Prostate Cancer Localized and Locally Advanced Treatment

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1. Treatment

Primary treatment options for localized prostate cancer consist of active surveillance, radical prostatectomy, or radiation therapy. **Treatment choice is guided by PCa risk stratification, patient life expectancy, assessment of oncologic and quality of life outcomes, and patient preference**. The concept of **"shared decision-making"** between the patient, urologist, and radiation oncologist has arisen to emphasize the critical role of an educated patient in choosing a prostate cancer management strategy most consistent with an individual's preferences and values.

No randomized trials have compared active surveillance as it is currently practiced in the United States with radical prostatectomy, but several trials have compared observation (or watchful waiting) versus radical prostatectomy(**Table 1**).[1,2,3,4,5]

- **The Scandinavian Prostate Cancer Group Study No. 4 (SPCG 4) reported an improvement in overall and disease-specific mortality for men undergoing radical prostatectomy compared to watchful waiting. The absolute OS benefit favoring prostatectomy was 12%, which translated to a median 2.9 years of life gained at median 23 years of follow-up.**
- **The Prostate Cancer Intervention Versus Observation Trial (PIVOT) found that radical prostatectomy did not improve overall or disease-specific mortality at a median follow-up of 12.7 years.[2,3] However, surgery reduced the risk of progression (40.9% vs 68.4%; HR 0.39, 95% CI 0.32-0.48) and treatment for progression (33.5% vs 59.7%; HR 0.45, 95% CI 0.36-0.56) compared to watchful waiting**.
- The **Prostate Testing for Cancer and Treatment (ProtecT) trial** randomized 1,643 men with screen-detected PCa to active monitoring, radical prostatectomy, or radiation therapy with curative intent. At a **median of 10 years, no differences in PCa mortality were observed across groups (PCa deaths per 1,000 person years: active monitoring 1.5, surgery 0.9, radiation 0.7, p = 0.48)**. Of note, more metastases were observed in the active monitoring group (6.3 per 1,000 person years) compared to surgery (2.4 per 1,000 person years) or radiation therapy (3.0 per 1,000 person years, p = 0.004).[6] A secondary analysis, according to treatment received, demonstrated increased incidence of disease progression (22.6% vs. 5.3%, p < 0.001) and initiation of ADT (8.4% vs. 4.5%, p = 0.002) in the active monitoring group compared with surgery and RT. [7]

Podcasts

Help patients decide on prostate cancer screening and treatment

Urology Care Episode 8: Prostate Cancer 101 with Dr. Scott Eggener

Urology Care Episode 26: How Early-Stage Prostate Cancer Treatments Impact Quality of Life with Dr. David Penson

Table 1: Randomized Trials Comparing Observation versus Radical Prostatectomy

Study	N	Median Follow-up	Overall Mortality	PCa Mortality
Bill-Axelson, et al.	695	23.6 years	Deaths: 261 (71.9%) RP vs 292 (83.8%) Obs RR: 0.74 (95% CI 0.62-0.87; p<0.001)	Deaths: 71 (21.5%) RP vs 110 (31.6%) Obs RR: 0.55 (95% CI 0.41-0.74; p<0.001)
Wilt, et al.	731	12.7 years	Deaths: 223 (61.3%) RP vs 245 (66.8%) Obs HR: 0.92 (95% CI 0.82-1.02)	Deaths: 27 (7.4%) RP vs 42 (11.4%) Obs HR: 0.65 (95% CI 0.41-1.03)
Hamdy, et al	1,643	10.0 years	59 Obs vs. 55 RP vs. 55 RT (p=0.87)	8 Obs vs. 5 RP vs. 4 RT (p=0.48)

1.1 Active Surveillance

- Active surveillance (AS) is defined as a treatment strategy wherein **men with low risk PCa are serially monitored for disease progression with the intent of pursuing definitive treatment in the setting of disease progression or per patient preference, thereby delaying or avoiding the risk of treatment-related morbidity**.[8]
    - See **Urology Care Podcast Episode 99: Facts About Active Surveillance for Prostate Cancer**
- Knowledge from PCa screening randomized trials and the high incidence of PCa in autopsy studies[9,10,11] has generated increased interest in AS as a preferred treatment option for many patients.
- Data indicates that AS is a safe and effective treatment option for appropriately selected PCa patients.[12,13,14,15,16]
- **The shared decision to pursue AS considers oncologic risk (risk of disease progression), patient comorbidities/competing risks and projected life expectancy, potential treatment-related harms, and patient preferences**.
- Importantly, AS differs from observation or watch waiting (WW) in that WW indicates a decision to avoid/forgo definitive therapy and palliate only if there is symptomatic metastatic progression.
- AS Entry Criteria
    - Entry criteria for AS protocols vary from institution to institution (**Table 2**). **Men with very low risk and low risk PCa per AUA and NCCN guidelines (or clinically insignificant disease per Epstein criteria) are typically candidates for AS**.[17,18] These criteria include:
        1. **Grade Group 1 (Gleason score ≤ 6)**
        2. **Clinical stage ≤ T2a**
        3. **PSA density < 0.15ng/mL/g**
        4. **< or ≤ 3 positive biopsy cores**
        5. **≤ 50% cancer in each core**
    - Several updated guidelines including the NCCN Guidelines for Prostate cancer (version 2.2020) also include AS as an option for patients with PSA < 10, stage ≤ T2a, and Grade Group 2 (Gleason 3+4) in fewer than 50% of biopsy cores (NCCN favorable intermediate risk disease) and greater than 10 years life expectancy[19,20,21]
    - 15-year metastasis-free survival was worse in patients with PSA < 20 and Grade Group 2 disease (84%) compared to patients with PSA 10-20 and Grade Group 1 disease (94%) in the Toronto series.[22]
    - Among 219 men with GG2 disease who elected AS in the MSKCC cohort, 29% elected treatment; of these, 3 patients experienced biochemical recurrence, and none developed metastatic disease at median 3.1 years of follow-up.[23]
    - **Acknowledging the heterogeneity of intermediate risk disease and limitations of histopathologic staining, patients with Grade Group 2 cancers should be followed closely with consideration of other risk factors including PSA density, presence of cribriform pathology, mpMRI findings, and genomic testing**
- AS Monitoring
    - Similar to entry criteria, the monitoring protocols vary across institutions.
        - PSA and digital rectal exam (DRE) every 3-6 months (may extend to annual assessments for older men with stable, low risk disease)[8]
            - Consideration of a confirmatory biopsy with mpMRI guidance (if not already performed) is recommended by some authors to allow more accurate baseline risk stratification[24]
            - Data suggest that **a systematic biopsy should be performed concurrently with an MRI-targeted biopsy** since a significant proportion of high-grade cancers are detected on systematic biopsies alone[25,26]
            - Repeat prostate biopsies (either scheduled or for-cause) are performed every 1-3 years. Use of standard TRUS-guided biopsy is the most common approach; however, fusion mpMRI may also be used.[27]

- The role of PSA kinetics (PSA doubling time, PSA velocity) remains uncertain.
- The role of molecular biomarkers is uncertain, and routine use is not recommended. However, biomarkers may improve risk stratification, inform management decisions, or influence repeat biopsy intervals [28]

- AS Indicators for Definitive Treatment
  - As with AS selection and monitoring, indicators of progression to trigger definitive treatment vary by institution. **An increase in Gleason grade, number of positive cores, or percentage of cores positive are common triggers for physicians to recommend definitive treatment. Increasing PSA and subsequent patient anxiety/fear of cancer or even repeat prostate biopsies are other common triggers for patients to electively choose definitive treatment.**
  - Biomarker testing with the use of Oncotype DX Prostate, Prolaris, Decipher, or Promark may help reveal patient mortality risk, disease stage, or biochemical recurrence or failure,[25] which may influence decision making.

Table 2: Active Surveillance Inclusion Criteria for Current Protocols

Institution	Clinical Stage	Gleason Score	Number of Cores	Cancer Percentage	PSA (ng/ml)	PSA Density (ng/ml/g)
Johns Hopkins[29]	≤T2a	≤3+3	≤2	≤50%	None	≤0.15
MSKCC[30]	≤T2a	≤3+3	≤3	≤50%	≤10	
PRIAS/ERSPC[31]	≤T2a	≤3+3	≤2	None	≤10	≤0.2
Royal Marsden[32]	≤T2a	≤3+3	≤50%	None	≤15	
U of Miami[33]	≤T2a	≤3+3	≤2	≤20%	≤10	
U of Toronto[13]	None	≤3+4	None	None	≤10	
UCSF[34]	≤T2a	≤3+3	≤33%	≤50%	≤10	

1.2 Radical Prostatectomy

- Radical prostatectomy (RP) is a curative treatment option for men with clinically localized PCa.
- Extirpation allows for accurate pathologic grading and staging and makes treatment failures easy to identify if and when PSA becomes detectable after surgery.
- Various surgical approaches for RP have evolved over the years including robotic, open retropubic, laparoscopic, and open/robotic perineal RP. Currently, the robotic-assisted laparoscopic and open retropubic approaches are performed most commonly in the US.
- Regardless of surgical approach, RP involves en bloc removal of the prostate and seminal vesicles followed by urethrovesical anastomosis.
- **NCCN (v1.2022) guidelines** recommend lymph node dissection when the probability of lymph node involvement is 2% or higher
- Preoperative imaging with mpMRI may facilitate identification of adverse pathologic features (EPE or SVI) and inform eligibility for nerve-sparing surgery through identification of neurovascular invasion, extracapsular disease. Further studies are needed to determine whether mpMRI should be a standard of care as part of staging.[35]
- **Following RP, the Decipher biomarker test** may be used to predict[36] future risk of metastasis in patients with high-risk features, such as positive margins, pT3 disease, and/or rising PSA.

1.3 Technique

- Open retropubic RP
  - Significant improvements in open retropubic RP technique due to early ligation of the DVC and identification and preservation of the neurovascular bundles during the 1980's and 1990's led to decreased complications and improved functional outcomes.[37,38,39]
  - A full description of open RP technique can be found in Campbell-Walsh Urology.[40]
- **Minimally Invasive (Robotic-assisted laparoscopic radical prostatectomy)**
  - The minimally-invasive laparoscopic approach was described in the 1990s but was quickly replaced by the robotic-assistance laparoscopic RP in the early 2000s.
  - Robotic-assisted laparoscopic RP has become the most utilized approach for the surgical treatment of PCa.
  - It was estimated that by 2010 67% to 85% of all prostatectomies performed in the US were done so robotically.[41]
  - The most common robotic RP technique mirrors the open retropubic RP, incorporating an anterior approach through the space of Retzius. Approximately 90% of robotic prostatectomies in the US are done this way.
  - RALP has led to recent innovation in surgical techniques such as the Retzius-sparing and anterior hood approaches. These modifications to the standard techniques may lead to improvement in short-term outcomes.[42]
  - A posterior Retzius-sparing approach that parallels the open perineal prostatectomy has seen increased interest due to its association with earlier return of continence, despite criticism due to higher reported positive margin rates.[43,44]
  - A full description of robotic RP technique can be found in Campbell-Walsh Urology.[40]
- Population-based studies during the dissemination-phase and post-dissemination of RALP have demonstrated that RALP is associated with fewer post-operative complications, less blood loss and shorter length of stay. However, it is essential to acknowledge the risk of selection bias.[45,46,47]
- Although RALP has become the predominant surgical approach for localized prostate cancer in the U.S studies have not shown an overwhelming improvement in functional and oncologic outcomes. Surgeon- and patient-specific factors likely have a bigger impact than the surgical approach
- An early clinical trial of 326 men, randomly allocated to RALP and ORP showed similar results in positive surgical margins (10% vs. 15%) and similar quality of life outcomes for sexual function and urinary control at 12 weeks. There was no difference in two-year functional outcomes.[48]

1.4 Outcomes (Oncologic, Quality of Life, and Cost)

- Compared to the open approach, **RALP is associated with lower blood loss, lower transfusion rate and shorter postoperative length of hospital stay**[49]
- Initial population-based studies found no apparent differences in adjusted perioperative complications between minimally invasive and open approaches;[50,51] but **contemporary analyses report statistically significant reduction of perioperative complications, including cardiac and respiratory adverse events favoring the robotic-assisted laparoscopic technique**.[52,53,54] (**Table 2**).
- **Positive surgical margin rates and short-term biochemical progression-free rates appear similar between the two approaches.**[55,56]
- 8-year follow-up data from the LAPRO trial reported lower PCSM in patients undergoing RALP (aRR 0.56, 95% CI 0.34-0.93)[57]
    - Lower PSM: 21% vs 34%
    - Lower BCR: 51% vs 69%[56,58]
- A SEER-MEDICARE analysis found RARP was associated with lower PSM rate and better early cancer control (judged by use of additional therapies within two years of surgery) compared to ORP (PSM: 13.6% vs. 18.3%)[47,44]
- Data comparing continence rates between the two RP surgical approaches have yielded mixed results, but a cumulative analysis in 2012 of five studies demonstrate a marginal advantage for the robotic approach (12-month urinary incontinence rates: open RP 11.3% versus robotic RP 7.5%) [59] (**Table 3**).
- Importantly, **pre-operative urinary continence and erectile function predict post-operative outcomes and detailed pre-operative assessment enables better counseling to educate patients on functional outcome recovery**. However, studies evaluating functional outcomes are mixed between physician assessment and patient-reported outcomes. Furthermore, functional outcomes vary depending on the person obtaining the data (patient, physician, 3rd party).
- The Retzius-sparing (posterior) approach to robotic radical prostatectomy is associated with a statistically significant earlier return to continence compared to the standard approach based on a Cochrane review, which included 5 randomized trials. Beyond 6-12 months there does not seem to be a difference between techniques
- Despite early population-based data suggesting inferior erectile function outcomes from robotic RP[50,51] more recent single institutional data favor the robotic approach (**Table 3**).
- A cumulative review of six studies using varying definitions of erectile dysfunction found lower 12-month erectile dysfunction rates for robotic RP (24%) versus open RP (48%) (odds ratio for potency with RARP versus open RP [OR]: 2.84; 95% confidence interval [CI]: 1.46–5.43);.[60]
- 8-year data from the Swedish LAPRO trial (4003 men undergoing either ORP or RALP) found no difference in urinary incontinence (RARP: 27% vs ORP: 29%), but slightly less ED with RALP (66% vs 70%)[57]
- **In a Phase III randomized trial comparing 150 men undergoing robotic prostatectomy and 146 men undergoing open radical retropubic prostatectomy, no differences in urinary function or erectile function scores were noted at 6, 12, or 24 months**.[48]
    - Robotic-assisted RP is more costly in the perioperative period than open RP.[61,62] However, this may be offset by decreased healthcare utilization during the year following surgery.[63]

Table 3: Oncologic Outcomes of Open versus Robotic RP: Biochemical Progression-Free Survival

Study	3-Year Biochemical PF-Open RP	3-Year Biochemical PF-Robotic RP	Follow-up (months)
Barocas[64]	84%	84%	Open = 17 Robotic = 8
Krambeck[65]	92%	92%	Open = 15.6 Robotic = 15.6
Magheli[59]	93%	94%	Open = 30 Robotic = 16
Schroeck[66]	NR	NR	Open = 16.4 Robotic = 13.1

Table 4: Functional Outcomes of Open versus Robotic RP: Urinary Continence and Potency

Study	Urinary Continence (% at 12 months)- Open RP	Urinary Continence (% at 12 months)- Robotic RP	Erectile Function (% at 12 months)- Open RP
Krambeck[67]	94% (n=564)	92% (n=286)	63% (n=417)
Kim[68]	—	—	28% (n=122)
Ficarra[69]	88% (n=105)	97% (n=103)	49% (n=41)
Di Pierro[70]	80% (n=75)	89% (n=75)	26% (n=47)
Thompson[71]	65.1% (n=230)	57.1 (n=379)	26.2% (n=230)

1.5 Complications of Radical Prostatectomy

- Perioperative complications have substantially decreased with the evolution of RP surgical techniques. The incidence of open and robotic RP complications is well-characterized in both population-based and institutional series.[37,54,72,73,74]
- Intraoperative complications include:
    - Transfusion: ORP: 16.5%/RALP: 1.8%[56]
    - Rectal/bowel injury (0.2% - 0.47%)[75]
    - Bladder/ureteral injury ORP: 0.05%/1.5%; RALP: 0.07%/0.1%[56]
    - Obturator nerve injury 0.4%[56]
    - DVT/PE: ORP: 1.0%/0.5%; RALP: 0.3%/0.3%[56]
- Postoperative risks include:
    - Venous thromboembolic events (0.2%)
    - Incontinence (4-31%)
    - Erectile dysfunction (10-46%)[76,77]
    - Vesico-urethral anastomotic leak (1.8%); (0.3% - 15.4%)[78]
    - Lymphocele (3.1%)
    - Urinary retention (0.7%)
    - Bladder neck contracture (0.9%: robotic/ 2.2% open)
    - Incisional Hernia[79,80]
        - Port site (extraction): 2.3% - 8.6%
        - Lateral port site: 1.1%
        - Incisional (open): 1.4%[80]
    - Inguinal Hernia[81]
        - Open RP: 13.7%
        - RALP: 7.9%
    - Neuropraxia (0.2%)
    - Hematoma (0.3%)
    - Wound Complication (0.5%)
    - Ileus: 0.8%[56]
    - Reoperation (1.6%)
    - Mortality (0.02%)

1.6 Surgery in High Risk/Locally Advanced Prostate Cancer

- Surgery in the setting of high risk and locally advanced (pT3/b) prostate cancer has seen a resurgence. With improved imaging techniques and understanding of surgical anatomy, surgery for locally advanced disease can be completed with acceptable oncologic and functional outcomes.
- Consideration of disease location and burden may require altering surgical approach or surgical extent of dissection. Robotic or open techniques have shown comparable outcomes, but approach should not dictate the extent of the operation.[82]
- Advanced disease has a greater risk of LN involvement and therefore **a pelvic lymph node dissection at the time of prostatectomy is recommended**.[83]
- Neoadjuvant systemic therapy with ADT alone (short- or long-term use), while showing improvements in preoperative PSA nadir and decreased surgical margins, has shown **no advantage in PFS or OS**.[84]
- More recently, the role of neoadjuvant therapy prior to radical prostatectomy was evaluated in the PUNCH trial. This study randomized patients with high-risk, clinically localized prostate cancer to neoadjuvant chemohormonal therapy with docetaxel and ADT plus radical prostatectomy or radical prostatectomy alone. Results indicated no difference in 3-year biochemical progression free rates, the primary endpoint. However, neoadjuvant

chemohormonal therapy was associated with improved MFS and OS compared to surgery alone. Authors note that consideration must be given to toxicity associated with systemic therapy.[85]

1.7 Pelvic Lymph Node Dissection

- A **standard PLND** includes removal of lymphatic tissue between the external iliac vein and the internal iliac artery (including tissue within the obturator fossa), proximally up to the bifurcation of the common iliac artery, and distally to Cooper's ligament.
- **Definitions of extended and super extended lymph node dissection have been introduced. Their role is currently under investigation.**[86]
    - **Extended LND**: External iliac, obturator fossa, hypogastric/internal iliac, common iliac below the point where the ureter crosses.
    - **Super-extended LND**: Above, plus pre-sacral lymph nodes and iliac below the aortic bifurcation.
- Low grade prostate cancer has a very low likelihood of positive LN involvement and patients are commonly placed on Active Surveillance, however if a prostatectomy is to be completed the utility of LND is unclear[87] and PLND is not currently included in the guidelines in this setting.[88]
- Bilateral PLND in intermediate risk prostate cancer is often performed. Nomograms may be used to estimate the risk of LN involvement.[89] Risk and benefits of the procedure should be discussed with the patient.
- Bilateral pelvic lymph node dissection (PLND) is believed by many to be an integral part of RP in men with high risk PCa because it aids in staging, prognostication, and may have a therapeutic benefit.[90,91]
- Substantial variation exists in PLND practice patterns and extent of dissection.[92,93]
- There is debate regarding the risk/benefit ratio related to increasing utilization of LND. Retrospective data has demonstrated a potential impact on urinary continence, erectile function and the potential for a greater risk for surgical and postoperative complications, particularly vascular injury and post-operative lymphoceles. [94]

2. Primary Radiation Therapy

2.1 General Concepts

- Radiation therapy (RT) most commonly uses high energy (6-15 Megavoltage) X-rays (i.e. photons) delivered to targets deep in the body.
- These X-rays are usually generated by a machine called a linear accelerator (LINAC). A LINAC uses an electrical source to power an electron gun, which generates electrons that are accelerated down a waveguide to a high energy. These electrons then strike tungsten, generating photons by a reaction called bremsstrahlung. These photons are then shaped by large metal jaws, and then smaller metal multileaf collimators (MLCs) into a usable beam of radiation that hits the patient’s tumor. The dimensions and intensity of the photon beam can be controlled with great precision.
- Biologically, X-rays deliver ionizing radiation that generates free radicals in cancer cells, which subsequently bind to and damage DNA, leading to mitotic catastrophe and cell death. Cancer cells are inherently more susceptible to RT than normal tissue because cancer often has impaired DNA repair pathways, whereas normal tissue can repair some of the radiation damage.
- RT is used to treat prostate cancer in the following ways:
    - **Definitive RT** directed at the prostate and seminal vesicles +/- regional lymph nodes, can be used instead of surgery as the **primary curative treatment modality**
    - **Adjuvant RT** directed at the prostate bed +/- regional lymph nodes can be used after radical prostatectomy in patients at **high risk of recurrence, but undetectable PSA**
    - **Salvage RT** directed at the prostate bed +/- regional lymph nodes can be used after radical prostatectomy in patients with **clinical or biochemical evidence of recurrent/persistent disease**
    - **Palliative RT** directed at a site of metastatic disease can be used for **symptom relief** (e.g., pain, hematuria, urinary obstruction)

- RT Dosing
  - Gray (Gy) is the unit of RT dose
    - 1 Gy = 100 centiGray (cGy)
    - The dose from 1 cGy roughly equals 1 CT scan
  - Dose prescription depends on:
    - Goal of treatment (curative > palliative)
    - Amount of disease (gross/definitive > microscopic/salvage)
    - RT sensitivity of tumor
    - RT sensitivity of surrounding normal tissue
  - **Biologically Effective Dose (BED)** depends not only on total dose, but how that dose is fractionated, and the tissue irradiated
    - e.g. the definitive dose of SBRT for prostate cancer is 36.25-40 Gy in 5 fractions, as compared to 70 Gy in 28 fractions IMRT
- Methods of RT Delivery
  - **External Beam Radiation Therapy (EBRT)**
    - Non-invasive, most common form of RT.
    - Subcategories of EBRT include 3-dimensional conformal radiation therapy (3DCRT), intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic body radiation therapy (SBRT), or proton therapy (PT)
    - A standard LINAC is most commonly used for 3DCRT, IMRT, VMAT, or SBRT. Other specialized treatment platforms like Cyberknife also can be used for SBRT. Proton therapy also requires a special machine.
    - Sometimes an implantable hydrogel spacer (SpaceOAR) is used to temporarily physically separate rectum from prostate to decrease rectal dose during EBRT.
  - **Interstitial Brachytherapy**
    - Minimally invasive radiation implant that is temporarily placed (in the case of High Dose Rate (HDR) brachytherapy, or permanently placed in the case of Low Dose Rate (LDR) brachytherapy.
    - The “seed implant” refers to LDR.
  - **Unsealed Source Brachytherapy**
    - Radiopharmaceuticals (e.g., Radium-223) is an α-emitting, bone-seeking element administered IV. It is indicated for patients with castrate-resistant prostate cancer and symptomatic bone metastases without other visceral metastases.[95]
- **Radiation treatment planning**
  - After a radiation oncologist has seen a patient for consultation to discuss treatment options, and it is determined that RT is appropriate, the treatment planning process begins with a computed tomography (CT) simulation. It is called a simulation because it “simulates” the position that the patient will be in for their subsequent treatments.
  - During the simulation, first an immobilization device (e.g. a form-fitted vacuum bag) is made for the patient to help them hold comfortably and reproducibly in the same position each day. A CT scan is then taken, which will be used for treatment planning. Tattoos are placed to mark the patient position in relation to the table as a frame of reference for the treatment plan. These tattoos triangulate a point called the isocenter and are used to reproduce the placement of the patient on the treatment couch every day for treatment. The patient is typically also given instructions to have a relatively full bladder each day for treatment, and to try to have a bowel movement daily during treatment, so that the rectum and bladder volumes are relatively similar each day, and the prostate is in a reproducible position. [96]
  - The simulation CT with superimposed isocenter is transferred to the radiation treatment planning system (TPS). The CT is calibrated to the TPS to accurately depict the tissue density correlating to CT Hounsfield units. Accurate measurement of tissue density is crucial to precise calculation of radiation dose.

- The radiation oncologist contours (i.e. draws using the computer software) the target structures (i.e. prostate, seminal vesicles, pelvic lymph nodes) and organs-at-risk (OARs) of toxicity (i.e. rectum, bladder, penile bulb, bowel, femoral heads) on the CT. MRI or PET images are sometimes co-registered with the CT, as indicated, for more accurate target delineation. Similar to a surgical margin, radiation target volumes incorporate a margin of a few millimeters in all directions to ensure that the target will be positioned within the radiation field despite normal variations in patient treatment positioning. These variations occur in aligning the patient in the treatment position and motion of internal organs.
- With this information, an EBRT treatment plan can be generated by a medical dosimetrist using the computer software. The dose to each delineated target and OAR structure is accurately calculated to assess the "quality" of a RT plan (i.e., probability of cure or toxicity). During treatment planning, the dosimetrist can control the number of radiation beams, the angle of the beams, and the allowable dose to OARs. In IMRT, SBRT, or proton therapy, the computer software can "optimize" the treatment plan by modulating the dose from each beam using MLCs, which shape the dose intensity in a concave or convex way to be highly conformal around curved targets. The MLCs are thin automated interdigitated metal leaflets that can quickly and accurately slide open or closed to create custom apertures. This technique is associated with reduced radiation of OARs, side effects and complications compared to the older 3DCRT technique. [97,98,99]
- Radiation treatment plans can be evaluated visually on the CT scan, by reviewing lines of dose around the target (i.e. isodose lines). A dose-volume histogram (DVH) is a graph that can show the dose received to a given volume of each target and OAR contoured.

- **Radiation treatment delivery & Image guidance**
  - The patient follows instructions for bladder and rectum filling to the best of their ability.
  - The radiation therapist brings the patient into a shielded treatment room where the LINAC resides. The patient is setup on the treatment table by the therapists using the patient's immobilization device.
  - The therapists then leave the room, and capture images of the patient daily before treatment to ensure that their bony and soft tissue anatomy are positioned appropriately so that the radiation can be delivered accurately, according to the treatment plan. The imaging platform is built into the LINAC and the patient can be shifted if necessary by the therapists controlling the table that the patient is lying on remotely, from the treatment console outside the room.
  - There are many forms of image guidance for RT. The most common is cone-beam CT (CBCT), which allows visualization of soft tissue anatomy. Sometimes 3 gold fiducial markers are implanted in the prostate before CT simulation and orthogonal X-rays are used to match those fiducials from day to day. For cyberknife, radiofrequency beacons may be implanted that are localized with electromagnetic triangulation and can be similarly tracked in real-time. Some newer LINACS also have built in MRI guidance. The better the immobilization and image guidance, the less of a margin needs to be used around a given target volume to ensure that it is covered completely by the radiation. [100,101]
  - The radiation treatment itself typically takes approximately 5 minutes to complete. The patient does not see or feel anything during treatment.
- **Proton Beam Therapy**
  - Unlike X-rays, protons are heavy, charged, particles that will stop within a target, theoretically avoiding much of the extra-target "scatter" dose received by surrounding tissues, which is inherent to IMRT treatment plans using high energy X-rays.
  - The theoretic advantage of proton therapy is decreased toxicity by avoiding the low dose spillage to the rectum and bladder that is inherent to photon radiotherapy. In practice, most RT toxicity comes from the higher dose area adjacent to the target, which is no different with proton therapy, and there is limited data at this time demonstrating a clear toxicity benefit to proton therapy (though trials are ongoing) [102]
  - Currently the major disadvantage of proton therapy is cost, which is approximately 3-fold higher than IMRT.

2.2 Hypofractionated Definitive EBRT

- Historically most EBRT for definitive treatment of prostate cancer was delivered once every weekday in 1.8 – 2.0 Gy fractions over 39-45 total fractions (i.e. **conventional fractionation**).[97,100,103]
- **Hypofractionation** describes using a fraction size greater than 2.0 Gy per daily treatment. For instance, typical hypofractionated RT for prostate cancer is 2.5 – 3 Gy per fraction to doses of 60-70.2 Gy delivered over 20-28 total fraction.
- **Ultrahypofractionation (i.e. SBRT)** uses of a fraction size of 7.25-8.0 Gy in 5 total fractions delivered once or twice per week, to a total dose of 36-40 Gy.

Table 5. Conventional, Moderate Hypofractionation, and "ultrahypofractionation"

Conventional Fractionation	Moderate Hypofractionation	SBRT ("Ultrahypofractionation")
78-81 Gy	60-70 Gy	36-40 Gy
39-45 fractions	19-28 fractions	5 fractions
8-9 weeks	4-5.5 weeks	1.5-2 weeks

- Hypofractionation was first investigated because, for slower growing tumors like many prostate cancers, a large dose per fraction has a higher BED with the potential to increase the cure rate.[104] Although randomized trials have not demonstrated any difference in effectiveness, they have also shown comparable rates of toxicity and long-term quality of life, and due to the shorter treatment time, increased patient convenience and cost-effectiveness.[105,106,107,108] (**Table 6**). Therefore, hypofractionation is standard in most situations for definitive prostate radiotherapy. It is not yet standard for post-prostatectomy adjuvant or salvage radiotherapy.

Table 6: Current published trials exploring hypofractionation versus conventional fractionation.

Study	'Longer Arm'	'Shorter Arm'	Efficacy at 5 years	Late Toxicity	PROs
CHHiP	74Gy/37Fx	60Gy/20Fx	Similar	Similar	Similar
PROFIT	78Gy/39Fx	60Gy/20Fx	Similar	Similar	Similar
NRG 0415	73.8Gy/41Fx	70Gy/28Fx	Similar	Small ↑ GU/GI	Not reported
HYPRO	78Gy/39Fx	64.6Gy/19Fx	Similar	↑GU	Not reported

- Ultrahypofractionation appears to have comparable efficacy and toxicity compared to conventional fractionation in Phase II clinical trials.[109] The PSA responses follow kinetics similar to those observed following HDR brachytherapy.[103,108,110] Data is maturing from the following randomized trials:
    - Scandinavian HYPO-RT-PC trial:[111]
        - 1200 men with intermediate or high-risk prostate cancer randomized to 78Gy/39Fx vs. 42.7Gy/7Fx
        - 80% of pts treated with 3D-CRT
        - No difference in 5Y-bPFS (~84%).
        - SBRT: small ↑ Grade > 2 acute urinary toxicity (23-28%) and late urinary toxicity (2-6%), but no difference in late GI toxicity.
    - UK PACE-B trial (Brand, 2019):[112]
        - 874 men with low- or favorable intermediate-risk prostate cancer randomized to 78Gy/39Fx or 62Gy/20Fx vs. 36.25Gy/5Fx
        - All pts were treated with SBRT
        - Results: No significant difference in Grade > 2 acute GI toxicity (~11%) or GU toxicity (~25%).

2.3 Interstitial Brachytherapy

- Brachytherapy utilizes radioisotopes implanted within the prostate to deliver radiation internally. The radioisotopes are implanted through hollow needles placed transperineally using transrectal ultrasound guidance, under anesthesia.
- Brachytherapy can be used in combination with EBRT for unfavorable intermediate and high risk patients,[113,114,115,116] or as monotherapy for low and favorable intermediate risk patients.[117]
- Factors that increase risk of complications with brachytherapy:
    - Severe urinary frequency/obstructive symptoms (AUA score > 15)
    - Previous TURP: risk for incontinence
    - Gland size > 60cc
    - higher rate of acute urinary retention
    - Substantial median lobe hyperplasia
    - Active IBD involving the rectum
    - Best if asymptomatic (w/o need for Tx) for at least 6 months.
    - Prior pelvic radiotherapy
    - History of multiple pelvic surgeries
    - Severe diabetes with healing problems
- Technical Difficulties that may lead to inadequate dose coverage with brachytherapy:
    - Previous TURP: risk for incontinence
- Gland size > 60cc
    - Prominent median lobe
    - Severe pubic arch interference (can preplan with pubic arch template to assess)
    - Gross seminal vesicle involvement
- Low dose rate (LDR)
    - A single procedure that involves permanent prostate seed implant using either Iodine-125, Palladium-103, or Cesium-131 radioactive seeds. These sources are implanted permanently in a single procedure. The majority of the radiation dose is delivered over the first 1-2 months.[118,119,120,121]
    - The dose received by 90% of the prostate volume (D90) and volume of prostate receiving the prescribed dose of radiation (V100) are important indices of implant quality.[122,123,124,125]
    - After the implant, radiation safety precautions are necessary until the sources decay to safer activities. This using condoms during intercourse for the first week and avoidance of prolonged close contact with pregnant women and young children

- High dose rate (HDR)
  - A temporary implant using a single Ir-192 on a wire that is passed through the hollow needles into specific positions, for specific periods of time, using a remote afterloader machine (which also houses the source when not in use). Each fraction is delivered over 10-20 minutes, depending upon the activity of the source and the prescribed dose.
  - HDR monotherapy is typically delivered over two separate implant procedures 1-2 weeks apart. An HDR boost in combination with EBRT typically requires only a single implant procedure.
  - Since the radioactive source is only in the patient for a short period of time, no radiation safety precautions are necessary after the patient goes home.
  - HDR has the advantage of a higher BED (potential benefit for higher grade tumors), and easier dose modulation without risk of seed migration. [126,127,128]
- The rationale for a brachytherapy boost after EBRT is that EBRT can better cover periprostatic tissue, seminal vesicles and LNs, whereas brachytherapy enables a higher prostate dose. For higher risk patients, each of these areas may harbor malignant cells, and outcomes are improved with combined modality therapy, as demonstrated in the ASCENDE-RT Trial [114]
  - 398 men, unfavorable intermediate & high risk, all received 12mo ADT
  - Randomized to 78/2Gy vs. 46/2+LDR
  - LDR: ↑ 7Y-bPFS (75-86%) but no difference in OS
  - Both int and high-risk patients benefited
  - LDR: ↑ late GU toxicity (5-18%, mostly urethral strictures)
  - For lower risk patients, there is not the same benefit and still increased risk of toxicity, as demonstrated in RTOG 0232 (Prestidge 2016):
  - cT1-2b/GS6 and PSA10-20/GS7 and PSA <10 (low & favorable intermediate risk)
  - Randomized to LDR monotherapy vs. EBRT+LDR boost
  - No difference in 5Y-PFS (~85%), but combined modality therapy: ↑ G3 toxicity (7-12%, mostly GU)

2.4 Side Effects of Radiation

- Acute toxicity from EBRT is common but generally mild and easily managed with supportive medications. Potential acute toxicities include cystitis or urethritis, proctitis, fatigue.
- Long-term toxicity from EBRT is typically due to fibrosis and is generally less reversible. Rates of severe (grade 3 or higher) toxicity are generally <5% by design. Potential late toxicities may include rectal urgency, rectal bleeding, erectile dysfunction. Radiation induced secondary malignancy is rare in most patients with prostate cancer (<1%). Compared to radical prostatectomy, with EBRT there is typically less urinary incontinence, more rectal toxicities, and more delayed erectile dysfunction. [6,129,130,131]
- With brachytherapy, the rectal dose is lower than with EBRT, but the urethra dose is higher. Therefore, brachytherapy typically has higher risk of acute urethritis and late urethral stricture as well as obstructive and irritative urinary symptoms, but less risk of acute or late proctitis. [130,132]

2.5 NCCN Guidelines Involving Definitive RT

- Definitive RT is an option for essentially all patients regardless of NCCN risk group.
- Surgery and RT are appropriate options for patients who have life expectancy of at least 10 years and have cancer confined to the prostate. Randomized evidence supports comparable cure rates for low-intermediate risk patients (ProTECT trial), with the treatment modality chosen depending on potential for toxicity and patient preference. [6] There is a lack of randomized evidence comparing surgery and RT for high risk group, though surgery alone is often insufficient in this setting due to risk of local recurrence or disseminated metastases. A multi-institutional analysis of EBRT + brachytherapy vs EBRT vs radical prostatectomy for men with Gleason score 9-10 demonstrated similar long-term outcomes for all three treatment approaches, though distant metastasis free survival was lowest among men treated with combined EBRT and brachytherapy. [133]

- EBRT or brachytherapy are options for low risk and favorable intermediate risk groups.
- For unfavorable intermediate risk, high risk, or very high risk groups, brachytherapy monotherapy is no longer recommended, but brachytherapy can be used as a boost in combination with EBRT. Unfavorable intermediate risk patients should receive 4-6months of androgen deprivation therapy (ADT) with EBRT, whereas 1-3 years ADT should be used for high risk patients.
- For regional risk (N+) group, brachytherapy boost is no longer recommended due to increased toxicity in patients less likely to be cured.

2.6 Addition of Androgen Deprivation Therapy to RT

1. Po**tential mechanisms by which ADT enhances effect of RT**:
    - Tumor volume reduction: ↓ number of viable clonogens
    - Improved blood flow
    - Eradication of microscopic deposits outside irradiated target
    - Decreased androgen stimulation: downregulation of DNA repair and enhanced apoptosis
2. Studies of ADT + RT have generally used complete androgen blockade for at least the first 4 months of treatment, using an anti-androgen (e.g. Bicalutamide) and an LHRH agonist (e.g. Lupron)
    - Whether the addition of the antiandrogen is necessary is not entirely clear
3. Use of ADT also impacts radiation toxicity:
    - Definite worsening of sexual function
    - Comparable late GU and GI toxicity
4. Low and Favorable Intermediate Risk Groups:
    - No role for ADT[134,135,136]
5. Unfavorable Intermediate Risk Group:
    - Usually would use 4-6mo ADT with EBRT[137,138,139]
6. High Risk and Regional Risk Groups:
    - Usually would use 18-36mo ADT with EBRT[140,141,142]
    - Have the option of as little as 12mo ADT if using a brachytherapy boost
    - Duration of ADT is generally guided by disease characteristics, patient age, life expectancy, and comorbidities
    - For younger healthier patients, better to go with longer duration
    - **Consider adding abiraterone for very high risk and cN+ patients**

2.7 Assessing for Recurrence

1. After Radical Prostatectomy:
    1. PSA should rapidly decrease to undetectable (assuming negative margins)
    2. **AUA definition of biochemical failure: PSA >0.2 ng/ml**
2. After External Beam RT and/or Brachytherapy:
    1. More gradual decline in PSA: **Mean time to nadir is 18 months after EBRT alone**
    2. **Biochemical Failure is defined as a rise of PSA 2 ng/mL above the nadir PSA**
    3. **PSA "bounce"** is a transient ↑ in PSA (usually 0.2-0.8 ng/mL) that does not signify a treatment failure. It is seen in ~25% of patients, a median of 12-18 months after RT. Bounces do not indicate an increased risk of subsequent biochemical recurrence.[143,144,145]

2.8 Radiation Therapy After Prostatectomy

- **Within 10 years of RP, 15-40% of patients will have PSA recurrence (40-70% if high risk features like ECE, SVI, or +margin)**
- RT directed at the prostate/SV bed + urethral anastomosis +/- pelvic nodes can still cure a high percentage of patients
- **“Adjuvant” describes RT for undetectable PSA but high-risk features (+margin, pT3a/b)**

- **“Salvage” describes RT for either persistently detectable post-op PSA or initially undetectable PSA that rose at a later date or palpable recurrence in prostatic fossa**
- Three randomized trials (EORTC 22911, SWOG 8794, ARO 96-02) established a ~20% absolute benefit in bPFS from adjuvant RT compared to observation.[146,147,148]
- Three recent randomized trials (RADICALS-RT, GETUG-AFU17, RAVES, **Table 7**) demonstrated that early salvage RT has comparable efficacy to adjuvant RT, with decreased toxicity of early salvage RT since some patients will never recur or need RT. However, only 20% of men in the 3 trials had high risk of progression (pT3b, N1, GS8-10). [149,150,151,152]

Table 7. Trials of adjuvant versus salvage radiation therapy after prostatectomy in patients at high risk of recurrence

RADICALS	N	Inclusion Criteria	Salvage Criteria	Outcomes (5-year BCR-free survival)
RADICALS	1,396	• Postop PSA ≤ 0.2 • 1 or more risk factors (pT3/4, Gleason 7-10, PSM, Preop PSA > 10)	• PSA ≥ 0.1	• 85% adjuvant • 88% salvage • (HR 1.1, 95% CI 0.81-1.49)
RAVES	333	• Postop PSA ≤ 0.1 • 1 or more risk factors (pT3/4, PSM)	• PSA ≥ 0.2	• 86% adjuvant • 88% salvage • (HR 1.03, 95% CI 0.65-1.63)
GETUG-AFU 17	424	• Postop PSA ≤ 0.1 • 1 or more risk factors (pT3-4 disease, PSM)	• PSA ≥ 0.2	• 92% adjuvant • 90% salvage • (HR 0.81, 95% CI 0.48-1.36)
ARTISTIC	2,153	Meta-analysis RADICALS, RAVES, GETUG	• see above	• 88% adjuvant • 89% salvage • (HR 0.95, 95% CI 0.75-1.21)

- Predictive Factors for Effectiveness of Salvage RT:
  - **Lower PSA at time of salvage RT is critical**.[153,154] Ideally treatment should be initiated when PSA is 0.2 (or sometimes 0.1 if other high-risk features are present).
  - Other factors predicting for better outcome: lower grade, no ECE, no SVI, positive margins, PSA initially nadired at undetectable levels after RP before rising, later rise in PSA after RP.[155]

2.9 Use of ADT with Salvage RT

- See **Table 8**
- **Clearest benefit when pre-RT PSA > 0.6**
- May also be indicated for patients with pre-RT PSA < 0.6 if other high-risk features (GS>7, SVI, PSA never undetectable post-RP, high genomic recurrence score[156,157,158])

Table 8. Trials comparing use of ADT during salvage radiation therapy for recurrent prostate cancer after prostatectomy

	Methods	Results
RTOG 96-01 (Shipley 2017)[159]	760 men s/p RP with pT3N0 or +margins and with elevated PSA (0.2-4.0, median = 0.6) - randomized to RT (64.8Gy) +/- 150mg bicalutamide (2 yrs)	Bicalutamide: ↑ 12Y-OS (71-76%), ↓ 12Y-DM (23-14%), ↓ BF (68% - 44%) and ↑ gynecomastia (11-70%). - Most benefit: pre-SRT PSA >1.5, GS8-10, +margin - pre-SRT PSA < 0.7: no benefit
GETUG-AFU-16 (Carrie 2017)	743 men s/p RP with pT2-4a, undetectable post-op PSA & pre-RT PSA 0.2-2.0 (median = 0.3, more favorable risk profile than RTOG 96-01) - randomized to RT (66Gy) +/- Goserelin (6mo).	GnRH agonist: ↑ 5Y-bRFS (62-80%), no difference yet in DM (~4%) or OS. - pre-SRT PSA < 0.5: less benefit

RTOG 05-34 (SPPORT Trial) Pollack[160]	1792 men s/p RP with PSA 0.2-2.0 ng/mL randomized to one of three arms: 1) RT to the prostate bed only vs.		Arm 1	Arm 2	Arm 3
		5Y-FFP	71%	83%	89%
		8Y-DMs	45	38	25

	2) RT to the prostate bed only with ncADT vs. 3) RT to the prostate bed & LNs with ncADT	

2.10 Salvage brachytherapy after local recurrence from EBRT

- Salvage local therapy may be considered after EBRT if patient is healthy, has biopsy proven local recurrence, and has no evidence of distant metastases
- Brachytherapy generally has less morbidity than radical prostatectomy or cryotherapy after prior EBRT. Outcomes of each modality are similar, with 5Y-bDFS ~50% based on relatively small published series

2.11 Radiation for Oligometastatic Prostate Cancer

- **NCCN guidelines currently recommend EBRT to the prostate for low volume castration-sensitive M1 disease**
- STAMPEDE Trial[161]
  - 2061 men with newly diagnosed M1 prostate cancer randomized to systemic therapy +/- Prostate RT (55Gy/20fx daily or 36Gy/6fx weekly)
  - The metastatic burden was classified according to the definition used in the CHAARTED trial (high metastatic burden = four or more bone metastases with one or more outside the vertebral bodies or pelvis, or visceral metastases, or both; all other assessable patients were considered to have low metastatic burden
  - For overall cohort, RT: ↑ FFS (HR 0.76) but not OS (HR 0.92)
  - 5% G3 or higher acute toxicity and 4% G3 or higher late toxicity
  - For the subgroup with low metastatic burden, RT: ↑ FFS (HR 0.59) and OS (HS 0.68)
- HORRAD trial[162]
  - 432 men with primary bone M1 prostate cancer randomized to ADT +/- prostate RT (70Gy/35fx)
  - RT: No difference in median OS or TTP (trend towards improvement if < 5 metastases)
- **Several relatively small Phase II studies also support consideration of metastasis-directed RT for oligometastatic disease. Phase III trials are ongoing.**

3. Local and Directed Therapies for Node Positive and Metastatic Prostate Cancer

3.1 Regionally Metastatic (pN1 and cN1) and Metastatic Disease (M1) Treatment of the Primary in Node Positive and Metastatic disease

- **Clinically negative lymph nodes (cN0) based on conventional imaging, but PET positive lymph nodes**
  - Recently, **prostate-specific membrane antigen (PSMA) PET** scan has emerged as a tool to identify metastatic prostate cancer undetectable on conventional imaging studies (Contrast-enhanced CT scan of the abdomen and pelvis and nuclear medicine bone scan)
  - The ProPSMA trial is a prospective multi-institutional study in which patients with high risk prostate cancer (PSA>20, clinical stage T3-4, Grade Group 3-5) were randomized to gallium-68-PSMA-PSMA-11 PET/CT vs conventional imaging (bone scan and CT scan)[152,163]
    - The primary objective was to compare accuracy of PSMA-PET/CT to conventional imaging for detecting nodal or metastatic disease
    - Patients were randomized 1:1 to conventional imaging or PSMA PET. Crossover imaging was performed at 14 days for all patients with 3 or fewer sites of metastatic disease on initial imaging. Biopsy confirmation of distant disease was encouraged, but not mandated. Hard (biopsy or bone lesion change) and soft criteria were assessed 6 months after randomization to determine which cases were positive for nodal or metastatic disease by the reference standard.
    - PSMA PET-CT was more sensitive (85% [74-96] vs. 38% [24-52]) and specific (91% [85-97] vs 98% [95-100]) than convention first-line imaging for the detection of nodal or metastatic disease.
    - First-line conventional imaging conferred management change less often (23 [15%] men [10-22] vs 41 [28%] men [21-36]; p=0·008) and had more equivocal findings (23% [17-31] vs 7% [4-13]) than PSMA

PET-CT
    - The authors concluded that PSMA PET-CT is a suitable replacement for conventional imaging, providing superior accuracy to the combined findings of CT and bone scan.
    - As of 12/2020 PSMA PET was approved by the FDA for use in the United States.
- Clinically positive node disease (cN1) based on conventional imaging
    - Preferred treatment for patients with clinically detectable lymph nodes on conventional imaging (CT/MRI) and >5 years life expectancy or symptomatic disease is systemic treatment with ADT +/- abiraterone +/- radiation therapy to the primary. ADT +/-abiraterone or radical prostatectomy with pelvic lymph node dissection are also options (NCCN v.4.2022). This is largely based on RTOG 85-31, which demonstrated improved survival when ADT/RT were provided vs RT with late ADT.[102] Recent retrospective and prospective observational studies have demonstrated improved survival with RT in addition to ADT compared to ADT alone.[164]
    - There is limited data evaluating surgery in cN1 prostate cancer. Available data is limited to a retrospective series showing patients who were clinically positive (cN1 and pathologically node positive) had similar survival outcomes to patient who were occult node positive (cN0 and pathologically N1).[165] **Currently, surgical management of cN1 patients should be restricted to patients enrolled in clinical trials** however the most recent update to the NCCN Guidelines include prostatectomy and pelvic lymph node dissection in the treatment options for cN1 prostate cancer (NCCN v.4.2022).
- **Pathologic node positive disease (pN1)**
    - Aborting radical prostatectomy due to occult lymph node involvement (pathologic node positive findings on frozen section) is no longer recommended. Although there is no prospective data, there is ample retrospective data demonstrating improved outcomes (survival and symptomatic progression) in men who have a completed prostatectomy compared to those who have an aborted RP.[164,166,167]
- **Metastatic (M1) disease**
    - There are currently no prospective surgical trials demonstrating improved outcomes in men undergoing treatment of their primary tumor (surgery) in the setting of metastatic prostate cancer. Two trials have evaluated radiation to the primary, HORRAD and STAMPEDE Arm H.[161] Both failed to demonstrate improvements in overall survival, but the STAMPEDE Arm H showed that in a sub-group analysis of men with low volume (less than 4 bone metastases involving only the vertebral bodies or pelvis) disease, there was a 3.6 month mean survival advantage in men receiving radiation in addition to ADT.[162] Therefore, consideration of definitive RT directed against the primary tumor in addition to ADT is reasonable for patients with low volume metastatic disease.
    - Several population-based, retrospective studies have demonstrated an association between treatment of the primary tumor (surgery or radiation) after a diagnosis of metastases and improved survival.[128,168] These studies have led to the hypothesis driven development of prospective randomized trials evaluating this concept. (NCT00268476, NCT01957436, NTR271, NCT01751438, ISRCTN15704862, NCT02454543) **Local therapy to the primary tumor in the setting of documented metastatic disease outside of a clinical trial is not currently recommended by AUA guidelines**.

3.2 Directed Therapies in Metastatic Disease

- Defining tumor burden has largely been based on clinical presentation. **The terms oligometastatic and polymetastatic are sometimes interchanged with low-volume and high-volume metastases**. Definitions vary and are largely based on the number or anatomic location of metastatic sites. A universally agreed upon definition does not currently exist. Biologic/molecular definitions are under investigation.
    - **Oligo- or low volume is variably defined across studies, but is most commonly defined as four or fewer extra-cranial metastatic lesions**.[169]
    - **High-volume metastases were defined in the CHAARTED trial as >4 bony sites including one outside the axial skeleton or any visceral metastases**.[170]
- **Metastasis-Directed Therapy (MTD)**.

- Radiotherapy to metastatic sites is commonly used for impending fractures as a palliative treatment.
- Radiotherapy to asymptomatic sites as a means of treating all imaging detected sites of disease is considered experimental and under intense investigation. Evaluation of this concept has taken place largely in men with oligometastatic prostate cancer. A prospective study stereotactic treatment of metastatic prostate (STOMP-NCT01558427) demonstrated a signal of effect with prolongation of progression free survival. [110] Further studies are needed to determine if oncologic benefits can be demonstrated with MTD.
- Surgical excision of recurrent lymph nodes or salvage lymph node dissection (sLND) has been used in the treatment of “oligo” progressive disease. Retrospective studies have demonstrated some response to treatment, but this approach is not currently recommended outside of a clinical trial. [171]

4. Focal Therapy in Clinically Localized Prostate Cancer

- Conceptual Framework
  - Focal therapy refers to subtotal, targeted treatment of a prostate zone or lesion with the goal of eliminating disease while preserving urinary and sexual function
  - Although prostate cancer is often multi-focal in nature, increasing evidence suggests that a dominant “index” lesion may be responsible for the clinical course of the disease
  - Focal therapy is still considered exploratory, but there is increasing evidence that partial gland ablation may be a viable alternative to standard whole gland therapies in select patients
- **Cryotherapy**
  - Cellular damage and tissue destruction occur through freeze/thaw cycles
  - Data indicate favorable short term oncologic and functional outcomes for focal cryotherapy[172]
- **High Intensity Focused Ultrasound (HIFU)**
  - In 2015, the FDA approved high-intensity focused ultrasound for ablation of prostate tissue
  - Rapid heating of the prostate tissue results in coagulative necrosis with relative precision.
  - Multicenter prospective data suggest reasonable failure free survival at 5 years among men with clinically significant cancer with limited impact on functional outcomes[173]
- Other energy sources
  - Several other focal therapy alternatives are being explored and show favorable early results including transurethral ultrasound ablation (TULSA), irreversible electroporation (IRE), vascular targeted photodynamic therapy (PDT), focal laser ablation (FLA) and focal brachytherapy[174,175,176,177,178]
- Conclusion
  - Regardless of which focal ablative modality is offered, thorough counseling for patients considering focal therapy is paramount
  - Patients must understand that focal therapy may leave areas of cancer untreated, and that additional therapy may be required for adequate cancer control
  - Furthermore, patients must be informed of the need for continued close monitoring

5. Abbreviations

AS: Active Surveillance
AUA: American Urological Association
CI: Confidence Interval
DRE: Digital Rectal exam
HR: Hazard Ration
NCCN: National Comprehensive Cancer Network
Obs: Observation
PCa: Prostate Cancer
PIVOT: Prostate Cancer Intervention Versus Observation Trial

PLND: Pelvic Lymph Node Dissection
PFS: Progression Free Survival
PSA: Prostate Specific Antigen
RP: Radical Prostatectomy
RR: Relative Risk
SPCG 4: Scandinavian Prostate Cancer Group Study No. 4
WW: Watch waiting
EBRT: external beam radiation therapy
LDR: low-dose rate
HDR: high-dose rate
bRFS: biochemical recurrence free survival
DMFS: distant metastasis free survival
PCSM: prostate cancer specific mortality
SADT: short course androgen deprivation therapy
LADT: long course androgen deprivation therapy
LINAC: linear accelerator SIM: simulation
IMRT: intensity modulated radiation therapy
IGRT: image guided radiation therapy
ADT: Androgen deprivation therapy
LHRH: Luteinizing-hormone-releasing hormone
CAB: Combined androgen blockade
PSADT: Prostate specific antigen (PSA) doubling time
DES: Diethylstilbestrol
RANKL: Receptor activator of nuclear factor kappa-B ligand

6. AUA Guideline Webcasts

- 012IC AUA Guidelines 2017: Localized Prostate Cancer
- AUA Guidelines 2017: Localized Prostate Cancer-Low Risk
- AUA Guidelines 2017: Localized Prostate Cancer-Intermediate Risk
- AUA Guidelines 2017: Localized Prostate Cancer-High Risk

Videos

Technical aspects of RALP in prostates (>75g)

OPTIMIZE ACCELERATED CONTINENCE RECOVERY

COMPLICATIONS DURING RADICAL PROSTATECTOMY

RADICAL PROSTATECTOMY AFTER EBRT, BRACHYTHERAPY OR HIFU FAILURE

Nerve Sparing Robotic Radical Prostatectomy

Rezum™ Prostate Vapor Ablation

Instructional Video on Performing an Extended Bilateral Pelvic Lymph Node Dissection

Single-Port Transvesical Robotic Radical Prostatectomy

Extraperitoneal Single Port Robotic Assisted Radical Prostatectomy wuth the da Vinci Single Port Platform: A Step-by-Step Approach

Presentations

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