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Medical Benefit		Effective Date: 06/01/20	Next Review Date: 03/21
Preauthorization	No	Review Dates: 03/20	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With localized prostate cancer and are undergoing definitive radiotherapy 	Interventions of interest are: <ul style="list-style-type: none"> Intensity-modulated radiotherapy 	Comparators of interest are: <ul style="list-style-type: none"> Three-dimensional conformal radiotherapy 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Morbid events Functional outcomes Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With prostate cancer and are undergoing radiotherapy after prostatectomy 	Interventions of interest are: <ul style="list-style-type: none"> Intensity-modulated radiotherapy 	Comparators of interest are: <ul style="list-style-type: none"> Three-dimensional conformal radiotherapy 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Functional outcomes Treatment-related morbidity

DESCRIPTION

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

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 of these studies. Relevant outcomes are overall survival, disease-free survival, quality of life (QOL), and treatment-related morbidity. Although there are few prospective comparative trials, the evidence has generally shown that IMRT provides tumor control and survival outcomes similar to three-dimensional conformal radiotherapy (3D-CRT) while reducing gastrointestinal and genitourinary 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 QOL 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 two trials, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-free survival, QOL, and treatment-related morbidity. Although the comparative studies are primarily retrospective, the evidence has generally shown that IMRT provides tumor control and survival outcomes similar to 3D-CRT. Notably, a retrospective comparative study found a significant reduction in acute upper gastrointestinal toxicity with IMRT compared with 3D-CRT, mainly due to better bowel sparing with IMRT. Another retrospective comparative study found a reduction in genitourinary toxicity. A reduction in clinically significant complications of RT is likely to improve the QOL for treated patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

POLICY

Intensity-modulated radiotherapy may be considered **medically necessary** in the treatment of localized prostate cancer (see Policy Guidelines).

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

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

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

POLICY GUIDELINES

LOCALIZED PROSTATE CANCER: RADIOTHERAPY 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.

The National Comprehensive Cancer Network (NCCN) has recommended a dose of 75.6 to 79.2 gray (Gy) in conventional fractions (with or without seminal vesicles) for patients with low-risk cancers (based on findings from Kuban et al [2008]). Low-risk features in localized prostate cancer are defined as stage T1 to T2a, a Gleason score of six or less, and a prostate-specific antigen (PSA) level less than 10 ng/mL.

NCCN has recommended doses up to 81.0 Gy for patients with intermediate- and high-risk cancers, defined as: intermediate risk: stage T2b to T2c or Gleason score of 7 or PSA levels between 10 ng/mL and 20 ng/mL; and high-risk: stage T3a or Gleason score of 8 to 10 or PSA level greater than 20 ng/mL (based on Eade et al [2007]; and Xu et al [2011]).

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 eight to ten.

Use of 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 RT applies total doses in excess of 74 Gy over up to nine weeks, whereas hypofractionated RT involves daily doses greater than 2 Gy and has an overall shorter treatment time. Published randomized controlled trials have failed to demonstrate the superiority of hypofractionation in definitive RT for prostate cancer, either for efficacy or late toxicity. Ongoing phase three noninferiority trials might provide insight.

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 four to six weeks) have been tested in randomized controlled trials, and efficacy and toxicity have been found similar to conventionally fractionated IMRT, hypofractionation may be considered as an alternative to conventionally fractionated regimens when clinically indicated.

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.

IMRT should be considered when a tumor is near organs at risk, and three-dimensional conformal radiotherapy planning does not meet dose-volume constraints for normal tissue tolerance.

Tables PG1 and 2 outline radiation doses generally considered tolerance thresholds for these normal structures in the pelvis.

Table PG1. Radiation Tolerance Doses for Normal Tissues of the Pelvis

Site	TD 5/5, Gray ^a			TD 50/5, Gray ^b			Complication End Point
	Portion of Organ Involved			Portion of Organ Involved			
	1/3	2/3	3/3	1/3	2/3	3/3	
Spinal cord	50	50	47	70	70	NP	Myelitis, necrosis
Small intestine	50	NP	40	60	NP	55	Obstruction, perforation
Colon	55	NP	45	65	NP	55	Obstruction, perforation, ulceration, fistula
Rectum	NP	NP	60	NP	NP	80	Severe proctitis, necrosis, stenosis, fistula
Bladder	NP	80	65	NP	85	80	Symptomatic bladder contracture and volume loss
Femoral head	NP	NP	52	NP	NP	65	Necrosis

Compilation from the following two sources:

Morgan MA (2011). Radiation Oncology. In DeVita, Lawrence and Rosenberg, Cancer (p.308). Philadelphia: Lippincott Williams and Wilkins.

Kehwar TS, Sharma SC. Use of normal tissue tolerance doses into linear quadratic equation to estimate normal tissue complication probability. Available online: <http://www.rooj.com/Radiation%20Tissue%20Tolerance.htm>

NP: not provided, cm: centimeters, TD: tolerance dose

^aTD 5/5, the average dose that results in a 5% complication risk within five years

^bTD 50/5, the average dose that results in a 50% complication risk within five years

Table PG2. Radiation Dose Volume (1.8-2.0 Gray per Fraction) for Normal Tissues of the Pelvis

Site	Radiation Dose Volume
Rectum	V75 <15%, V70 <20%, V65 <25%, V60 <35%, V50 <50%
Bladder	V80 <15%, V75 <25%, V70 <35%, V65 <50%
Femoral head	V50 <5%

Compiled from: Hristov et al. Radiation Oncology: A Question-Based Review. Lippincott Williams & Wilkins, 2010.

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 three randomized controlled trials that showed a significant increase in biochemical recurrence-free survival.¹⁻³ 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.⁴

RT TECHNIQUES

Conventional External-Beam Radiotherapy

Methods to plan and deliver RT have evolved in ways that permit more precise targeting of tumors with complex geometries. Most early trials used two-dimensional treatment planning, based on flat images and radiation beams with cross-sections of uniform intensity that were sequentially aimed at the tumor along two or three intersecting axes. Collectively, these methods are termed conventional external-beam radiotherapy.

Three-Dimensional Conformal Radiotherapy

Treatment planning evolved by using three-dimensional images, usually from computed tomography (CT) scans, to delineate the boundaries of the tumor and to discriminate tumor tissue from adjacent normal tissue and nearby organs at risk for radiation damage. Computer algorithms were developed to estimate cumulative radiation doses delivered to each volume of interest by summing the contribution from each shaped beam. Methods were also 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. Collectively, these methods are termed 3D-CRT.

Intensity-Modulated Radiotherapy

IMRT, which uses computer software along with CT and magnetic resonance images, offers better conformality than 3D-CRT because it modulates the intensity of the overlapping radiation beams projected on the target and uses multiple shaped treatment fields. Treatment planning and delivery are more complex, time-consuming, and labor-intensive for IMRT than for 3D-CRT. The technique uses a multileaf collimator [MLC]), which, when coupled with a computer algorithm, 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 thus may 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.

Technologic development has 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.

IMRT methods to plan and deliver RT are not uniform. IMRT may use beams that remain on as MLCs move around the patient (dynamic MLC) or that are off during movement and turn on once the MLC reaches prespecified positions ("step and shoot" technique). A third alternative uses a very narrow, single beam that moves spirally around the patient (tomotherapy). Each method uses different computer algorithms to plan treatment and yields somewhat different dose distributions in and outside the target. Patient position can alter target shape and thus affect treatment plans. Treatment plans are usually based on a single imaging scan, a static 3D-CT image. Current methods seek to reduce positional uncertainty for tumors and adjacent normal tissues by various techniques. Patient immobilization cradles and skin or bony markers are used to minimize day-to-day variability in patient positioning. In addition, many tumors have irregular edges that preclude drawing tight margins on CT scan slices when radiation oncologists contour the tumor volume. It is unknown whether omitting some tumor cells or including some normal cells in the resulting target affects the outcomes of IMRT.

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), 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.

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.

RELATED PROTOCOL

Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary

Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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