Taipei Veterans General Hospital Practices Guidelines Oncology

Prostate Cancer

2022.05.30修訂

Definition of Risk Group in Prostate Cancer (NCCN V1.2019)

Risk Group	Clinical/Pathologic Features See Staging (ST-1)		
Very low[e]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core • PSA density <0.15 ng/mL/g		
Low[e]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL		
Intermediate[e]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[f]
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[f]
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL		
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5		

Definition of Histologic Grade Group (G)

Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

IRFs; cT2b-c, prostate-specific antigen [PSA] 10-20, or Gleason score 7.

Histologic Grade Group (G)

- **A new prostate cancer grading system was developed during the 2014 International Society of Urological Pathology (ISUP) Consensus Conference.82 Several changes were made to the assignment of Gleason pattern based on pathology. The new system assigns Grade Groups from 1 to 5, derived from the Gleason score.**
  - Grade Group 1: Gleason score ≤6; only individual discrete well- formed glands
  - Grade Group 2: Gleason score 3+4=7; predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands
  - Grade Group 3: Gleason score 4+3=7; predominantly poorly formed/fused/cribriform glands with lesser component of well- formed glands
    - For cases with >95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy, the component of <5% well-formed glands is not factored into the grade.
  - Grade Group 4: Gleason score 4+4=8; 3+5=8; 5+3=8
    - Only poorly formed/fused/cribriform glands; or
    - Predominantly well-formed glands and lesser component lacking glands (poorly formed/fused/cribriform glands can be a more minor component); or
    - Predominantly lacking glands and lesser component of well-formed glands (poorly formed/fused/cribriform glands can be a more minor component)
  - Grade Group 5: Gleason score 9-10; lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands
    - For cases with >95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy, the component of <5% well-formed glands is not factored into the grade.

Principles of Radiation Therapy

See Practice Guidelines of Radiation Therapy for general standard operating procedures, tolerance dose of critical normal structures, quality assurance, DVH criteria for plan approval, and etc.

- **Radiation therapy for newly diagnosed prostate cancer**
- **Radiation therapy for postoperative prostate cancer**
- **Radiation Therapy for recurrent or metastatic disease**

Principle of Radiation Therapy

• Definitive Radiation Therapy General Principles

- Highly conformal RT techniques should be used to treat localized prostate cancer.
- Photon or particle EBRT are both effective at achieving highly conformal radiotherapy with acceptable and similar biochemical control and long-term side effect profiles.
- Ideally, the accuracy of treatment should be verified by daily prostate localization, with any of the following: techniques of IGRT using CT, ultrasound, implanted fiducials, or electromagnetic targeting/tracking. Endorectal balloons may be used to improve prostate immobilization. Perirectal spacer materials may be employed when the previously mentioned techniques are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic geometry or other patient related factors, such as medication usage and/or comorbid conditions. Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo perirectal spacer implantation.
- Various fractionation and dose regimens can be considered depending on the clinical scenario (See Table 1). Dose escalation has been proven to achieve the best biochemical control in men with intermediate and high risk disease.
- SBRT is acceptable in practices with appropriate technology, physics, and clinical expertise. SBRT for metastases can be considered in the following circumstances:
  - In a patient with limited metastatic disease to the vertebra or paravertebral region when ablation is the goal (eg, concern for impending fracture or tumor encroachment on spinal nerves or vertebra)
  - In a patient with oligometastatic progression where progression free survival is the goal
  - In a symptomatic patient where the lesion occurs in or immediately adjacent to a previously irradiated treatment field.
- Biologically effective dose (BED) modeling with the linear-quadratic equation may not be accurate for extremely hypofractionated (SBRT/SABR) radiation

External Beam Radiation Therapy

- Three-dimensional (3D) CRT (**3D-CRT**) uses computer software to integrate CT images of the patients' internal anatomy in the treatment position, which allows higher cumulative doses to be delivered with lower risk of late effects.[1-4]
- Intensity-modulated RT (**IMRT**) reduced the risk of gastrointestinal toxicities and rates of salvage therapy compared to 3D- CRT.
- Moderately **hypofractionated** image-guided IMRT regimens (2.4 – 4 Gy per fraction over 4–6 weeks) have been tested in randomized trials, and their efficacy has been similar or non-inferior to conventionally fractionated IMRT, with one trial showing fewer treatment failures with a moderately fractionated regimen.[5-14] Toxicity was similar between moderately hypofractionated and conventional regimens in some [5,9,12,13] but not all of the trials.[7,10,11]
- Daily prostate localization using image-guided RT (**IGRT**) is essential with either 3D-CRT or IMRT for target margin reduction and treatment accuracy. Imaging techniques, such as ultrasound, implanted fiducials, electromagnetic targeting and tracking, or endorectal balloon, can improve cure rates and decrease complications.
- A dose of 75.6 to 79.2 Gy in conventional fractions to the prostate (with or without seminal vesicles) is appropriate for patients with low-risk cancers. Intermediate-risk and high-risk patients should receive doses of up to 81.0 Gy.[4,15,16]
- PSA nadir is the lowest value reached after EBRT or brachytherapy.

Principle of Radiation Therapy

- ***Definitive Radiation Therapy by Risk Group***

- **Very low risk**

  - Men with NCCN very low risk prostate cancer are encouraged to pursue active surveillance. EBRT or brachytherapy might considered for patients with expected survival ≧ 20 years.

- **Low risk**

  - Men with NCCN low-risk prostate cancer are encouraged to pursue active surveillance.
  - EBRT or brachytherapy might considered for patients with expected survival ≧ 10 years.

  Prophylactic lymph node radiation should NOT be performed routinely. ADT or antiandrogen therapy should NOT be used routinely.

Principle of Radiation Therapy

- ***Definitive Radiation Therapy by Risk Group***

- **Favorable intermediate risk**

  EBRT or Brachytherapy alone.

  Prophylactic lymph node radiation is not performed routinely,

  and ADT or antiandrogen therapy is not used routinely. Prophylactic lymph node radiation and/or ADT use is reasonable if additional risk assessments suggest aggressive tumor behavior.

- **Unfavorable intermediate risk**

  EBRT + ADT (4 – 6 months)

  EBRT + Brachytherapy ± ADT(4 – 6 months)

  Prophylactic nodal radiation can be considered if additional risk assessments suggest aggressive tumor behavior. ADT should be used unless additional risk assessments suggest less- aggressive tumor behavior or if medically contraindicated. SBRT combined with ADT can be considered when delivering longer courses of EBRT would present medical or social hardship

Principle of Radiation Therapy

- ***Definitive Radiation Therapy by Risk Group***

- **High risk or very high risk**

For expected survival > 5 years or symptomatic

EBRT + ADT (1.5 – 3 years; category 1) ± docetaxel (category 1 for very high risk only)
EBRT + brachytherapy + ADT (1 - 3 years, category 1 for ADT)
Prophylactic nodal radiation should be considered. ADT is required unless medically contraindicated. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT, can be considered when delivering longer courses of EBRT would present a medical or social hardship.

For expected survival ≦ 5 years and asymptomatic

Observation or ADT or EBRT

- **Regional disease**

For expected survival > 5 years or symptomatic

EBRT + ADT
EBRT + ADT + abiraterone
EBRT + ADT + fine-particle abiraterone (category 2B)
Nodal radiation should be performed. Clinically positive nodes should be dose-escalated as dose-volume histogram parameters allow. ADT is required unless medically contraindicated.

Principle of Radiation Therapy

- ***Radiation Therapy metastatic disease***
- **Low-volume metastatic disease**
- Low-volume disease is defined as < 4 bone metastases, no visceral metastases. (CHAARTED criteria)
- Radiation therapy to the prostate is an option in patients with low-volume castration-naive metastatic disease, without contraindications to radiotherapy. ADT is required unless medically contraindicated.
- This recommendation is based on the STAMPEDE phase 3 randomized trial, which randomized 2,061 patients to standard systemic therapy with or without radiotherapy to the primary. The overall cohort had a significant improvement from the addition of radiotherapy to the primary in failure-free survival, but not overall survival. The prespecified low-volume subset had a significant improvement in both failure-free survival and overall survival.
- Minimizing toxicity is paramount when delivering radiation therapy to the primary in patients with metastatic disease.
- Whether treatment of regional nodes in addition to the primary improves outcomes remains uncertain; nodal treatment should be performed in the context of a clinical trial.
- Dose escalation beyond biologically effective dose equivalents of the two dose prescriptions used in STAMPEDE (55 Gy in 20 fractions or 6 Gy x 6 fractions) is not recommended given the known increase in toxicity from dose intensification without overall survival improvement in localized disease.
- Brachytherapy is not recommended.
- **High-volume metastatic disease**
- High-volume disease is defined as presence of visceral metastases and/or ≥4 bony metastases with at least one outside of the vertebral column and pelvis. (CHAARTED criteria)
- Radiation therapy to the prostate should NOT be performed in men with high-volume metastatic disease outside the context of a clinical trial unless for palliative intent.
- This recommendation is based on two randomized trials, HORRAD and STAMPEDE, neither of which showed an improvement in overall survival from the addition of radiotherapy to the primary when combined with standard systemic therapy.

Radiation Dose Regimen

Table 1: Below are examples of regimens that have shown acceptable efficacy and toxicity. The optimal regimen for an individual patient warrants evaluation of comorbid conditions, voiding symptoms and toxicity of therapy. Additional fractionation schemes may be used as long as sound oncologic principles and appropriate estimate of BED are considered.

√ indicates an appropriate regimen option if radiation therapy is given. See PROS-3, PROS-4, PROS-5, PROS-6, PROS-7, PROS-9, PROS-13, and PROS-G for other recommendations, includin recommendations for neoadjuvant/concomitant/adjuvant ADT.

Regimen	Preferred Dose/Fractionation	NCCN Risk Group (✓ indicates an appropriate regimen option if radiation therapy is given)					
		Very Low and Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High[c]	Regional N1	Low Volume M1[a]
EBRT							
Moderate Hypofractionation (Preferred)	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	✓	✓	✓	✓	✓	
	2.75 Gy x 20 fx						✓
Conventional Fractionation	1.8–2 Gy x 37–45 fx	✓	✓	✓	✓	✓	
Ultra-Hypofractionation	7.25–8 Gy x 5 fx 6.1 Gy x 7 fx	✓	✓	✓	✓		
	6 Gy x 6 fx						✓
Brachytherapy Monotherapy							
LDR Iodine 125 Palladium 103 Cesium	145 Gy 125 Gy 115 Gy	✓	✓				
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants	✓	✓				
EBRT and Brachytherapy (combined with 45–50.4 Gy x 25–28 fx or 37.5 Gy x 15 fx)							
LDR Iodine 125 Palladium 103 Cesium	110–115 Gy 90–100 Gy 85 Gy			✓	✓		
HDR Iridium-192	15 Gy x1 fx 10.75 Gy x 2 fx			✓	✓		

[a] High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.

[a] Active surveillance is preferred for men with very low risk and life expectancy ≥20 y and for men with low risk and life expectancy ≥10 y.

[b] "Good" or "Poor" prognostic is not strictly defined. Predictive nomograms and/or molecular testing can be used to prognosticate 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 remains unknown.

[c] Prophylactic nodal radiation may be considered if estimate of nodal metastasis is high.

Principle of Radiation Therapy

- ***Post-Prostatectomy adjuvant/salvage Radiation Therapy***
- The panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, PSADT, and Decipher molecular assay to individualize treatment discussion. Patient with high Decipher genomic classifier scores (GC>0.6) should be strongly considered for EBRT and addition of ADT when the opportunity of early EBRT has been missed.
- EBRT with two years 150 mg/daily of bicalutamide demonstrated improved overall and metastasis-free survival on a prospective randomized trial (RTOG 9601) versus radiation alone in the salvage setting. A secondary analysis of RTOG 9601 found that patients with PSA $\leqq$ 0.6 ng/mL had no OS improvement with the addition of the antiandrogen to EBRT. In addition, results of retrospective analysis of RP specimens from patients in 9601 suggest that those with low PSA and a low Decipher score derived less benefit (development of distance metastases, OS) from bicalutamide than those with high Decipher score.
- EBRT with 6 months of ADT (LHRH agonist) improved biochemical or clinical progression at 5 years on a prospective randomized trial (GETUG-16) versus radiation alone in patients with raising PSA in levels between 0.2 ng/Ml and 2.0 ng/mL after RP .
- The ongoing SPPORT trial (NCT00567580) of patients with PSA level between 0.1 and 2.0 ng/mL at least 6 weeks after RP has reported preliminary results on *clinicaltrials.gov* . The primary outcome measure of percentage of participants free for progression (FFP) at 5 years was 70.3 (95% CI 66.2-74.3) for those who received EBRT to the prostate bed and 81.3 (95% CI, 77.9-84.6) for those who also received 4-6 months of ADT (LHRH agonist plus antiandrogen).

- ***Post-Prostatectomy adjuvant/salvage Radiation Therapy***

- The panel recommends consultation with the American Society for Radiation Oncology (ASTRO)/AUA Guidelines. Evidence supports offering adjuvant/salvage RT in most men with adverse pathologic features or detectable PSA and no evidence of disseminated disease.
- Indications for adjuvant RT include pT3a disease, positive margin(s), or seminal vesicle involvement. Adjuvant RT is usually given within 1 year after RP and after operative side effects have improved/ stabilized. Patients with positive surgical margins may benefit the most.
- Indications for salvage RT include an undetectable PSA that becomes subsequently detectable and increases on 2 measurements or a PSA that remains persistently detectable after RP. Treatment is more effective when pre-treatment PSA is low and PSADT is long.
- The recommended prescribed doses for adjuvant/salvage post- prostatectomy RT are 64 to 72 Gy in standard fractionation. Biopsy- proven gross recurrence may require higher doses.
- Nuclear medicine advanced imaging techniques can be useful for localizing disease with PSA levels as low as 0.5 ng/mL
- Nomograms, and tumor-based molecular assays, can be used to prognosticate risk of metastasis and prostate cancer-specific mortality in patients with adverse risk features after RP.
- Target volumes include the prostate bed and may include the whole pelvis according to physician discretion.

- ***Post-Prostatectomy adjuvant/salvage Radiation Therapy***

Available Tissue-Based Tests for Prostate Cancer Risk Stratification/Prognosis

Test	Platform	Populations Studied	Outcome(s) Reported (Test independently predicts)	Selected References	Molecular Diagnostic Services Program (MolDX) Recommendations
Decipher	Whole-transcriptome 1.4M RNA expression (46,050 genes and noncoding RNA) oligonucleotide microarray optimized for FFPE tissue	Post radical prostatectomy (RP), adverse pathology/high-risk features	• Metastasis • Prostate cancer-specific mortality • Postoperative radiation sensitivity (PORTOS)	155,158,159,580,845-858	Cover post-biopsy for NCCN very-low-, low-risk, favorable intermediate, and unfavorable intermediate risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
		Post RP, biochemical recurrence/PSA persistence	• Metastasis • Prostate cancer-specific mortality • PORTOS		
		Post RP, adjuvant, or post-recurrence radiation	• Metastasis • Prostate cancer-specific mortality • PORTOS		
		Biopsy, localized prostate cancer post RP or EBRT	• Non-organ confined (pT3) or grade group 3 disease at RP • Lymph node metastasis • Biochemical failure/recurrence • Metastasis • Prostate cancer-specific mortality • Grade Group ≥4 disease at RP		
		M0 CRPC	• Metastasis-free survival		
Ki-67	IHC	Biopsy, conservatively managed (active surveillance)	• Prostate cancer-specific mortality	859-862	Not recommended
		Biopsy, low- to intermediate-risk treated with RP	• Non-organ-confined pT3 or Grade Group ≥4 disease on RP		
Oncotype DX Prostate	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls	Biopsy, very low- to high-risk treated with RP	• Non-organ-confined pT3 or Grade Group 4 disease on RP • Biochemical recurrence • Metastases • Prostate cancer-specific mortality	157,863,864	Cover post-biopsy for NCCN very-low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
Prolaris	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	Biopsy, conservatively managed (active surveillance)	• Prostate cancer-specific mortality	150-153,865-867	Cover post-biopsy for NCCN very-low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
		Biopsy, localized prostate cancer	• Biochemical recurrence • Metastasis		
		Biopsy, intermediate-risk treated with EBRT	• Biochemical recurrence		
		RP, node-negative localized prostate cancer	• Biochemical recurrence		
		Biopsy, Gleason grade 3+3 or 3+4	• Non–organ-confined pT3 or Grade Group ≥3 on RP		
PTEN	Fluorescence in situ hybridization or IHC	Biopsy, Grade Group 1	• Upgrading to Grade Group ≥3 on RP	868-872	Not recommended
		RP, high-risk localized disease	• Biochemical recurrence		

- ***Radiopharmaceutical Therapy***
- Radium-223 is an alpha-emitting radiopharmaceutical that has been shown to extend survival in patients who have CRPC with symptomatic bone metastases, but no visceral metastases. Radium-223 alone has not been shown to extend survival in patients with visceral metastases or bulky nodal disease (>3–4 cm). Radium-223 differs from beta-emitting agents, such as samarium-153 and strontium-89, which are palliative and have no survival advantage. Radium-223 causes double-strand DNA breaks and has a short radius of activity. Grade 3–4 hematologic toxicity (ie, 2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at low frequency.
- Radium-223 is administered intravenously once a month for 6 months by an appropriately licensed facility, usually in nuclear medicine or RT departments.
- Prior to the initial dose, patients must have absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L, and hemoglobin ≥10 g/dL.
- Prior to subsequent doses, patients must have ANC ≥1 x 10^9/L and platelet count ≥50 x 10^9/L (per label). Radium-223 should be discontinued if a delay of 6–8 weeks does not result in the return of blood counts to these levels.
- Non-hematologic side effects are generally mild, and include nausea, diarrhea, and vomiting. These symptoms may occur because radium-223 is eliminated predominantly by fecal excretion.
- Radium-223 is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression, except in a clinical trial.
- Radium-223 may increase fracture risk when given concomitantly with abiraterone.
- Radium-223 is not recommended for use in combination with docetaxel or any other systemic therapy except ADT.
- Concomitant use of denosumab or zoledronic acid is recommended; it does not interfere with the beneficial effects of radium-223 on survival.

Principle of Radiation Therapy

- ***Oligometastatic and Palliative Radiotherapy***

- 8 Gy as a single dose is as effective for pain palliation at any bony site as longer courses of radiation, but re-treatment rates are higher.
- Widespread bone metastases can be palliated using strontium-89 or samarium-153 with or without focal external beam radiation.
- SBRT can be considered, in the following circumstance
  a. In a patient with limited metastatic disease to the vertebra or paravertebral region when ablation is the goal (eg, concern for impending fracture or tumor encroachment on spinal nerves or vertebra).
  b. In a patient with oligometastatic progression where progression free survival is the goal
  c. In a symptomatic patient where the lesion occurs in or immediately adjacent to a previously irradiatied treatment field.
- Treatment of the primary site in men with metastatic disease can be used to palliate obstructive symptoms due to tumor. Definitive external beam dosing regimens, or traditional palliative regimens (eg, 30 Gy/10 fx or 37.5 Gy/15 fx), can be used depending on clinical scenario.

Cancer of Prostate

General Radiation Information

General Radiation Information

– Treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team including surgical, radiation, medical oncologists, radiologists, and pathologists.

– initial PSA level, pathology, CT/MR scans, Whole body bone scan reports and/or MR, when available, should be reviewed by the multidisciplinary team. This will allow an informed determination of treatment volume and field borders prior to simulation.

Simulation

– Immobilization device is strongly recommended for reproducibility of daily set-up

To minimize setup variability, a customized immobilization device for both knee and foot (Alpha Cradle; Smithers Medical Product, Inc., North Canton, OH) was applied to each patient in the supine position.

- Full bladder (200-300 mL water drinking 30-60 minutes before simulation) and empty rectum are recommended every patient.
- MR imagine fusion is strongly recommended

Retrograde urethrogram* is recommended if no MR imagine fusion.

- CT simulation and 3D treatment planning is necessary.

A treatment planning computed tomography scan was performed using 5-mm slices. The CT scans were obtained from the L2 vertebral body to 5 cm below the ischial tuberosities with an average of 80 images per patient. All patients had a full bladder and empty rectum during scanning and simulation. During daily treatment they were instructed to have a full bladder.

Principle of Target volume delineation

Definitions of target volumes and critical structures

- Following the International Commission on Radiation Units and Measurements ICRU 62 recommendations, a clinical target volume (CTV) was delineated on individual axial computed tomography slices in all patients by our radiation oncologist and reviewed by another.

Gross Target Volume (GTV) delineation

- Target volume delineation based on CT simulation images. Diagnostic CT/MR reports, and PET/CT scans should be reviewed, when available, for precise delineation of GTV.
- MR imagine fusion is strongly recommended

Retrograde urethrogram is recommended for define of prostate apex if no MR imagine fusion available.

Clinical Target Volume (CTV) delineation

- The clinical target volume should include GTV and the areas at risk for microscopic disease

For definitive radiotherapy:

- CTV_H: prostate + proximal bilateral seminal vesicles(cT2-3a) or bilateral SV(cT3b)
- CTV_M: prostate + proximal or bilateral SV ± LAP(MR/CT).
- CTV_L: prostate + bilateral seminal vesicles ± pelvic LNs# for pelvic radiotherapy

For postoperative radiotherapy:

- CTV_H: prostatic fossa
- CTV_M: prostatic fossa ± pelvic LNs
- Biopsy-proven gross recurrent tumor may be designated as CTV_XH
- The final target volume should consider the relative risk of nodal metastases at specific nodal location, which is dependent on the origin site of primary tumor.

Principle of Target volume delineation

Pelvic LNs:

a. Prophylactic nodal radiation can be considered for patients of unfavorable intermediate risk or high risk group; and should be considered for patients of very high risk group. For patients of favorable intermediate risk group, prophylactic nodal radiation is reasonable if additional risk assessments suggest aggressive tumor behavior.

b. Prophylactic nodal radiation should include entirety external iliac (the transition from the external iliac to the inguinal nodes occurs when the external iliac vessels cross beneath the inguinal ligament into the inguinal canal), internal iliac and obturator nodal basin

c. Pelvic nodal radiation should be performed in N1 disease. In these cases, pre-sacral, common iliac should be covered as well.

Principle of Target volume delineation

Planning Target Volume (PTV) delineation

- The margins of PTV should consider respiratory motion and setup errors
- For single-phase CT simulation, the recommended margins to compensate organ motions are as follows: (IMRT/IGRT)

PTV_H = CTV_H + Superior-inferior: 8/5 mm, Right-left: 8/5 mm, anterior: 8/5 mm, posterior: 5/4 mm
PTV_M = CTV_M + Superior-inferior: 10/8 mm, Right-left: 10/8 mm, anterior: 7/6 mm, posterior: 5/5 mm
PTV_L = CTV_L + Superior-inferior: 10/8 mm, Right-left: 10/8 mm, anterior: 7/6 mm, posterior: 5/5 mm

Radiation dose

- Definitive Radiotherapy

*Conventional fractionation:
PTV_H: 75.6 – 80 Gy/36–40 Fx
PTV_M: 66 – 72 Gy/33-36 Fx
PTV_L: 50.4 – 54 Gy/27-28 Fx
*Moderately hypofractionation image-guided IMRT regimens with 2.4-4.0 Gy/Fx, 4–6 weeks might be considered.
* Other dose regimens can be referred to NCCN guideline (Prostate V12.2019, Table 1)

- Postoperative radiotherapy:

PTV_H: 64–72 Gy/32–40 Fx (Higher dose for biopsy proved recurrent gross tumor)
PTV_M: 50.4 Gy/ 28Fx if pelvic radiotherapy is needed.

***Radiation technique*:**

- IMRT or IGRT
- Ideally, the accuracy of treatment should be verified by daily prostate localization, for examples, IGRT using CBCT.

Androgen deprivation therapy(ADT) in combination with RT

- Definitive RT
  - For favorable intermediate risk group, short-term ADT (4-6 months) is reasonable if additional risk assessments suggest aggressive tumor behavior.
  - ADT should be used in unfavorable intermediate risk group unless medical contraindicated. The duration of ADT can be reduced when combined with EBRT and brachytherapy. Brachytherapy combined with ADT (without EBRT), or SBRT combine with ADT can be considered if delivering longer courses of EBRT would present medical or social hardship.
  - For high risk group, very high risk group and node positive disease, long-term ADT (2-3 years) is required unless medically contraindicated.
- Postoperative RT
  - Two years of ADT with 150 mg/daily of bicalutamide (RTOG 9601) or 6 months of ADT (GETUG-16) have both demonstrated improved overall and metastasis-free survival on prospective randomized trials versus radiation alone in the salvage setting.

Carbon ion Radiotherapy (CIRT)

- Indication:
  - Stage: cT1-4N0M0 (T4 for bladder neck invasion)
  - No previous RP or prostate cancer radiotherapy history
- Dose: 51.6 Gy(RBE)/12 Fx, 4 Fx/week
- Technique:
  - IGRT with fiducial markers (gold seeds, lipoid diposit…etc) + orthogonal X-ray or CT scan
  - Empty rectum (Anal pumping) and bladder volume of 100-150 mL (ultrasound bladder scan)
- Contouring
  - MR image fusion for GTV contouring (prostate and seminal vesicle).
  - CTV= prostate + proximal SV (whole SV for cT3b)
  - PTV = CTV + 0.8 cm (bilateral), 0.5 cm (others)
  - ORA: bladder, bowel, rectum (1.0 cm above and below CTV)

CIRT management of prostate cancer

Risk Group	Factor	Treatment
Low	PSA ≦10 ng/mL cT1-T2a GS≦6	CIRT alone
	cT2b or GS: 3+4	CIRT alone
Intermittent	10<PSA≦20 or GS = 4+3	CIRT + ADT 3 months
	10<PSA≦20 cT2b-2c GS = 7	CIRT + ADT 6 months
High	PSA > 20 ng/mL >cT3a GS >8	CIRT + ADT 24 months

Abbreviation

- RT: Radiation Therapy
- 3D-CRT: 3D Conformal Radiation Therapy
- IMRT: Intensity Modulated Radiation Therapy
- IGRT: image guided radiotherapy
- GTV: Gross Tumor Volume
- CTV: Clinical Target Volume
- PTV: Planning Target Volume
- MRI: Magnetic Resonance Image
- PET: Positron Emission Tomography
- CIRT: Carbon ion Radiotherapy

Reference

1. Dearnaley DP, Khoo VS, Norman AR, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. Lancet 1999;353:267-272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9929018.

2. Hanlon AL, Watkins Bruner D, Peter R, Hanks GE. Quality of life study in prostate cancer patients treated with three-dimensional conformal radiation therapy: comparing late bowel and bladder quality of life symptoms to that of the normal population. Int J Radiat Oncol Biol Phys 2001;49:51-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11163497.

3. Koper PC, Stroom JC, van Putten WL, et al. Acute morbidity reduction using 3DCRT for prostate carcinoma: a randomized study. Int J Radiat Oncol Biol Phys 1999;43:727-734. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10098427.

4. Michalski JM, Bae K, Roach M, et al. Long-term toxicity following 3D conformal radiation therapy for prostate cancer from the RTOG 9406 phase I/II dose escalation study. Int J Radiat Oncol Biol Phys 2010;76:14-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19577865.

5. Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. J Clin Oncol 2013;31:3860-3868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24101042.

6. Arcangeli S, Strigari L, Gomellini S, et al. Updated results and patterns of failure in a randomized hypofractionation trial for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2012;84:1172-1178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22537541.

7. Arcangeli G, Saracino B, Arcangeli S, et al. Moderate Hypofractionation In High-Risk, Organ-Confined Prostate Cancer: Final Results Of A Phase III randomized trial. J Clin Oncol 2017;35:1891-1897. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28355113.

8. Incrocci L, Wortel RC, Alemayehu WG, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2016;17:1061-1069. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27339116.

9. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016;17:1047-1060. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27339115.

Reference

10. Aluwini S, Pos F, Schimmel E, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. Lancet Oncol 2015;16:274-283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25656287.

11. Lee WR, Dignam JJ, Amin MB, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. J Clin Oncol 2016;34:2325-2332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27044935.

12. Catton CN, Lukka H, Gu CS, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. J Clin Oncol 2017;35:1884-1890. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28296582.

13. Hoffman KE, Voong KR, Levy LB, et al. Randomized trial of hypofractionated, dose-escalated, intensity-modulated radiation therapy (IMRT) versus conventionally fractionated IMRT for localized prostate cancer. J Clin Oncol 2018;36:2943-2949. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30106637.

14. Bruner DW, Pugh SL, Lee WR, et al. Quality of life in patients with low-risk prostate cancer treated with hypofractionated vs conventional radiotherapy: A phase 3 randomized clinical trial. JAMA Oncol 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30763425.

15. Xu N, Rossi PJ, Jani AB. Toxicity analysis of dose escalation from 75.6 gy to 81.0 gy in prostate cancer. Am J Clin Oncol 2011;34:11-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20101167.

16. Eade TN, Hanlon AL, Horwitz EM, et al. What dose of external-beam radiation is high enough for prostate cancer? Int J Radiat Oncol Biol Phys 2007;68:682-689. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17398026.