Radiotherapy Guideline for Prostate Cancer

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RT Indication

All patients diagnosed with intermediate-, high-, very-high-, regional-risk, low-volume metastatic castration-sensitive prostate cancer (mCSPC) and oligometastatic castration-resistant prostate cancer (mCRPC) are recommended to be evaluated by a radiation oncologist as part of a multidisciplinary discussion of treatment options.

General Principles

EBRT (External Beam Radiation Therapy)

- Treatment Planning: Intensity modulated RT (IMRT) is recommended over 3-dimensional conformal RT to improve dose conformality.

- Image Guidance: Methods to improve accuracy and enable a reduction in planning target value (PTV) margins are encouraged, which may include one or more of the following:
  - Daily 3D imaging with either a cone beam CT (CBCT) or MRI.
  - Devices like fiducial markers or endorectal balloons to assist with optimal image guidance or reduce motion.
  - Real-time intrafraction volumetric tracking.

- Online adaptive radiotherapy if the target is near mobile organs, such as a positive pelvic lymph node adjacent to the bowel.

- Beam Type: Both photon and proton RT are acceptable forms of EBRT and appear to have similar outcomes regarding toxicity, quality of life, and tumor control.

- Fractionation: An extensive list of fractionation schedules has been studied and are grouped into three categories: conventional fractionation (1.8–2 Gy/fraction), moderate hypofractionation (>2.5 to 4 Gy/fraction), and ultra-hypofractionation (>6 Gy/fraction).
  - Iso-effective moderate hypofractionation dosing has demonstrated noninferior tumor control, toxicity, and quality of life compared to conventional fractionation and is generally preferred.
  - Ultra-hypofractionation, which encompasses stereotactic body radiation therapy (SBRT), has also been demonstrated to be noninferior.
  - SBRT is recommended and preferred specifically when: performing metastasis-directed radiotherapy (MDRT), for limited progression or residual disease, when the lesion is in or adjacent to a previously irradiated field, or at physician discretion for more durable pain control than typical palliative regimens.

Brachytherapy

- Patient Selection: Providers should consider gland size, baseline urinary symptoms, and prior procedures like transurethral resection of the prostate, which may increase the risk of adverse effects.
- Dose Rate: Both low-dose rate (LDR) and high-dose rate (HDR) are acceptable as monotherapy or as a boost combined with EBRT in higher-risk disease. Post-implant dosimetry is required for LDR implants to verify dosimetry.
- Monotherapy: Brachytherapy monotherapy has been shown to have fewer side effects than when used with EBRT for intermediate-risk disease without compromising tumor control.
- Combination Therapy: EBRT with an LDR brachytherapy boost has been shown to improve biochemical control over conventionally fractionated EBRT with ADT. This comes at the expense of an increase in high-grade toxicity, so careful patient selection and contemporary planning are essential.

Elective Nodal Irradiation (ENI)

- ENI can be considered in select patients.
- The use of IMRT with image guidance is recommended when performing ENI.
- If performing ENI, it is recommended to include the common, internal, and external iliac, pre-sacral, and obturator lymph node stations. Para-aortic lymph nodes should not be included in patients who do not have evidence of para-aortic lymph node involvement.
- Biocompatible and Biodegradable Perirectal Spacers

- These devices may be implanted between the prostate and rectum to displace the rectum from high radiation dose regions for the purpose of toxicity reduction.
- Patients with grossly apparent true posterior extraprostatic extension should not undergo perirectal spacer implantation.

Definitive RT

- Low Risk:
  - Patients are encouraged to pursue active surveillance.
  - Those electing RT may receive EBRT or brachytherapy as monotherapy.
  - The target should include the prostate and consideration of treatment of the proximal seminal vesicles.
  - Patients should not be treated with ENI, ADT, or combination brachytherapy boost with EBRT.

- Favorable Intermediate Risk:
  - The target should include the prostate and consideration of treatment of the proximal or full seminal vesicles.
  - Patients electing RT may receive EBRT or brachytherapy as monotherapy.
  - Patients should not be treated with ENI or a combination brachytherapy boost with EBRT. ADT is generally not recommended, but can be considered if additional risk assessments suggest aggressive tumor behavior.

- Unfavorable Intermediate Risk:
  - The target should include the prostate and the seminal vesicles (proximal or full).
  - RT options include EBRT, brachytherapy monotherapy, or EBRT with a brachytherapy boost.
  - ENI should not be used routinely.
  - Short-term ADT is recommended unless additional risk assessments suggest less aggressive tumor behavior or if medically contraindicated.

- High Risk:
  - The target should include the prostate and the full seminal vesicles.
  - RT options include EBRT or a brachytherapy boost combined with EBRT.

- The use of ENI is at the discretion of the treating physician.
- Long-term ADT (12–36 months) is recommended for patients with a life expectancy >5 years or who are symptomatic unless medically contraindicated.

- Very-High-Risk:
- The target should include the prostate and the full seminal vesicles.
- RT options include EBRT. Carefully selected patients may receive EBRT with a brachytherapy boost.
- Combination brachytherapy boost with EBRT should not be used routinely.
- Long-term ADT (18–36 months) is recommended for patients with a life expectancy >5 years or who are symptomatic unless medically contraindicated.

- Regional Disease:
- EBRT is recommended to include the prostate, seminal vesicles, and pelvic lymph nodes.
- A simultaneous integrated boost to involved lymph nodes is recommended.
- The use of a brachytherapy boost is not recommended in these patients. The addition of abiraterone is recommended.

Postoperative RT

- Adjuvant RT (aRT):
  - aRT involves the use of EBRT post-radical prostatectomy for patients with adverse pathologic features (e.g., pT3 and/or positive surgical margins) in the setting of an undetectable postoperative PSA.
  - Waiting for a detectable PSA and using an early secondary RT (sRT) approach is recommended for most patients to avoid overtreatment. The use of aRT may be reasonable for patients with multiple adverse features and/or lymph node involvement.
  - Multiple dose/fraction schedules have been used, including conventionally fractionated (60–64 Gy in 30–36 fractions) and moderately hypofractionated regimens (52.5 Gy in 20 fractions).

- Secondary RT (sRT):
  - sRT is the use of EBRT post-RP when a patient has a detectable PSA.
  - Early sRT at a PSA of 0.1–0.2 ng/mL is recommended for most patients who experience biochemical recurrence (BCR) post-RP.
  - The use of ADT with sRT should be personalized based on pre-RT PSA, clinicopathologic risk factors, patient age, life expectancy, comorbidities, and preferences.
  - Multiple dose/fraction schedules have been used, including conventionally fractionated (64–70.2 Gy in 32–39 fractions) and moderately hypofractionated regimens (52.5 Gy in 20 fractions or 62.5 Gy in 25 fractions). These moderately hypofractionated regimens have demonstrated noninferior tumor control, toxicity, and quality of life.

RT in Advanced Disease

- Synchronous mCSPC:
  - Treatment of the Primary Tumor: Minimizing toxicity is paramount when delivering RT to the primary tumor in patients with metastatic disease.

- Low Volume: Treatment of the primary is recommended with EBRT.

- High Volume: Treatment of the primary tumor with EBRT can be considered for select patients.
  - Treatment of Metastases: Metastasis-directed therapy (MDT), which typically uses SBRT, may be used for patients with a limited burden of lymph node or osseous disease.

- Metachronous mCSPC:
  - A greater level of evidence supports the role of MDT in the metachronous setting compared to synchronous mCSPC. This is commonly delivered using SBRT.
  - The use of MDT in this setting has been shown to delay the need for ADT compared to observation.

- mCRPC:
  - The use of MDT has been shown to prolong progression-free survival (PFS) and radiographic progression-free survival (rPFS) when used for patients with oligometastatic CRPC treated with ADT + an androgen receptor pathway inhibitor (ARPI) as compared to systemic therapy alone.

EBRT Regimen	Preferred Dose/Fraction	Definitive RT						Post-Treatment RT		Advanced Disease	
		Low	FIR	UIR	High	Very-High	Regional	Post-RP		Primary Tumor	Metastases
								aRT	sRT	sRT	mCSPC M0 CRPC mCRPC
Conventional	1.8 – 2 Gy x 37 – 45 fx	☆	☆	☆	☆	✓	✓				☆
	1.8 – 2 Gy x 30 – 39 fx							✓	✓		☆
Moderate Hypofractionation	3 Gy x 20 fx (preferred)[d]	☆	✓	✓	✓	✓	✓			☆	☆
	2.7 Gy x 28 fx										
	2.5 Gy x 28 fx										
	2.63 – 2.75 Gy x 20 fx							✓	✓	☆	✓
	2.5 Gy x 25 fx										
Ultra Hypofractionation (SBRT)	9.5 Gy x 4 fx	☆	✓	✓	✓	☆	☆		☆	✓	✓
	7.25 – 8 Gy x 5 fx										
	6 Gy x 6 fx										

EBRT Regimen	Preferred Dose/Fraction	Definitive RT					Post-Treatment RT		Advanced Disease	
	6.1 Gy x 7 fx 9 – 10 Gy x 3 fx 12 Gy x 2 fx 16 – 24 Gy x 1 fx 6.2 – 6.4 Gy x 5 fx						☆			
EBRT Boost Techniques										
EBRT with simultaneous integrated boost	See footnote b	☆		✓	✓	☆	☆		☆	☆ ☆
EBRT with sequential SBRT boost	*Prostate*									
	1.8 Gy x 23 – 28 fx	☆		☆	☆					
	Boost									
	6 Gy x 3 fx									
	9.5 Gy x 2 fx									

(✓ Preferred; ☆ Acceptable based on clinical and medical need; Regimens shaded gray are not recommended)

Constraints for organ at risk

Normal organ dose responses from the QUANTEC project.

Reference

NCCN Practice Guidelines in Oncology, 2024

Perez and Brady's : Principles and Practice of Radiation Oncology, 7th ed, 2018

Eric K. Hansen, Handbook of Evidence-Based Radiation Oncology

K.S. Clifford Chao. Practical Essentials of Intensity Modulated Radiation Therapy, 3rd ed, 2013