included in 77301
Basic Dosimetry	77300	2	
Isodose plan, simple	77306	1	Not on the same day as 77300; may not bill 77306 and 77307 together
Isodose plan, complex	77307	1	Same as above
Special Dosimetry	77331	1	
Treatment devices	77331, 77332,	1	Maximum of one of these codes per course of treatment
Treatment devices	77334	1	Only allowed for compensator-based IMRT; with delivery code G6016
Multi-leaf collimater	77338	1	Only allowed with delivery codes 77385 or 77386; not allowed with G6015
Special radiation physics consult	77370	0	May allow x 1; documentation of medical necessity required
Special physician consult	77470	0	May allow x 1; documentation of medical necessity required
Medical physics management	77336	8	Allowed once per 5 courses of therapy
Radiation therapy management	77427	8	Allowed once per 5 courses of therapy
Radiation delivery	77385 or G6015	28	Documentation of medical necessity needed for more than 28 treatments

NCCN guidelines categorized patients according to the following risk of recurrence or disease progression/recurrence:

- **Very Low Risk:** clinical stage T1c, biopsy Gleason score less than or equal to 6 Gleason grade group 1, PSA less than 10 ng/ml, presence of disease in fewer than 3 biopsy cores, less than or equal to 50% prostate cancer involvement in any core, and PSA density less than 0.15 ng/ml/g
- **Low Risk:** clinical stage T1 to T2a, Gleason score 6/Gleason grade group 1, and serum PSA level less than 10 ng/ml
- **Intermediate Risk:** clinical stage T2b to T2c, Gleason score 7/Gleason grade group 2 to 3, or PSA value of 10 ng/ml to 20ng/ml

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- **High Risk:** clinical stage T3a, Gleason score 8 to 10/Gleason grade group 4 to 5, or PSA level greater than 20 ng/ml
- **Very High Risk:** clinical stage T3B to T4, primary Gleason pattern 5 or more than 4 biopsy cores with Gleason score 8 to 10/Gleason grade group 4 to 5

Post Prostatectomy: Radiotherapy as Adjuvant or Salvage Therapy
Radiotherapy (RT) after prostatectomy is used as adjuvant therapy in patients at a higher risk of recurrence. In the adjuvant setting, adverse pathologic findings at prostatectomy include positive surgical margins, seminal vesicle invasion, extraprostatic extension, and Gleason scores of 8 to 10.

Use of radiotherapy (RT) as salvage therapy included treating the prostate bed and possibly surrounding tissues, including lymph nodes, in a patient with locoregional recurrence after surgery. In the salvage setting, biochemical recurrence is defined as a detectable or rising PSA level of 0.2 ng/mL or more after surgery, with a confirmatory test level of 0.2 ng/mL or higher.

American Urological Association and American Society for Radiation Oncology (Thompson et al [2013]) guidelines recommend a minimum dose of 64 to 65 Gy in the post prostatectomy setting.

Fractionation
In the treatment of prostate cancer, conventional radiotherapy (RT) applies total doses in excess of 74 Gy over up to 9 weeks, whereas hypofractionated RT involves daily doses greater than 2 Gy and has an overall shorter treatment time.

The National Comprehensive Cancer Network (NCCN) guidelines state that because, in the treatment of prostate cancer, moderately hypofractionated intensity-modulated radiotherapy (IMRT) regimens (2.4-4 Gy per fraction over 4-6 weeks) have been tested in randomized controlled trials, and efficacy and toxicity have been found similar to conventionally fractionated IMRT, hypofractionation may be considered a preferred alternative to conventionally fractionated regimens when clinically indicated.

When radiation therapy is provided to the same target volume by two different modalities, e.g., brachytherapy with IMRT boost, the combined dose is used to determine compliance with this policy.

Radiation Tolerance of Normal Tissue
Organs at risk are defined as normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed radiation dose. Organs at risk may be particularly vulnerable to clinically important complications from radiation toxicity.

*The following Normal Tissue Constraint Guidelines are derived from the textbook: Radiation Oncology: A Question-Based Review published by Lippincott Williams & Wilkins, 2010 [author: Hristov et al., 2010]). According to the author, most dosages were derived from randomized studies or consensus guidelines however; pediatric dose constraints will vary greatly from protocol to protocol. Sources used in the development of the guidelines included the American Brachytherapy Society (ABS); Clinical practice guidelines from Johns Hopkins Hospital (JHH); the International Journal of Radiation Oncology *Biology* Physics (IJROBP); the National Comprehensive Cancer Network (NCCN), Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC); and the Radiation Therapy Oncology Group (RTOG) protocols at the time of publication.

The following guidelines are only intended to serve as a guide and may not be applicable to all clinical scenarios.

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Table PG2. Radiation Dose Volume (1.8-2.0 Gy/fx) for Normal Tissues of the Pelvis

Organ	Constraints
Central Nervous System (1.8-2.0 Gray/fraction [Gy/fx])	
• Spinal Cord	max 50 Gy (full cord cross-section); tolerance increases by 25% 6 mos after 1st course (for re-irradiation)
• Brain	max 72 Gy (partial brain); avoid >2 Gy/fx or hyperfractionation
• Chiasm/Optic Nerves	max 55 Gy
• Brainstem	Entire brainstem <54 Gy, V59 Gy <1–10 cc
• Eyes (globe)	mean <35 Gy, max 54 Gy
• Lens	max 7 Gy
• Retina	max 50 Gy
• Lacrimal Gland	max 40 Gy
• Inner ear/cochlea	mean </=45 Gy (consider constraining to </=35 Gy with concurrent cisplatin)
• Pituitary gland	max 45 Gy (for panhypopituitarism, lower for GH deficiency)
• Cauda equina	max 60 Gy
Central Nervous System (single fraction)	
• Spinal Cord	max 13 Gy (if 3 fxs, max 20 Gy)
• Brain	V12 Gy <5–10 cc
• Chiasm/Optic Nerves	max 10 Gy
• Brainstem	max 12.5 Gy
• Sacral plexus	V18 <0.035 cc, V14.4 <5 cc
• Cauda equina	V16 <0.035 cc, V14 <5 cc
Head and Neck (1.8–2.0 Gy/fx)	
• Parotid gland(s)	mean <25 Gy (both glands) or mean <20 Gy (1 gland)
• Submandibular gland(s)	mean <35 Gy
• Larynx	mean </=44 Gy, V50 </=27%, max 63–66 Gy (when risk of tumor involvement is limited)
• TMJ/mandible	max 70 Gy (if not possible, then V75 <1 cc)
• Oral cavity	Non-oral cavity cancer: mean <30 Gy, avoid hot spots >60 Gy Oral cavity cancer: mean <50 Gy, V55 <1 cc, max 65 Gy
• Esophagus (cervical)	V45 <33%
• Pharyngeal constrictors	mean <50 Gy
• Thyroid	V26 <20%
Thoracic (1.8–2.0 Gy/fx)	
• Brachial plexus	max 66 Gy, V60 <5%
• Lung (combined lung for lung cancer treatment)	mean <20–23 Gy, V20 <30%–35%
• Lung (ipsilateral lung for breast cancer treatment)	V25 <10%
• Single lung (after pneumonectomy)	V5 <60%, V20 <4–10%, MLD <8 Gy
• Bronchial tree	max 80 Gy
• Heart (lung cancer treatment)	Heart V45 <67%; V60 <33%
• Heart (breast cancer treatment)	V25 <10%
• Esophagus	V50 <32% ;V60 <33%
Thoracic (hypofractionation) Note: the max dose limits refer to volumes >0.035 cc (~3 mm^3).	
• Spinal cord	1 fraction: 14 Gy 3 fractions: 18 Gy (6 Gy/fx) 4 fractions: 26 Gy (6.5 Gy/fx) 5 fractions: 30 Gy (6 Gy/fx)
• Esophagus	1 fraction: 15.4 Gy 3 fractions: 30 Gy (10 Gy/fx) 4 fractions: 30 Gy (7.5 Gy/fx) 5 fractions: 32.5 Gy (6.5 Gy/fx)
• Brachial plexus	1 fraction: 17.5 Gy 3 fractions: 21 Gy (7 Gy/fx) 4 fractions: 27.2 Gy (6.8 Gy/fx)

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Organ	Constraints
	5 fractions: 30 Gy (6 Gy/fx)
• Heart/Pericardium	1 fraction: 22 Gy 3 fractions: 30 Gy (10 Gy/fx) 4 fractions: 34 Gy (8.5 Gy/fx) 5 fractions: 35 Gy (7 Gy/fx)
• Great vessels	1 fraction: 37 Gy 3 fractions: 39 Gy (13 Gy/fx) 4 fractions: 49 Gy (12.25 Gy/fx) 5 fractions: 55 Gy (11 Gy/fx)
• Trachea/Large Bronchus	1 fraction: 20.2 Gy 3 fractions: 30 Gy (10 Gy/fx) 4 fractions: 34.8 Gy (8.7 Gy/fx) 5 fractions: 40 Gy (8 Gy/fx)
• Rib	1 fraction: 30 Gy 3 fractions: 30 Gy (10 Gy/fx) 4 fractions: 32 Gy (7.8 Gy/fx) 5 fractions: 32.5 Gy (6.5 Gy/fx)
• Skin	1 fraction: 26 Gy 3 fractions: 30 Gy (10 Gy/fx) 4 fractions: 36 Gy (9 Gy/fx) 5 fractions: 40 Gy (8 Gy/fx)
• Stomach	1 fraction: 12.4 Gy 3 fractions: 27 Gy (9 Gy/fx) 4 fractions: 30 Gy (7.5 Gy/fx) 5 fractions: 35 Gy (7 Gy/fx)
Gastrointestinal (GI) (1.8–2.0 Gy/fx)	
• Stomach	TD 5/5 whole stomach: 45 Gy
• Small bowel	V45 <195 cc
• Liver (metastatic disease)	mean liver <32 Gy (liver = normal liver minus gross disease)
• Liver (primary liver cancer)	mean liver <28 Gy (liver = normal liver minus gross disease)
• Colon	45 Gy, max dose 55 Gy
• Kidney (bilateral)	mean <18 Gy, V28 <20%, V23 Gy <30%, V20 <32%, V12 <55%. If mean kidney dose to 1 kidney >18 Gy, then constrain remaining kidney to V6 <30%.
Gastrointestinal (GI) (single fraction)	
• Duodenum	V16 <0.035 cc, V11.2 <5 cc
• Kidney (Cortex)	V8.4 <200 cc
• Kidney (Hilum)	V10.6 <66%
• Colon	V14.3 <20 cc, V18.4 <0.035 cc
• Jejunum/Ileum	V15.4 <0.035 cc, V11.9 <5 cc
• Stomach	V16 <0.035 cc, V11.2 <10 cc
• Rectum	V18.4 <0.035 cc, V14.3 <20 cc
Genitourinary (GU) (1.8-2.0 Gy/fx)	
• Femoral heads	V50 <5%
• Rectum	V75 <15% , V70 <20%, V65 <25%, V60 <35%, V50 <50%
• Bladder	V80 <15%, V75 <25%, V70 <35%, V65 <50%
• Testis	V3 <50%
• Penile bulb	Mean dose to 95% of the volume <50 Gy. D70 </=70 Gy, D50 </=50 Gy
Genitourinary (GU) (LDR prostate brachytherapy)	
• Urethra	Volume of urethra receiving 150% of prescribed dose (Ur150) <30%
• Rectum	Volume of rectum receiving 100% of prescribed dose (RV100) <0.5 cc
Gynecological (GYN)	
• Bladder point (cervical brachytherapy)	Max 80 Gy (LDR equivalent dose)

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Organ	Constraints
• Rectal point (cervical brachytherapy)	Max 75 Gy (LDR equivalent dose)
• Proximal vagina (mucosa) (cervical brachytherapy)	Max 120 Gy (LDR equivalent dose)
• Distal vagina (mucosa) (cervical brachytherapy)	Max 98 Gy (LDR equivalent dose)

Coding

The following CPT codes for simple and complex IMRT delivery are available:

- **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

The Centers for Medicare & Medicaid Services (CMS) decided not to implement these CPT codes and instead created HCPCS G codes using the language of the previous CPT codes. The following codes may be used for IMRT:

- **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 3 or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session

Code 77301 remains valid:

- **77301**: Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications

The following codes may also be used:

- **77338**: Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
- **77261**: Therapeutic radiology treatment planning; simple
- **77262**: Therapeutic radiology treatment planning; intermediate
- **77263**: Therapeutic radiology treatment planning; complex
- **77293**: Respiratory motion management simulation (List separately in addition to code for primary procedure)
- **77300**: Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface and depth dose, as required during course of treatment, only when prescribed by the treating physician
- **77306**: Teletherapy isodose plan; simple (1 or 2 unmodified ports directed to a single area of interest), includes basic dosimetry calculation(s)
- **77307**: Teletherapy isodose plan; complex (multiple treatment areas, tangential ports, the use of wedges, blocking, rotational beam, or special beam considerations), includes basic dosimetry calculation(s)
- **77331**: Special dosimetry (e.g., TLD, microdosimetry) (specify), only when prescribed by the treating physician
- **77332**: Treatment devices, design and construction; simple (simple block, simple bolus)
- **77334**: Treatment devices, design and construction; complex (irregular blocks, special shields, compensators, wedges, molds or casts)
- **77370**: Special medical radiation physics consultation
- **77470**: Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation)
- **77336**: Continuing medical physics consultation, including assessment of treatment parameters, quality assurance of dose delivery, and review of patient treatment documentation in support of the radiation oncologist, reported per week of therapy
- **77427**: Radiation treatment management, 5 treatments

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- **77014**: Computed tomography guidance for placement of radiation therapy fields
- **77417**: Therapeutic radiology port image(s)
- **77387**: Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
- **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
- **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

Code 77338 is to be reported only once per IMRT plan and should not be reported with 0073T.

Description

Radiotherapy (RT) is an integral component of prostate cancer treatment. Intensity-modulated radiotherapy (IMRT) 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.

Related Policies

- Brachytherapy for Clinically Localized Prostate Cancer Using Permanently Implanted Seeds
- Charged-Particle (Proton or Helium Ion) Radiotherapy for Neoplastic Conditions
- High-Dose Rate Temporary Prostate Brachytherapy
- Radiation Oncology
- Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 through the 510(k) process. Intensity modulators include the Innocure Intensity Modulating Radiation Therapy Compensators (Innocure), cleared in 2006, and the decimal tissue compensator (Southeastern Radiation Products), cleared in 2004. FDA product code: IXI. Intensity modulators may be added to standard linear accelerators to deliver IMRT when used with proper treatment planning systems.

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RT planning systems have also been cleared for marketing by the FDA through the 510(k) process. They include the Prowess Panther™ (Prowess) in 2003, TiGRT (LinaTech) in 2009, the RayDose (RaySearch Laboratories) in 2008, 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 cleared for marketing by the FDA through the 510(k) process is the Varian IMRT system (Varian Medical Systems). FDA product code: IYE.

Rationale

Background

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, RT 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.[6,7,8] Professional society guidelines have recommended adjuvant RT to patients with adverse pathologic findings at the time of prostatectomy and salvage RT for patients with prostate-specific antigen recurrence or local recurrence after prostatectomy in the absence of metastatic disease.[9];[5]

Radiotherapy Techniques

Radiation therapy may be administered externally (i.e., a beam of radiation is directed into the body) or internally (i.e., a radioactive source is placed inside the body, near a tumor).[10] External radiotherapy (RT) 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.[10] Bony landmarks bones 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 Radiotherapy

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.[10] 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.

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Intensity-Modulated Radiotherapy

IMRT 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.[10.] 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 that may further improve RT 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.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 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 technology, 2 domains are examined: the relevance, and 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

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IMRT treatment benefit, and it is difficult to relate dosing study results to actual effects on health outcomes.

Comparative studies of radiation-induced adverse events from IMRT vs alternative radiation delivery would constitute definitive evidence of 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 patients 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 question addressed in this evidence review is: Does IMRT improve the net health outcome for individuals who have localized prostate cancer and are undergoing definitive therapy?

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

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

Interventions
The test being considered is IMRT.

RT is an integral component of prostate cancer treatment. IMRT 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.

IMRT is performed by radiation oncologists in an outpatient clinical setting.

Comparators
The following test is currently being used to make decisions about the treatment of localized prostate cancer: 3D-CRT.

3D-CRT is performed by radiation oncologists in an outpatient clinical setting.

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.

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- To assess long-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 (total n=9556 patients) that compared IMRT with 3D-CRT for gastrointestinal (GI), genitourinary (GU), and rectal toxicity, biochemical control, and OS.[11] 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 intervals (CI) did not overlap at 1 at the $p<0.05$ level. IMRT 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 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

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

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.[12] 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 events between IMRT and 3D-CRT. The RCT (n=78 patients) 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=0.001), grade 3 or 4 toxicity (0% vs 13%, p=0.001), and for acute proctitis (15% vs 38%, p=0.03). 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 (total n=3333 patients), 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.[12]

A systematic review by Hummel et al (2010) conducted for the Health Technology Assessment Programme evaluated the clinical effectiveness of IMRT for the radical treatment of prostate cancer.[13] 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 with 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

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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[11] are summarized below.

Viani et al (2016) reported on a pseudorandomized trial (sequential allocation) that compared toxicity levels between IMRT and 3D-CRT in 215 men who had localized prostate cancer.[14] Treatment consisted of hypofractionated RT at a total dose of 70 Gy in 2.8 Gy per fraction for either IMRT or 3D-CRT. The primary endpoint 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 trial 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 more 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=6933) or 3D-CRT (n=16289) between January 2010 and December 2013 and whose data were available in various databases within the English National Health Service.[15] 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. GI 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 (4.9) than patients in the 3D-CRT group, who saw an average 6.5 GI 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=5962 [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 a 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 on comparative data for IMRT and 3D-CRT from the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial.[16] 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=0.039). On multivariate analysis, there was a 26% reduction in grade 2, 3,

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and 4 GI toxicity for the IMRT group but this difference was not statistically significant (p=0.099). 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.[17] Median dose delivered was 76 Gy (range, 70-77 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=0.001).

Wong et al (2009) reported on a retrospective study of radiation dose escalation in 853 patients with localized (T1c-T3N0M0) prostate cancer.[18] RTs 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, 3-121 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 brachytherapy alone; and 94%, 100%, and 97%, respectively, for external-beam RT plus brachytherapy.

Dosing for Low-Risk vs Intermediate- to High-Risk Prostate Cancer
The National Comprehensive Cancer Network (NCCN) has recommended use of RT for patients with prostate cancer based on risk stratification by clinical and pathologic findings. These recommendations are based on 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 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 (n=31 and n=30), intermediate (n=71 and n=68), and high (n=48 and n=53), respectively. When analyzed by risk group, patients with low-risk disease treated to 78 Gy vs 70 Gy, had freedom from a biochemical or clinical failure of 88% and 63%, respectively (p=0.042). The intermediate-risk patients showed no statistically significant difference in freedom from biochemical or clinical failure based on dose level (p=0.36). Patients with high-risk disease showed a significant difference in freedom from biochemical or clinical failure based on dose (63% vs 26%, p=0.004), 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)[19], as evidence for a dose of 75.6 to 79.2 Gy (with or without the 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 after that (median follow-up, 3 years). The 81.0-Gy group had higher rates of grade 2 acute GU toxicity (p<0.001), late GU toxicity (p=0.001), and late GI toxicity (p=0.082) but a lower rate of acute GI toxicity (p=0.002). There were no notable differences in final GU (p=0.551) or final GI (p=0.194) toxicity levels compared with the 75.6 Gy group.

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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, with the group receiving 80 Gy or more having a median follow-up of 45.6 months. Adjusted 5-year estimates of freedom from biochemical failure for the 4 groups were 60%, 68%, 76%, and 84% using the American Society for Radiation Oncology criteria and 70%, 81%, 83%, and 89% using Phoenix criteria, respectively. Adjusted 5- and 10-year estimates of freedom from distant metastases for the 4 groups were 96% and 93%, 97% and 93%, 99% and 95%, and 98% and 96%, 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: Intensity-Modulated Radiotherapy 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 the quality of life for treated patients.

Intensity-Modulated Radiotherapy for Prostate Cancer After Prostatectomy
Clinical Context and Test Purpose
The purpose of IMRT in patients 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 question addressed in this evidence review is: Does IMRT improve the net health outcome in patients who have prostate cancer and are undergoing RT after prostatectomy?

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

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

Interventions
The test being considered is IMRT. IMRT is performed by radiation oncologists in an outpatient clinical setting.

Comparators
The following tool is currently being used to make decisions about the treatment of localized prostate cancer after prostatectomy: 3D-CRT.

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

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.[9] Reviewers attempted to determine which RT technique and

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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 2-dimensional 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 acute toxicity results from a phase 2 trial of hypofractionated IMRT with a simultaneous integrated boost to the pelvic nodes and prostate bed after prostatectomy.[20] Between 2008 and 2012, 49 patients considered to be at a 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 Gy) 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=0.02). 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 statistically 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.[21] 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

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

Single-Arm Studies

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

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Prostate and Lymph Node Irradiation With Integrated Boost-IMRT After Neoadjuvant Antihormonal Treatment (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).[22] 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.

Radiation Therapy of the Prostate Bed With or Without the Pelvic Lymph Nodes (PRIAMOS1) Trial

Acute toxicity results from the Hypofractionated RT of the Prostate Bed With or Without the Pelvic Lymph Nodes (PRIAMOS1) trial were reported by Katayama et al (2014).[23] 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 pre-operative staging, patients were risk-stratified as low (n=2), intermediate (n=27), or high (n=10). Ten weeks after completing therapy, there were no adverse events exceeding 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 events in men at high-risk of recurrence 2 years after prostatectomy and IMRT.[24] 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, 60-72 Gy). quality of life data was 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: Intensity-Modulated Radiotherapy for Prostate Cancer After Prostatectomy

The evidence on the use of IMRT for prostate cancer after prostatectomy includes non-randomized 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 OS, disease-free survival, 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 3D-CRT while reducing GI and 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

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the quality of life for treated patients. The evidence is sufficient to determine that the technology results in a meaningful 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 OS, 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 a meaningful improvement in the net health outcome.

Supplemental Information
Practice Guidelines and Position Statements

National Comprehensive Cancer Network
The National Comprehensive Cancer Network guidelines (v.2.2020) on prostate cancer indicate that highly conformal radiotherapy (RT) should be used in conventional fraction doses of 75.6 to 79.2 Gy for low-risk prostate cancer and up to 81 Gy for intermediate- and high-risk prostate cancer.[1,] For adjuvant and salvage external-beam RT, the recommended dose ranged from 64 to 72 Gy in standard fractionation. The Network guideline also indicates that intensity-modulated radiotherapy (IMRT 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 in some but not all older retrospective and population-based studies, although treatment cost is increased." 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."

American Society for Radiation Oncology et al.
The American Society for Radiation Oncology, American Society of Clinical Oncology, and the American Urological Association (2019) published guidelines on hypofractionated external beam RT in localized prostate cancer with the following recommendations:[25,]

Table 4. Recommendations on Hypofractionated EBRT 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%

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Statement	RS	QOE	Consensus
"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.[5,9] 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

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Statement	Evidence Strength
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.

American College of Radiology

The American College of Radiology Appropriateness Criteria (2014) have indicated IMRT is the standard for definitive external-beam RT of the prostate.[26.]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing 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			
NCT00326638	Randomized Phase III Trial of 3D Conformal Radiotherapy Versus Helical Tomotherapy IMRT in High-Risk Prostate Cancer	72	Jun 2020
NCT03526510	Randomized Trial of Concomitant Hypofractionated IMRT Boost Versus Conventional Fractionated IMRT Boost for Localized High Risk Prostate Cancer	178	Dec 2023
NCT00392535	Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer: CHHIP	3216	Jun 2021

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and radiation oncology consultation report including:
  - Medical necessity for performing IMRT rather than conventional or 3D treatment planning
  - Past history of radiation (site) (if applicable)
  - Past surgical procedures (pertaining to request)
  - Primary cancer type and location
- Goals/requirements of the IMRT treatment plan and proposed IMRT treatment dose (dose volume histogram [DVH] -in color preferred; organs at risk)
- Comparison 3D-CRT dose volume histogram (DVH) (in color preferred; organs at risk) (as applicable)
- Radiology report(s) for the past 2 months

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

Type	Code	Description
CPT®	77014	Computed tomography guidance for placement of radiation therapy fields
	77261	Therapeutic radiology treatment planning; simple
	77262	Therapeutic radiology treatment planning; intermediate
	77263	Therapeutic radiology treatment planning; complex
	77293	Respiratory motion management simulation (List separately in addition to code for primary procedure)
	77300	Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface and depth dose, as required during course of treatment, only when prescribed by the treating physician

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Type	Code	Description
	77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
	77306	Teletherapy isodose plan; simple (1 or 2 unmodified ports directed to a single area of interest), includes basic dosimetry calculation(s)
	77307	Teletherapy isodose plan; complex (multiple treatment areas, tangential ports, the use of wedges, blocking, rotational beam, or special beam considerations), includes basic dosimetry calculation(s)
	77331	Special dosimetry (e.g., TLD, microdosimetry) (specify), only when prescribed by the treating physician
	77332	Treatment devices, design and construction; simple (simple block, simple bolus)
	77334	Treatment devices, design and construction; complex (irregular blocks, special shields, compensators, wedges, molds or casts)
	77336	Continuing medical physics consultation, including assessment of treatment parameters, quality assurance of dose delivery, and review of patient treatment documentation in support of the radiation oncologist, reported per week of therapy
	77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
	77370	Special medical radiation physics consultation
	77385	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
	77386	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex
	77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
	77417	Therapeutic radiology port image(s)
	77427	Radiation treatment management, 5 treatments
	77470	Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation)
HCPCS	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
	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 3 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

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/30/2015	Policy title change from Intensity Modulated Radiation Therapy (IMRT)

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Effective Date	Action
	BCBSA Medical Policy adoption Policy revision without position change
05/01/2016	Policy revision without position change
09/01/2017	Policy revision without position change
06/01/2018	Policy revision without position change
09/01/2018	Policy revision without position change
09/01/2019	Policy revision without position change
05/01/2020	Administrative update. Policy statement updated.
11/20/2020	Annual review. Policy statement, guidelines and literature updated. Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

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