Chapter

Evaluation of Patients for Radiotherapy for Prostate Adenocarcinoma

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Abstract

Prostate adenocarcinoma is the most common non-cutaneous malignancy among men in the United States, and the second leading cause of death. However, most prostate adenocarcinoma diagnoses are now diagnosed at early stages and are curable, or if they recur, are associated with such long survival times that the patients usually succumb to competing co-morbidities. This chapter would discuss a brief history of prostate cancer evaluation and its pertinence today, including the Gleason scoring system, advent of PSA testing, and development of the NCCN classification system that is used today. Alternative classification systems, such as the UCSF-CAPRA scoring system, would also be discussed. The latter half of the chapter will discuss the evolution from personalized medicine to precision medicine, including PSMA imaging and prostate cancer genomics, with ongoing trials and future directions. Furthermore, included within this chapter would be a discussion of selecting appropriate men for active surveillance, and appropriate regimens for active surveillance.

Keywords: epidemiology, clinicopathologic risk factors, risk stratification, genomics

1. Introduction

Prostate adenocarcinoma is the second most common diagnosed malignancy and the fifth leading cause of cancer death among men worldwide in 2020, with an estimated 1,414,259 new cases reported in men, along with 375,000 deaths [1]. The incidence and mortality rate of prostate cancer correlates with increasing age, with the average age at diagnosis being 66 years old [2]. The highest incidences of prostate cancer were in North America, Southern Africa, Northern and Western Europe, the Caribbean, and Australia/New Zealand; the lowest incidence rates were in Asia and North Africa.

In the United States between 2012 and 2017, the incidence rate of prostate cancer for all races combined was 104/100,000 persons; it was 97/100,000 for non-Hispanic whites, 173/100,000 for blacks, and 52/100,000 for Asian/Pacific Islanders. The mortality rate for all races combined was 19/100,000 persons; 18/100,000 for non-Hispanic whites, 38/100,000 for blacks, and 18/100,000 for Asian/Pacific Islanders.

2. PSA testing

In the United States, the incidence of prostate cancer increased in the early 1990s due to the widespread use of prostate-specific antigen (PSA) monitoring that was formally approved by the Food & Drug Administration in 1986, and dramatically increased the detection of asymptomatic/early-stage disease. Incidence rates declined suddenly between 2007 and 2014, and stabilized around 2016. In 2012, the United States Preventive Services Task Force (USPSTF) recommended against routine PSA screening for prostate cancer due to overdiagnosis and overtreatment that could potentially affect quality of life for patients. This recommendation likely led to the decrease in the overall reported incidence rates, but later resulted in an increase in the incidence of advanced-stage disease [3]. In 2018, the USPSTF released updated guidelines for PSA screening as follows: [4].

1. For men between the ages of 55–69, the decision to be screened should be on an individualized basis, and patients are encouraged to discuss the potential risks and benefits of screening with their physicians including overdiagnosis and overtreatment, which can lead to long-term complications.

2. Men 70 years or older are recommended to not undergo PSA screening.

However, the American Cancer Society has released guidelines that are more in favor of PSA testing, recommending that the decision for PSA testing should take place as follows: [5].

1. Age 50 for men who are at average risk of prostate cancer and are expected to live at least 10 more years

2. Age 45 for men at high risk of developing prostate cancer. This includes African Americans and men who have a first-degree relative (father or brother) diagnosed with prostate cancer at an early age (younger than 65).

3. Age 40 for men at even higher risk (those with more than one first-degree relative who had prostate cancer at an early age).

3. Development of the Gleason score

The Gleason grading system for prostate adenocarcinoma originated in the 1960s from a randomized prospective study performed at the Veterans Administration that included nearly 3000 patients. Dr. Donald Gleason detailed and summarized the histological growth patterns (grades) of prostate adenocarcinoma, and the correlation with clinical data such as staging and prognosis were analyzed.

At the 2014 International Society of Urological Pathology Consensus Conference, a new prostate adenocarcinoma grading system was developed from the latest Gleason scoring system that was last revised in 2005, which included a new system of Grade Groups from Gleason scores 1–5, as follows: [6].

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 components 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.

4. Assessment of prostate cancer risk

4.1 D'Amico risk classification of prostate cancer

In 1998, Dr. Anthony D'Amico created a model that stratified patients with prostate cancer into those with a low, intermediate, or high risk of biochemical recurrence-free survival after surgery based on Gleason score at biopsy, clinical tumor-nodal-metastasis (TNM) stage, and pre-operative PSA level, as follows, in **Table 1** [7].

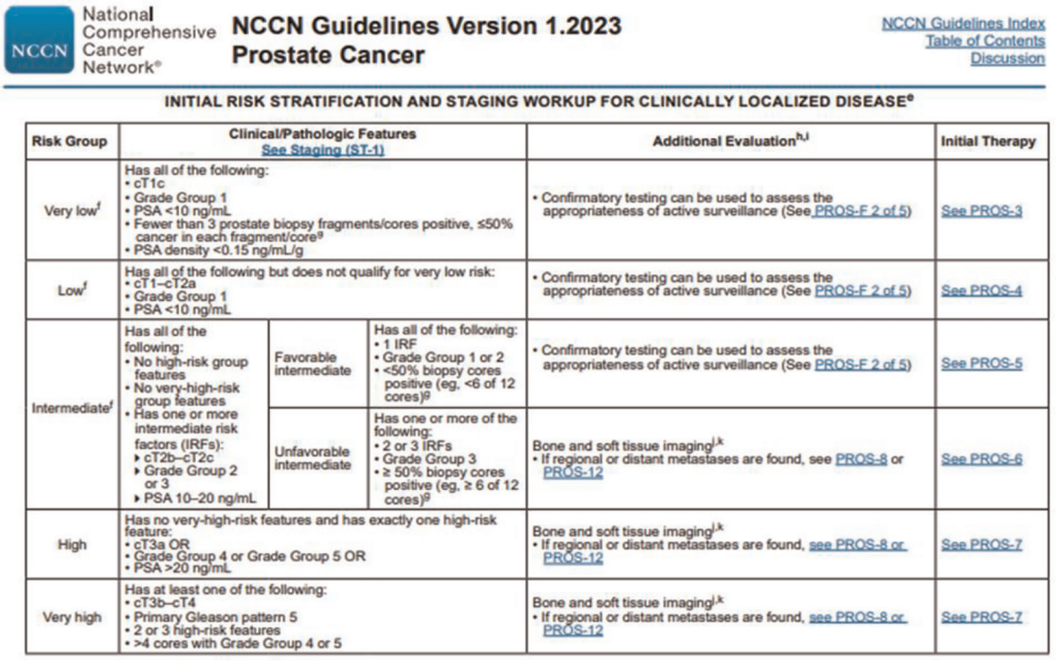
4.2 Modern NCCN classification system

The modern National Comprehensive Cancer Network (NCCN) classification system includes a six-tier system, with very low-risk, low-risk, favorable intermediate-risk (FIR), unfavorable intermediate-risk (UIR), high-risk, and very high-risk (see **Figure 1**) [8].

Importantly, this new system divides the heterogenous group of intermediate-risk prostate adenocarcinoma into favorable and unfavorable classifications. This bifurcation is based on research led by Drs. Zachary Zumsteg and Michael Zelefsky at Memorial Sloan Kettering Cancer Center between 1992 and 2007, on 1208 patients with intermediate-risk prostate cancer treated with dose-escalated external beam radiotherapy (EBRT) to 81 Gy or 86.4 Gy in 1.8 Gy daily fractions with or without

Low-Risk	Intermediate-Risk	High-Risk
Gleason Score ≤ 6, and PSA <10 ng/ml, and Clinical Stage ≤T2a	Gleason Score of 7, or PSA of 10 to <20 ng/ml, or Clinical Stage T2b	Gleason Score ≥ 8, or PSA ≥20 ng/ml, or Clinical Stage ≥T2c

Table 1.
Original D'Amico three-tier classification system.



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Discussion

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE[e]

Risk Group	Clinical/Pathologic Features (See Staging (ST-1))			Additional Evaluation[h,i]	Initial Therapy
Very low[f]	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[g] • PSA density <0.15 ng/mL/g			• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	See PROS-3
Low[f]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL			• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	See PROS-4
Intermediate[f]	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)[g]	• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	See PROS-5
		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)[g]	Bone and soft tissue imaging[j,k] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-6
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			Bone and soft tissue imaging[j,k] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7
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			Bone and soft tissue imaging[j,k] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7

Figure 1.
NCCN prostate initial risk stratification and staging work-up for clinically localized disease [8].

short-term androgen deprivation therapy (ADT) [9]. FIR prostate cancer was defined as having NCCN intermediate-risk disease and all the following: a single intermediate risk factor, Gleason 3 + 4 = 7, and < 50% of biopsy cores positive. UIR prostate cancer was classified as any intermediate-risk patient with at least one of the following: primary Gleason pattern of 4, ≥50% of biopsy cores positive, PSA ≥10, and cT2b-cT2c. The results demonstrated that patients with UIR disease had a 2.4x increase in PSA recurrence, 4.3x increase in distant metastases, and 7.4x increases in prostate cancer-specific mortality; therefore, it was concluded that a bifurcation could be made within the intermediate-risk category.

4.3 UCSF-CAPRA scoring system

The UCSF-Cancer of the Prostate Risk Assessment (CAPRA) score is another model developed to predict the aggressiveness of a diagnosed prostate adenocarcinoma, including primary endpoints such as prostate cancer–specific mortality, all-cause mortality, and metastatic disease in patients post-treatment (see **Figure 2** and **Table 2**) [10].

5. Estimates of life expectancy

Upon consultation, an estimation of life expectancy is crucial for shared decision-making between a physician and patient, as prostate cancer can often be an indolent disease prone to overtreatment, leading to unnecessary side effects. Various nomograms are available to assist in estimating life expectancy, and aiding these decisions prior to treatment. For example, the Memorial Sloan Kettering Cancer Center website has a "Male Life Expectancy" calculator [11]. Nevertheless, this estimation should be

Actuarial survival outcomes stratified by Cancer of the Prostate Risk Assessment (CAPRA) score*

	Metastasis-free interval, % likelihood (95% CI)		Prostate cancer–specific survival, % likelihood (95% CI)		Overall survival, % likelihood (95% CI)	
CAPRA score(s)	5 y	10 y	5 y	10 y	5 y	10 y
0	100	100	100	100	100	100
1	99.5 (98.8 to 99.8)	99.0 (97.1 to 99.6)	99.7 (99.3 to 99.9)	98.2 (93.3 to 99.5)	93.0 (91.2 to 94.5)	76.7 (69.7 to 82.4)
2	99.1 (98.5 to 99.5)	96.9 (94.7 to 98.2)	99.8 (99.3 to 99.9)	96.7 (94.2 to 98.1)	92.1 (90.7 to 93.4)	69.1 (64.9 to 73.0)
3	97.3 (96.3 to 98.1)	95.5 (93.7 to 96.8)	99.1 (98.3 to 99.5)	94.4 (91.7 to 96.3)	90.2 (88.4 to 91.7)	64.1 (59.8 to 68.0)
4	97.2 (95.8 to 98.2)	92.7 (89.2 to 95.1)	98.4 (97.2 to 99.1)	89.7 (84.9 to 93.0)	91.0 (88.7 to 92.8)	57.9 (52.1 to 63.3)
5	95.4 (93.2 to 96.9)	88.7 (83.3 to 92.4)	97.8 (95.9 to 98.8)	87.4 (81.1 to 91.7)	89.3 (86.3 to 91.6)	52.1 (45.2 to 58.5)
6	93.6 (90.9 to 95.6)	84.7 (78.4 to 89.3)	95.3 (92.6 to 97.0)	79.3 (71.8 to 85.0)	83.2 (79.2 to 86.5)	45.7 (38.7 to 52.4)
7	91.1 (87.3 to 93.8)	84.6 (76.7 to 90.0)	94.1 (90.3 to 96.5)	78.6 (67.9 to 86.1)	77.0 (71.4 to 81.6)	36.3 (28.0 to 44.7)
8–10	83.0 (77.9 to 87.1)	79.2 (72.8 to 84.3)	88.7 (83.6 to 92.4)	78.9 (70.0 to 85.4)	72.4 (66.0 to 77.8)	41.5 (33.1 to 49.8)
0–2	99.3 (98.8 to 99.5)	97.5 (95.9 to 98.5)	99.7 (99.9 to 99.5)	97.1 (98.2 to 95.1)	92.5 (91.5 to 93.5)	71.4 (67.8 to 74.7)
3–5	96.9 (96.2 to 97.5)	93.3 (91.7 to 94.6)	98.6 (99.0 to 98.1)	91.6 (93.4 to 89.5)	90.2 (89.0 to 91.3)	59.7 (56.7 to 62.7)
6–10	90.4 (88.4 to 92.0)	83.4 (79.6 to 86.6)	93.4 (94.9 to 91.5)	79.1 (83.1 to 74.3)	78.7 (75.9 to 81.2)	42.0 (37.4 to 46.5)

Figure 2.
CAPRA scores and associated endpoint predictions [10].

PSA at Diagnosis (ng/mL)		Gleason Score at Biopsy (Primary/Secondary pattern)		Age at Diagnosis (Years)		Clinical Tumor Stage		% of Biopsy Cores Positive for Cancer	
<6.0	0	1–3/1–3	0	<50	0	T1a-T2c	0	≤33	0
6.0–10	1	1–3/4–5	1	≥50	1	T3a	1	>33	1
10.01–20	2	4–5/1–3	3						
20.01–30	3								
>30	4								

Table 2.
Calculating CAPRA scores.

made in coordination with physicians who have a longitudinal assessment of the patient, such as the primary medical doctor and cardiologist.

6. Imaging for prostate cancer

6.1 MRI imaging

Magnetic resonance imaging (MRI) is an essential modality for both staging and planning treatment, as it enables enhanced soft tissue resolution over computed tomography (CT). Multi-parametric MRI (mpMRI) includes standard MRI images obtained with at least one additional sequence such as diffusion-weighted imaging (DWI) or dynamic contrast-enhanced (DCE) images in addition to anatomic T2-weighted images. This imaging modality has aided in prostate cancer detection and risk stratification, has been widely used in patients who have a rising PSA with negative biopsies, and in patients who are undergoing active surveillance [12]. Due to its essential role for EBRT treatment, especially for high-dose stereotactic body radiation therapy (SBRT), if a patient is unable to obtain an MRI or his MRI imaging is sub-

optimal due to issues such as implanted metallic hardware, other treatment modalities such as prostatectomy or brachytherapy may be considered, as appropriate.

6.2 PSMA pet/CT

Several recent clinical trials have demonstrated the diagnostic and therapeutic benefits of prostate-specific membrane antigen (PSMA) in positron emission tomography (PET) imaging. The PSMA peptide is a transmembrane glycoprotein primarily expressed along the extracellular surface of the prostate cancer cell, enabling small molecule binding. The binding site serves as a target for biomarkers for both diagnostic and therapeutic purposes [13]. PSMA demonstrates 100-1000x greater overexpression in prostate adenocarcinoma cells compared to benign prostate tissue, which aids in detecting malignancy [14]. The proPSMA trial demonstrated increased sensitivity with PSMA PET/CT scan in identifying nodal metastatic prostate adenocarcinoma compared to conventional imaging, including the combined findings of CT and bone scans [15].

Both gallium-68 (68 Ga)-PSMA-11 (gozetotide) and fluorine-18 (18 F)-based PSMA compounds are currently widely in use for PET/CT imaging, and PSMA imaging has led to significant changes in clinical management. For example, in the CONDOR trial investigating the use of 18 F-DCFPy (Pylarify®, piflufolastat) in patients suspected to have a biochemical recurrence after prostatectomy or radiotherapy, among the 208 patients enrolled in the trial, the authors reported a 63.9% rate of change in management [16].

The SPOTLIGHT trial was presented at the American Urological Association Conference, which studied 18F-rhPSMA-7.3 in the biochemical recurrence setting in patients with elevated PSAs. All patients had negative results on conventional imaging, as read by three radiologists; however, on exploratory analysis, this radiotracer led to a 45–47% rate of upstaging [17].

7. Treatment for clinically localized disease

Evaluation of prostate cancer begins with a history and physical (H&P), assessing for baseline urinary function (e.g., American Urological Association [AUA] score/International Prostate Symptom Score [IPSS]); sexual function (Sexual Health Inventory for Men [SHIM] score); bowel function; and prostate abnormalities on digital rectal examination (DRE) such as enlargement, induration, nodularity, extracapsular extension, and/or invasion. PSA and velocity (doubling time) should be calculated, and a prostate biopsy should be obtained, if not already.

7.1 Treatment options

This chapter discusses radiotherapy options for prostate adenocarcinoma, and will not delve into radical prostatectomy/surgical options. Potential radiotherapy options include photon EBRT, proton EBRT, and brachytherapy; EBRT includes standard fractionation (about nine weeks), moderate hypofractionation (about 4–5 weeks), or SBRT (about 4–5 sessions, recommended every other day to reduce toxicities). Intensity-modulated radiotherapy/image-guided radiotherapy (IMRT/IGRT) is strongly recommended to enable dose escalation, while reducing genitourinary (GU) and gastrointestinal (GI) toxicities. Fiducial markers are strongly recommended for

SBRT due to the extreme level of precision required and low number of fractions, and potentially for other EBRT treatments [8]; hydrogel spacers between the prostate and rectum may also be important for SBRT and brachytherapy to reduce the rectal dose, and in certain other EBRT cases [8].

Compared to conventional fractionation, moderate hypofractionation has demonstrated similar efficacy and toxicity in randomized trials, such as the CHHIP and PROFIT trials [18, 19]; however, some trials such as the HYPRO trial have demonstrated worse toxicity [20]. An ASTRO/ASCO/AUA evidence-based guideline concluded that hypofractionation is justified for routine use in this setting [21]. Common moderate hypofractionation regimens in the United States include 70 Gy/28 fractions, 70.2 Gy/26 fractions, and 60 Gy/20 fractions.

SBRT delivers highly-conformal, high-dose radiation in typically 4–5 fractions. Most of the data supporting SBRT are phase 2 trials demonstrating excellent biochemical progression-free survival and similar early toxicity to standard radiotherapy, but one phase 3 trial demonstrates non-inferiority of SBRT [22, 23]. Better candidates for SBRT have lower IPSS scores and prostates that are not significantly enlarged. SBRT with elective nodal irradiation is being explored, such as in the SATURN trial [24]. As well, SBRT is also being investigated as a neoadjuvant therapy before radical prostatectomy in high-risk patients, with phase I trials showing feasibility and safety, though one recent phase I trial assessing maximum tolerable dose was stopped early due to unacceptable toxicity [25, 26]. Additionally, some trials are looking at boosting the dominant intra-prostatic lesions to higher doses [27].

Brachytherapy monotherapy may be offered in the form of low-dose rate (LDR) or high-dose rate (HDR) brachytherapy. Alternatively, brachytherapy may be used as a boost after EBRT to 45–50.4 Gy for UIR, high-risk, and very high-risk prostate adenocarcinoma.

Proton radiotherapy has not demonstrated clear superior or inferior outcomes or differences in toxicity over photon radiotherapy, though one large Surveillance, Epidemiology, and End Results (SEER) study did demonstrate increased bowel toxicity [28]. Of note, proton therapy for prostate cancer is typically several times the cost of IMRT/IGRT treatments. The NCCN recommends proton therapy as a potential alternative to photon EBRT. Clinical trials are ongoing.

8. Very low- and low-risk prostate cancer

Patients with an NCCN risk-stratified very low- or low-risk prostate cancer and a life expectancy >10 years are usually recommended active surveillance (AS) [8]. This option involves obtaining a PSA no more often than every 6 months, DRE no more often than every 12 months, repeat biopsy no more often than yearly unless clinically indicated, and consideration of repeat mpMRIs no more often than every 12 months. Patients on AS are usually recommended curative-intent therapy if there is an increase in Gleason grade on repeat biopsy, tumor volume, or PSA density. Patient anxiety is also an important factor in management decisions, as patients may elect to come off of AS.

For patients with localized very low- or low-risk prostate cancer and a life expectancy of <5–10 years, observation ("watchful waiting") is generally recommended [8]. This process involves monitoring with a H&P and PSA no more often than every 12 months without biopsies until symptoms develop, or are thought to be imminent. Therapy is palliative only.

Per the NCCN guidelines, EBRT, proton therapy, SBRT, and brachytherapy monotherapy are potential radiotherapy treatment options for very low- and low-risk prostate cancer [8].

8.1 Favorable intermediate-risk (FIR) prostate cancer

Patients with FIR prostate cancer and a life expectancy >10–20 years are usually recommended curative-intent therapy [8]. However, active surveillance may be offered if there are more favorable tumor characteristics, significant co-morbidities, poor urinary function, and/or strong patient preference; patient compliance is important if active surveillance is chosen.

Per the NCCN guidelines, EBRT, proton therapy, SBRT, and brachytherapy monotherapy are potential radiotherapy treatment options for FIR [8].

8.2 Unfavorable intermediate risk (UIR) prostate cancer

UIR prostate cancer has been demonstrated to have an increased risk of pelvic and distant metastases versus FIR disease, and additional metastatic work-up is recommended, including either a CT abdomen/pelvis plus bone scan or alternatively a PSMA PET/CT [8, 9]. Treatment is recommended for those patients with >10 years life expectancy, while patients with <10 years are recommended observation. Brachytherapy may be offered as a boost, per the ASCENDE-RT trial, which demonstrated a significant difference at 10 years in biochemical disease-free survival, though no difference in OS and with more toxicities [29]; some researchers extrapolate that an overall survival (OS) difference may be reached with the passage of more time in this study.

Neoadjuvant, concurrent, and adjuvant short-term ADT is recommended in addition to radiotherapy in the form of a leutinizing hormone-releasing hormone agonist (e.g., goserelin or leuprolide) or antagonist (e.g., degarelix or relugolix) [8]. This recommendation is based on a modest but significant improvement in OS at 10 years in UIR patients receiving short-term ADT [30, 31]. ADT is usually initiated 2 months before RT, though the sequencing is subject to change. It is hypothesized that ADT radiosensitizes prostate cancer by decreasing non-homologous end-joining DNA repair, thereby acting synergistically with radiotherapy. ADT may also shrink the prostate and primary tumor, which may theoretically decrease the target volume and GI/GU toxicities. With combination EBRT/brachytherapy boost for UIR prostate cancer, short-term ADT may be omitted [8].

Per the NCCN guidelines, EBRT, proton therapy, SBRT, and combination EBRT/brachytherapy are potential radiotherapy treatment options for UIR [8].

9. High-risk and very high-risk prostate cancer

For high- and very-high risk prostate cancer, curative intent treatment is recommended for men with life expectancies >5 years or who are symptomatic, whereas men asymptomatic with <5 years life expectancy may be managed with observation, ADT alone, or EBRT alone [8]. With the publication of the POP-RT study incorporating Pylarify PET/CTs, the authors recommend treating the pelvic lymph nodes, as the arm treating the pelvic lymph nodes had improved 5-year disease-free survival over the prostate-only arm of 89.5% vs. 77.2% ($p = 0.002$) [32]. The NRG

now recommends that for pelvic lymph node treatments, the superior border starts at L5-S1 and extends to L4-L5 [33]. Long-term ADT for 1.5–3 years is recommended based on an OS benefit demonstrated with long-term ADT over RT alone or short-term ADT [34–36].

Per the NCCN guidelines, EBRT, proton therapy, SBRT, and combination EBRT/brachytherapy are potential radiotherapy treatment options for high-risk and very high-risk prostate adenocarcinoma [8]. However, the authors wish to comment that treating the prostate/seminal vesicles with SBRT alone, and not addressing the lymph nodes, may conflict with the results of the POP-RT study, in which addressing the pelvic lymph nodes demonstrated a disease-free survival benefit [32].

10. Adjuvant and early salvage radiotherapy

Unfortunately, 20–50% of patients may experience either biochemical recurrence or a persistently-elevated PSA within 5–10 years after prostatectomy [37]. Three randomized trials established the benefit of adjuvant radiotherapy, which improved the 10-year biochemical recurrence-free survival to about 60% from about 30–40% [38]. There has been ongoing debate as to the timing of radiotherapy, i.e. whether it should be delivered in the adjuvant setting (within 12–16 weeks post-prostatectomy while PSA remains undetectable) or as salvage radiotherapy (initiated in the presence of detectable PSA or a palpable nodule on DRE). The ARTISTIC meta-analysis found that adjuvant RT did not improve the 5-year event free survival over salvage radiotherapy in localized or locally-advanced disease, supporting the use of early salvage treatment [39].

The decision of whether to treat should include risk stratification based on multiple factors such as age, co-morbidities, size/number of positive margin(s), the absolute PSA level, PSA doubling time, nomograms, and molecular assays (e.g., Decipher® Score). Given conflicting conclusions in studies comparing adjuvant versus salvage radiotherapy, the NCCN recommends curative intent adjuvant or early salvage radiotherapy in patients with life expectancies >5 years with detectable PSA and adverse pathologic features (e.g., positive margins, seminal vesical invasion or extra-prostatic extension), or positive nodes [8]. The work-up for post-operative patients with evidence of persistent or recurrent disease includes H&P, DRE, PSA, MRI, and PSMA PET/CT (preferred over CT plus bone scan, per NCCN 2023 update), consecutive PSA measurements ≥0.2 ng/ml, and potentially a biopsy of the prostate bed.

The ASTRO/AUA guidelines recommend at least 64–65 Gy in the post-operative setting, with no distinction between adjuvant and salvage treatment [40]. Hypofractionated regimens in the adjuvant and salvage setting are currently being investigated. Three phase 2 trials utilized regimens of 65 Gy/26 fractions, 54 Gy/18 fractions, and 51 Gy/17 fractions, and demonstrated excellent efficacy and low rates of toxicity [41–43]. The NRG-GU003 phase 3 trial is randomizing patients to conventional fractionation (66.6 Gy/37) vs. hypofractionation (62.5 Gy/25 fx); it is currently closed to accrual, with expected completion in 2026 [44].

The RTOG 96–01 trial assessed the addition of 24 months of bicalutamide to radiotherapy in patients with biochemical failure, and demonstrated improved 12-year OS in salvage patients with PSA >0.61 ng/mL, but men with PSA ≤ 0.6 ng/mL (i.e., early salvage patients) experienced increased other-cause mortality and cardiac events [45]. The GETUG-AFU 16 trial assessed the addition of 6 months of ADT for patients with biochemical failure; at 120 months, the progression-free survival was

64% for patients with radiotherapy plus goserelin and 49% for patients with radiotherapy alone (HR = 0.54, $p < 0.0001$) [46]. The NRG Oncology/RTOG 05–34 SPPORT trial has demonstrated an improved 5-year freedom from progression with the addition of ADT to prostate bed radiotherapy (PBRT) over PBRT alone, 81% vs. 71% [47]. The SPPORT trial is also assessing the addition of pelvic nodal radiotherapy to PBRT+ADT, and demonstrated an improved 5-year freedom from progression (87%) versus the groups mentioned above. Acute toxicities are significantly worse with the addition of ADT and with ADT + pelvic nodal radiotherapy, but no differences were seen in late toxicities.

The NCCN now recommends obtaining the Decipher® molecular assay to help individualize treatment decisions in the post-operative setting; patients with a high Decipher® genomic classifier Score (>0.6) should be strongly considered for EBRT with ADT in patients who have not received early salvage therapy [8].

11. Approach to a patient with a rising PSA after radiotherapy

Following definitive therapy for prostate adenocarcinoma, the NCCN recommends obtaining a PSA every 6–12 months for 5 years, and then annually thereafter [8]. As well, a PSA may be obtained as frequently as every 3 months to clarify disease status in certain cases, especially for patients with aggressive disease. PSA failure post-radiotherapy is defined by the Phoenix Consensus as a PSA increase by 2 ng/mL or more above the nadir. A work-up for recurrence can begin prior to reaching nadir +2 ng/mL, especially for candidates for salvage treatments with long life expectancies, and if there is a rapid increase in the PSA. However, it is important to note that many patients do experience 1–2 PSA upward "bounces" that resolve. There are data demonstrating that a PSA nadir >0.5 ng/mL is associated with lower rates of biochemical control, distant metastasis-free survival, prostate cancer specific survival, and OS [48].

Work-up in the setting of current or impending biochemical failure includes PSMA imaging, MRI-prostate, and testosterone. Prostate biopsy is required for confirmation of recurrence, especially if local salvage therapy (e.g., high-dose rate [HDR] brachytherapy, low-dose rate [HDR] brachytherapy, SBRT, radical prostatectomy, high intensity focused ultrasound, or cryotherapy) is desired.

NRG Oncology/RTOG 0526 prospectively analyzed patients who had prior EBRT and experienced local failure, and were treated with salvage LDR [49]. This study included patients treated with EBRT for low- or intermediate-risk prostate adenocarcinoma with EBRT and biopsy-proven local failure >30 months after definitive treatment. Inclusion criteria also included PSA <10 ng/mL, and no regional/distant disease. Between May 2007–January 2014, 20 centers administered salvage treatment to 100 patients, of whom 92 patients were analyzable. The median prior EBRT dose was 74 Gy, and median follow-up was 6.7 years, with LDR administered at a median time of 85 months after EBRT. ADT was combined with salvage radiotherapy for only 16% of patients. Ten-year OS was 70%, with disease-free survival of 61% at 5 years and 33% at 10 years; of note, local failure was rare at 5% at 10 years.

A meta-analysis was performed of salvage treatments after definitive radiotherapy, consisting of 150 studies, seeking to compare the efficacy and toxicity of the six techniques listed above (HDR, LDR, SBRT, radical prostatectomy, high intensity focused ultrasound, and cryotherapy) [50]. HDR brachytherapy and SBRT had the highest rates of adjusted 5-year recurrence free-survival at 60%, while cryotherapy

had the lowest at 50%. CTCAE grade ≥ 3 GU toxicity was the lowest for SBRT at 4.2%, and the highest for HIFU at 23%; as well, CTCAE grade ≥ 3 GI toxicity was the lowest for SBRT and HDR at 0.0%, and the highest for radical prostatectomy at 1.9%. From this retrospective meta-analysis, the authors concluded that the radiotherapy techniques appeared most effective in reducing recurrence and limiting severe GU toxicity; severe GI toxicity remained low regardless of technique.

12. Evaluation for treatment of oligo-metastatic and poly-metastatic disease

When a patient presents with a metastatic focus (or foci) after prior definitive treatment, the decision for a biopsy is often not answerable by a straightforward algorithm. The clinical situation as a whole has to be evaluated. Some pertinent questions include:

- What was the original NCCN risk category? What were the Gleason score, volume of disease, pre-treatment PSA, MRI findings, and DRE findings?
- On the pre-treatment work-up/imaging, were any abnormalities noted on the suspicious focus/foci?
- What is the current PSA? Is the patient currently on ADT?
- What is the size of the lesion and its SUV on PSMA PET/CT?
- How many lesions are there?
- Is the focus actually the ureter(s) (very common conflation with a positive lymph node on PSMA PET/CT readings)?
- Is the focus accessible to biopsy?

These questions may be best addressed in a multi-disciplinary setting, such as a Genitourinary Tumor Board. As well, shared decision-making regarding the risks/benefits and logistics of a biopsy with the patient is important.

Numerous studies have provided insight into the value of treating the primary site and/or metastatic sites for prostate adenocarcinoma. The HORRAD trial from the Netherlands was a multi-center randomized controlled trial to determine whether OS is prolonged by adding prostate EBRT to ADT for patients with metastatic prostate adenocarcinoma [51]. From 2004 to 2014, the study recruited 432 patients with a PSA >20 ng/mL and metastatic prostate adenocarcinoma on bone scan. The patients were then randomized to either ADT with EBRT (radiotherapy group) or ADT alone (control group). OS was the primary endpoint, and PSA progression was the secondary endpoint. In this trial, the median PSA was 142 ng/mL, and 67% of patients had >5 osseous metastases. At a median follow-up of 47 months, the median OS was 45 months in the radiotherapy group and 43 months in the ADT alone group, which was not statistically significant (HR = 0.90, CI = 0.70–1.14, p = 0.4). There was a benefit in time to PSA progression for the radiotherapy group of 15 months versus 12 months (HR = 0.78, CI = 0.63–0.97, p = 0.02).

On a subgroup analysis of 160 patients with <5 bone metastases, an OS benefit started to emerge with HR = 0.68 (CI = 0.42–1.10). However, in this study, the number of bone metastases were categorized as 1–4, 5–15, and > 15; the authors postulated that an upper cut-off of 1–3 metastases may have been statistically significant for the radiotherapy group for OS.

The "Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy" (STAMPEDE) trial studied if local radiotherapy to the prostate would improve OS in men with metastatic prostate adenocarcinoma, with the benefit greatest in men with a low metastatic burden [52]. This study randomized 2061 patients in a 1:1 ratio to standard of care (control group) or standard of care and radiotherapy (radiotherapy group). Standard of care consisted of lifelong ADT, with up-front docetaxel allowed starting from December 2015. The radiotherapy arm received either 55 Gy/20 fractions over 4 weeks, or 36 Gy/6 fractions over 6 weeks. Overall, radiotherapy to the prostate did not improve OS for unselected patients; however, within the subgroup that had a low metastatic burden (non-regional lymph nodes or ≤ 3 bone metastases without visceral metastases), local radiotherapy to the prostate did confer an OS advantage of 65% vs. 53% at 5 years (HR = 0.64, $p < 0.001$) [53].

Radiotherapy to the prostate was not recommended for patients with high-volume metastatic disease unless in the context of a clinical trial or for palliative intent. The concern was that this aggressive treatment would increase toxicity, without a meaningful effect on OS. Of note, many experts would argue that the definition of low-volume disease should not be applied to metastases only detected on Pylarify PET/CT (and not on bone scan/conventional CT), since this imaging modality was not used in the STAMPEDE trial, and will detect smaller metastases.

The "Observation versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer" (ORIOLE) phase II randomized trial studied whether SBRT to the oligometastases improves oncologic outcomes for men with oligometastatic prostate adenocarcinoma, and may thereby delay initiation of ADT [54]. The study randomized 54 men with recurrent hormone-sensitive prostate cancer and 1–3 metastases detectable by conventional imaging in a 2:1 ratio to receive SBRT or observation. SBRT improved median progression-free survival (not reached vs. 5.8 months, HR = 0.30, $p = 0.02$), and the risk of progression at 6 months from 61–19%. There were no acute grade ≥ 3 toxicities.

Data from the ORIOLE trial appeared to indicate that sub-total metastasis-directed therapy (MDT) is not beneficial in extending progression-free survival. In this study, the treating radiation oncologists did not have access to PSMA PET/CT, and treated based upon conventional imaging; therefore, within the SBRT arm (36 patients), 16 patients actually had untreated lesions. The progression-free survival was 63% at 6 months in the sub-total consolidation arm, which was similar to the observation arm (61%). The authors concluded that MDT of all radiotracer-avid disease could potentially provide excellent progression-free survival for oligo-metastatic disease, with limited acute toxicity.

As well, the "Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial" (STOMP) study also analyzed the benefit of MDT in a randomized phase II trial [55]. The trial included patients with asymptomatic prostate cancer with a biochemic recurrence after primary treatment, 1–3 extracranial metastatic lesions, and serum testosterone levels >50 ng/mL (non-castrate level). Sixty-two patients were randomly assigned at 1:1 to either surveillance or MDT of all lesions, with local therapy including

surgery or SBRT. At a median follow-up time of 3 years, the median ADT-free survival was 13 months for the surveillance group, versus 21 months for the MDT group. Quality-of-life measures were similar between the two arms at baseline, as well as at 3 months and 12 months; there were no grade 2–5 toxicities. The STOMP study also concluded that MDT increases progression-free survival, as well as ADT-free survival.

A recent non-randomized, prospective phase II trial incorporated PSMA PET/CT-staged patients for confirmation of oligometastatic disease after local curative treatment (surgery and/or radiotherapy), and to demonstrate the efficacy and safety of "local ablative radiotherapy" (*authors' designation, though many patients received the non-ablative fractionation of 50 Gy/25 fractions*) [56]. The OLI-P study used gallium-68 PSMA PET/CT to stage patients at two German cancer centers between 2014 and 2018. Patients with ≤5 PSMA PET-positive bone (OSS-MET) or lymph node (LN-MET) metastases without local tumor recurrence or visceral metastases were included in the trial; as well, they must have had no ongoing ADT, PSA <10 ng/mL, and life expectancy ≥5 years. Fractionation schedules were either 30 Gy/3 fractions (stereotactic) or 50 Gy/25 fractions (conventional). The primary endpoint was treatment-related toxicity (grade ≥ 2) at 24 months after the start of local ablative radiotherapy; second endpoints included PSA progression-free time (event defined as initial PSA value +20%, or the start of ADT), progression-free survival (event defined as PSA progression, start of ADT, distant progression, or death), and OS.

A total of 72 patients were recruited, with 63 patients receiving local ablative radiotherapy; five patients were later determined to not fulfill the inclusion criteria, and for another four patients, a decision was made during radiotherapy planning not to proceed due to a very significant overlap with prior radiotherapy fields for the primary tumor. The study's median follow-up time was 37.2 months. There were 68 LN-METS and 21 OSS-METS treated; of note, most patients (n = 45, 71%) only had one lesion.

During follow-up, there were no treatment-related grade ≥ 2 adverse events by two years after local ablative radiotherapy. Regarding secondary endpoints, the median time to PSA progression was 13.2 months, progression-free survival was 21.4% at 3 years, and OS was 94.6% at 3 years. The authors concluded that local ablative radiotherapy was a safe and an effective option for selected patients to delay systemic therapy.

In view of the data, the ESTRO-ACROP Delphi consensus published the following four recommendations in *Radiotherapy & Oncology* in October 2022: [57].

- PSMA PET imaging is the preferred staging and restaging imaging modality for oligometastatic, oligorecurrent, and oligoprogressive prostate cancer patients

- Metastasis-directed radiotherapy (MDRT) may be considered for patients diagnosed with up to 5 lymph nodal, bone, or visceral metastases in all disease settings

- Systemic therapy with loco-regional irradiation and MDRT of all metastatic lesions is the preferred option for synchronous *de novo* oligometastatic hormone-sensitive patients

- MDRT of all lesions without switch of systemic therapy is recommended for patients with oligoprogressive castration-resistant prostate cancer

Ongoing phase III trials for MDT include the following, in **Table 3** [58–62].

Study	Name	Primary Objective
NCT02759783	Conventional Care Versus Radioablation (Stereotactic Body Radiotherapy) for Extracranial Oligometastases	Progression-free survival at 60 months post-treatment; time from randomization to evidence of progression of cancer at any site or death from any cause; includes prostate, breast, and non-small cell lung cancer primary tumors
NCT02685397	Management of Castration-Resistant Prostate Cancer with Oligometastases (PCS IX)	Radiographic progression-free survival, or the start of new anti-neoplastic therapy
NCT02274779	Salvage Radiotherapy Combined with Hormonotherapy in Oligometastatic Pelvic Node Relapses of Prostate Cancer (OLIGOPELVIS)	Biochemical or clinical relapse-free survival at 2 years
NCT03143322	Standard Treatment +/− SBRT in Solid Tumors Patients with Between 1 and 3 Bone-Only Metastases (STEREO-OS)	Progression-free survival (to evaluate the impact of SBRT on progression-free survival at 1 year according to RECIST 1.1 and PERCIST 1.0 criteria)
NCT03569241	PEACE V: Salvage Treatment of OligoRecurrent Nodal Prostate Cancer Metastases (STORM)	Metastasis-free survival

Table 3.
Ongoing prospective trials for metastasis-directed therapy.

13. Prostate genomics

The six-tier NCCN risk group classification system provides a highly-validated basic framework for standard treatment recommendations [8]. However, a variety of advanced risk stratification tools have been developed and are in various stages of validation that independently improve stratification. The NCCN recommends ordering these tests for borderline cases as an extra data point that may potentially change management; patients with low-risk, favorable intermediate-risk, unfavorable intermediate-risk, and high-risk tumors with a life expectancy ≥10 years may be candidates for Decipher®, Oncotype Dx Prostate®, or Prolaris® [63]. Indeed, research has demonstrated that the current risk stratification systems are frequently poor prognosticators for clinically-meaningful endpoints; for distant metastases rates at 10-years, the concordance index (c-index) for the NCCN classification system was 0.73 (95% CI, 0.60–0.86) and for CAPRA was 0.74 (95% CI, 0.65–0.84) [64]. Per the NCCN, Decipher® currently has the highest level of evidence for validation among the major genomic classifiers (GCs), having been validated in the context of multiple clinical trials with consistent results (see **Table 4**) [63].

Numerous studies have been performed, and are ongoing, to validate GCs. One notable example includes validation of the 22-gene Decipher® GC from the biobank from the phase III randomized trial NRG Oncology/RTOG 0126 [64]. This trial compared men with intermediate-risk prostate cancer randomized to 70.2 Gy versus 79.2 Gy, without androgen deprivation therapy. RNA was extracted from the highest grade tumor foci, and for 215 patients (of the 1532 patients in the study), the material passed quality control. GC data were generated and compared to the patients' respective clinical outcomes on the study, for a retrospective analysis of the prospective trial. The GC proved independently prognostic for disease progression ($p = 0.03$),

Genomic Classifier	Level of Evidence for Validation
Decipher®	1
Prolaris®	3
Oncotype®	3

Level 1: Validation in the context of multiple clinical trials with consistent results.
Level 2: Validation in multiple prospective registry/observational cohorts with consistent results.
Level 3: Validation in multiple independent retrospective studies with consistent results.
Level 4: Validation in a single retrospective study, or multiple independent retrospective studies with inconsistent results.

Table 4.
Levels of evidence for major prostate genomic classifiers [8].

biochemical failure ($p < 0.001$), distant metastasis ($p = 0.01$), and prostate cancer-specific mortality ($p < 0.001$). The authors deemed that the GC can be used to help personalize treatment for intermediate-risk prostate adenocarcinoma.

In 2021, prostate cancer researchers published "A Systematic Review of the Evidence for the Decipher Genomic Classifier in Prostate Cancer" in *European Urology* [65]. This systematic review incorporated 42 studies and 30,407 patients with localized, post-prostatectomy, non-metastatic castration-resistant, or metastatic hormone-sensitive prostate adenocarcinoma. The patients were part of retrospective studies (n = 12,141), prospective registries (n = 17,053), and prospective and post-hoc randomized trial analyses (n = 1213). For 32 studies, the GC proved independently prognostic for all study endpoints (adverse pathology, biochemical failure, metastasis-free survival, cancer-specific survival, and OS) on multi-variate analysis, and improved discrimination over the standard of care in 24 studies. As well, the GC changed management for the AS (NNT = 9) and post-prostatectomy (NNT = 1.5–4) settings. Its utility was deemed strongest for decision-making with intermediate-risk prostate adenocarcinoma and post-prostatectomy. Indeed, despite the ongoing debates about adjuvant and salvage radiotherapy in the setting of adverse pathologic risk factors without biochemical failure, the NCCN Prostate Guidelines now (Version 1.2023) recommends that Decipher® "should be considered if not previously performed to inform adjuvant treatment if adverse features are found post-RP;" [63] as well, as discussed previously, the NCCN recommends strongly considering post-prostatectomy radiotherapy and ADT when the Decipher® GC score is high (>0.6) [63].

A clinical-genomic model has been developed that incorporates the NCCN risk groups with the Decipher® GC, thereby creating a clinical-genomic point system. This model has an improved c-index of 0.84 (95% CI, 0.61–0.93), versus 0.73 (95% CI, 0.60–0.86) for the NCCN six-tiered classification system alone (see **Figure 3**) [64].

Regarding patients on AS, several studies have demonstrated the utility of GCs in determining which patients would have biopsy reclassification on serial biopsies, and therefore stop AS in favor of definitive treatment. A study at the University of California, San Francisco studied men with clinically low-risk prostate cancer prospectively enrolled on AS between 2000 and 2016 [66]. In this study, biopsy re-classification was defined as Gleason grade group ≥2 on subsequent biopsy. On multivariate analysis, biopsy re-classification at 3–5 years was strongly associated with a high genomic score (HR = 2.81); it was also strongly associated with a PSA density ≥ 0.15 (HR = 3.37), rapid PSA kinetics (HR = 2.19), and percentage biopsy cores positive (HR = 1.27). Of note, a PI-RADS 4–5 score on MRI was not associated with

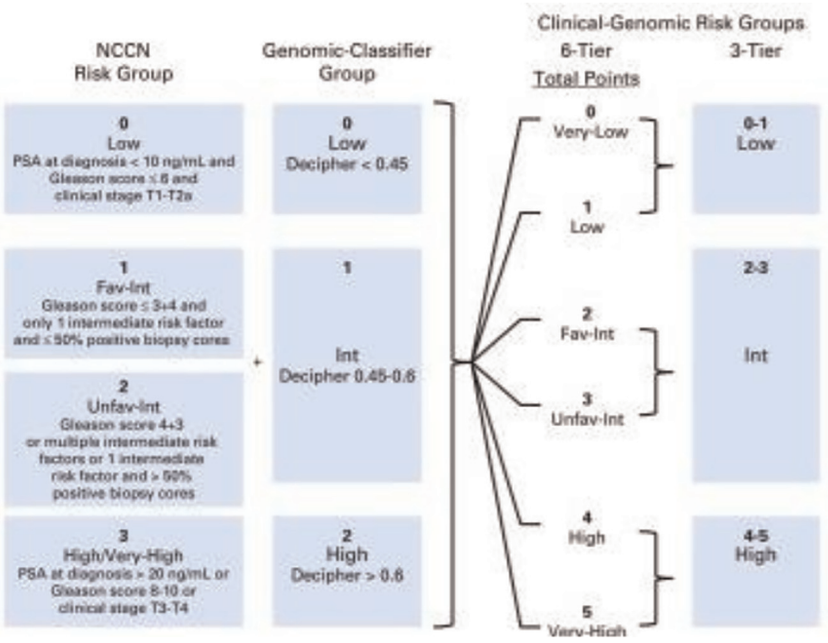

Figure 3.
Clinical-genomic point system using a genomic classifier [63, 64].

biopsy re-classification. In a multi-institutional study led by the University of Michigan, 855 men underwent Decipher® testing of their prostate biopsies between February 2015–October 2019, of whom 264 (31%) proceeded with AS [67]. For the men who chose AS, after adjusting for NCCN risk group and all risk factors, a high-risk Decipher® score was independently associated with a shorter time to treatment failure (HR = 2.51, $p < 0.001$). Of note, for the men who proceeded with radical therapy, a high Decipher® score was independently associated with a shorter time to treatment failure on multi-variate analysis.

Numerous prospective trials are currently ongoing to evaluate the effectiveness of these markers, and to better assess their utility for enhancing risk stratification, including the following studies, as demonstrated in **Table 5** [68–70].

Additionally, while the usage of artificial intelligence is still an NCCN category IIB recommendation at this time for aiding with risk stratification, new studies suggest it will have an increasing role in cancer therapy precision [8, 71].

14. Summary

The evaluation of patients who have been diagnosed with prostate adenocarcinoma is a changing paradigm, and an important one for an extremely prevalent, but often non-aggressive malignancy. Since the advent of PSA testing, patients are usually diagnosed at earlier stages, often creating the difficult questions of who needs to be treated, when, and how aggressively. As well, patient evaluation is important in the adjuvant and locally-recurrent scenarios. With increasing data on treating oligometastatic cancers, local treatment and MDT are increasingly supported by data and utilized to improve cancer endpoints. Enhanced imaging, such as PSMA PET/CT, is improving the sensitivity of detecting metastases and recurrent disease, and thereby helping in patient selection and ensuring meaningful local treatment and MDT, given the potential for toxicity.

Study	Name	Primary Objective
NRG Oncology GU-009	Parallel Phase III Randomized Trials or High Risk Prostate Cancer Evaluating De-Intensification For Lower Genomic Risk and Intensification of Concurrent Therapy for Higher Genomic Risk with Radiation (Predict-RT*) *Prostate RNA Expression/Decipher To Individualize Concurrent Therapy with Radiation	De-Intensification Study: To determine whether men with NCCN high-risk prostate cancer who are in the lower 2/3 of Decipher genomic risk (≤0.85) can be treated with 12 months of ADT plus RT instead of 24 months ADT + RT and experience non-inferior metastasis-free survival Intensification Study: To determine whether men with NCCN high-risk prostate cancer who are in the upper 1/3 of Decipher genomic risk (>0.85) or have node-positive disease by conventional imaging (MRI or CT scan) will have a superior metastasis-free survival (MFS) through treatment intensification with apalutamide added to the standard of RT plus 24 months of ADT
NRG Oncology GU-010	Parallel Phase III Randomized Trials of Genomic-Risk Stratified Unfavorable Intermediate Risk Prostate Cancer: De-Intensification and Intensification Clinical Trial Evaluation (Guidance)	De-Intensification Study: To determine whether men with unfavorable intermediate-risk prostate cancer and lower Decipher genomic risk (<0.40) treated with RT alone instead of 6 months ADT + RT experience non-inferior rate of distant metastasis Intensification Study: To determine whether men with unfavorable intermediate-risk prostate cancer who are in the higher genomic risk (Decipher score ≥ 0.40) will have a superior metastasis-free survival through treatment intensification with darolutamide added to the standard of RT plus 6 months of ADT
NCT 04396808	Genomics in Michigan to AdJust Outcomes in Prostate cancer (G-MAJOR) for Men with Newly Diagnosed Favorable Risk Prostate Cancer	Binomial proportion of men on active surveillance without treatment at 2 years (studies active surveillance with genomic classifiers including Decipher®, Prolaris®, and Oncotype Dx®)

Table 5.
Ongoing prospective trials for validation of genomic classifiers.

The NCCN Prostate Panel itself acknowledges that the six-tier classification system has limited predictive/prognostic value, which has been confirmed in studies, and it recommends additional studies for borderline cases. GCs have demonstrated significant prognostic value, and are undergoing increasing validation in numerous studies. As medicine increasingly progresses from personalized medicine to precision medicine, and GCs' prospective studies have an opportunity for maturation of their data, GCs will very likely have a much more significant impact on patient evaluation and ensuring the most appropriate treatment regimens.

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