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Updates on controversies surrounding the staging and management of newly diagnosed localized prostate cancer using prostate-specific membrane antigen (PSMA) positron emission tomography

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Abstract

There are controversies surrounding indications for prostate-specific membrane antigen (PSMA) positron-emission tomography (PET) and the subsequent management of localized disease. Conventional imaging is not a necessary prerequisite to PSMA PET, which serves as an equally effective, if not more effective frontline imaging tool. However, research conducted in different countries has shown conflicting results regarding its cost-effectiveness. Following accurate staging using PSMA PET, subsequent management is discussed by our expert team in this review, which incorporates the latest updates: (1) Brief global overview: the sustainability and cost-effectiveness of routine PET, as well as the treatment sequences of neoadjuvant vs. adjuvant androgen deprivation therapy (ADT) with radiotherapy, require further research. (2) Gonadotropin-releasing hormone antagonists demonstrate better response rates, lower recurrence rates, and fewer complications compared to agonists. (3) The unfavorable intermediate-risk group may undergo prostatectomy or radiotherapy combined with 4–6 months of ADT. Radiotherapy alone may be considered for patients with co-morbidities, Gleason score 7 (3 + 4), and positive biopsy cores < 50%, provided an escalated radiation dose is applied. (4) Three Prostate Advances in Comparative Evidence

(PACE) studies demonstrated that stereotactic radiotherapy, greatly relying on PSMA PET, is as effective as surgery or conventional radiotherapy. (5) Findings from clinical trials indicate that pelvic nodal radiotherapy coverage provides a survival benefit. (6) A brachytherapy boost provides better outcomes compared to external beam boost, eliminating the need for ADT in intermediate-risk cancers and reducing ADT duration to 6 months in high-risk cancers. Even short-term use (4–6 months) of gonadotropin releasing hormone agonists can lead to cardiac morbidity. In summary, localized prostate cancer, as identified through the relatively new PSMA PET, can be managed in various ways. This review highlights significant updates on controversial issues relevant to both cancer patients and researchers.

Keywords

Prostate cancer, radiotherapy, immunotherapy, chemotherapy, androgen deprivation therapy, prostate-specific antigen, positron emission tomography, prostate-specific membrane antigen

Introduction

There have been numerous controversies regarding the indications and utility of prostate-specific membrane antigen (PSMA) positron-emission tomography (PET) scans, as well as the appropriate course of action following a positive result. Current debates surrounding the use of hormonal therapy or androgen deprivation therapy (ADT) for radical treatment include its role in patients treated with brachytherapy, its use in the unfavorable intermediate-risk group, and the optimal duration of therapy in various scenarios. Questions arise regarding the optimal choice of ADT, as many options are available, including gonadotropin-releasing hormone antagonists, anti-androgen monotherapy, and androgen receptor pathway inhibitors. Our expert team has focused on management controversies in this review and provides updates on these issues by searching PubMed, websites of large institutes, and Google. We aim to derive answers from the most recent updates within the past five years. The search term used was the specific controversy in question. We are pleased to present this work with the latest references to benefit prostate cancer patients, oncologists, and researchers, ensuring no commercial conflict of interest or bias against any industry products.

The three PSMA assays currently approved for use in PSMA PET imaging by the U.S. Food and Drug Administration include Gallium-68 PSMA-11, Flotufolastat F 18 (Posluma), and Piflufolastat F 18 (Pylarify) [1]. This review focuses on recent publications that critically address the following questions and controversies regarding the application of PSMA PET in prostate cancer: (1) A summary of the global situation, including information from American, Australian, Canadian, and European guidelines, as well as websites of major institutes [2–11]. (2) What are the indications and utility of PSMA PET? Is it cost-effective? (3) What are the radical or curative treatment options, and how do they compare with each other? (4) What are the optimal sequences for multi-modality treatment? (5) What supportive therapies are available? (6) How should the disease be monitored?

Rather than offering a standard systemic review of all major landmark studies, this article focuses on **selected practical studies, highlighting controversies and emphasizing the need for caution**. While we cannot include all available information regarding PSMA, it summarizes management controversies as assessed by our experienced expert team. Many of the aforementioned controversies are frequently debated during Multidisciplinary Disease Team Rounds at cancer centers worldwide. These controversies have been carefully organized within a single article for the convenience of busy physicians. We strive to provide a valuable resource for prostate cancer patients, specialists, and researchers.

Brief global overview of prostate cancer

Prostate cancer is less prevalent in Asian countries. However, it is the fourth most common cancer globally and the second most common cancer in men, after lung cancer [12]. The high incidence of prostate cancer in Western countries is likely linked to dietary factors, although genetic factors also play a significant role.

There is a rising trend in prostate cancer cases among Asian men [12]. However, due to the relatively lower incidence, screening is generally not considered necessary in Asian countries, whereas its necessity remains a controversial topic in the Western world. Differences between American and European screening studies can be attributed to baseline screening practices in the United States, where individuals often undergo screening through their family doctors before participating in screening trials [13, 14]. We refer to this as "contamination", where pre-screened individuals naturally derive less benefit from screening trials. In contrast, baseline screening is less common in Europe, resulting in lower prostate cancer mortality among those enrolling in screening trials. Unfortunately, in the United States, such contamination has led to a decrease in prostate-specific antigen (PSA) screening rates [13].

Prostate cancer disproportionately affects countries with a low social-demographic index (SDI), primarily due to inadequate preventive and treatment methods in these regions. The highest mortality rates are observed in African countries, where harmful mutations linked to disease aggressiveness are prevalent. It is suspected that global prostate cancer incidence continues to rise [15]. Unfortunately, in many developing countries, access to PSMA PET remains limited, and the results of related trials may not be applicable to these regions.

What are the indications and utility of PSMA PET?

The role of PSMA PET is best summarized in the updated statement from the 1.2025 version of the National Comprehensive Cancer Network (NCCN) in the United States [3]: "Because of the increased sensitivity and specificity of PSMA PET tracers for detecting micro-metastatic disease compared to conventional imaging, e.g., computerized tomography (CT)/bone scan at both initial staging and biochemical relapse, conventional imaging is not a necessary prerequisite to PSMA PET and that PSMA PET/CT or PSMA PET/MRI (magnetic resonance imaging) can serve as an equally effective, if not more effective frontline imaging tool.". The Radiographic Assessments for Detection of Advanced Recurrence (RADAR) study also provides guidance on next generation imaging [16, 17].

The 2024 update of the European Association of Urology guidelines [10] recommends prioritizing PSMA PET imaging over conventional bone scans and CT for staging high-risk localized or locally advanced prostate cancer.

Sood et al. [18] reviewed a total of 148 studies—130 focused on PET and 18 on biomarkers—and concluded that PSMA PET use led to a management change in 20–30% of patients [19]. Similarly, tissue-based prognostic biomarkers, including Decipher, Prolaris, and Oncotype Dx, in the pretherapy primary prostate cancer setting resulted in management changes for up to 65% of patients. Notably, in the postsurgical primary prostate cancer setting, biomarker-guided adjuvant radiation therapy (RT) was associated with improved oncological control, demonstrated by a 22% reduction in 2-year biochemical failure (level 2b) [18].

The utility of PSMA PET in guiding RT has been highlighted in the American Society of Clinical Oncology guideline (2020) and the Advanced Prostate Cancer Consensus Conference (2024) [4, 14, 20]. PSMA PET can be used for initial staging and confirming local relapse in the prostate bed and pelvic lymph nodes. When the disease is extra-nodal or in cases of biochemical recurrence, PSMA PET seems to be more cost-effective than conventional imaging. Furthermore, the 2023 American Urological Association advanced prostate cancer guideline emphasized the preferential use of PSMA PET imaging over conventional imaging in cases of biochemical recurrence after local therapy failure, citing its superior sensitivity [4]. The use of whole-body MRI for staging is less well known [21]. The Australian Prostate-Specific Membrane Antigen PET-CT (ProPSMA) study in patients with high-risk prostate cancer prior to curative-intent surgery or radiotherapy found that the scan offers superior accuracy, more definitive results, and lower radiation exposure compared to conventional imaging [22]. ProPSMA study showed other important results. One that is often overlooked is the high kappa, which speaks to the reliability of the test: reporter agreement was high for both nodal (kappa 0.87, 95% CI 0.81–0.94) and distant metastatic disease (kappa 0.88, 95% CI 0.92–0.94). It also facilitates curative treatments while avoiding unnecessary and potentially harmful

interventions [22]. A health economics assessment demonstrated its cost-effectiveness compared to standard imaging [23]. However, a joint European and United States study reported conflicting findings [24].

Limitations of PSMA PET

The following could be viewed as concerns regarding PSMA PET, arguing against its widespread adoption:

(1) False negative results may occur due to the urinary bladder obscuring pelvic nodes or bony lesions, dedifferentiation of the tumor and no longer expresses PSMA [25]. To resolve this, ^{18}F-FDG (fluorodeoxyglucose) or choline tracers can be used, although choline generally does not perform well in low PSA values [26]. False positivity within the prostate gland can be due to prostatitis. This affects focal boost radiotherapy treatment planning. Regarding false positive disease in distant sites, patients may be denied local treatment due to the perceived presence of metastatic disease. However, with the HORRAD and arm H of the **S**ystemic **T**herapy in **A**dvancing or **M**etastatic **P**rostate cancer: **E**valuation of **D**rug **E**fficacy (STAMPEDE) studies, oligometastatic disease of less than five sites would be considered for local radiotherapy [27, 28]. The doses used in these trials are lower than those typically administered at American academic centers [e.g., 36 Gy (Gray is a unit of absorbed dose) in 6 weekly fractions or 55 Gy in 20 fractions (55 Gy/20 f) over 4 weeks, which is a common British dose-fractionation].

(2) Accessibility issues arise because PSMA PET centers are concentrated in highly populated regions of developed countries, requiring patients and caregivers to travel to these locations. Globally, developing countries have less access to these scans.

(3) Variations in sensitivity have been observed across different patient populations, depending on the PSA velocity of the cancer [29, 30].

(4) Cost-effectiveness of PSMA PET in replacing conventional imaging or avoiding additional biopsies for the diagnosis of prostate cancer has yet to be confirmed [31–33].

After PSMA PET staging, what are the local radical/curative treatment options?

For individuals with negative PSMA PET results and no distant metastases, surgery and/or radiotherapy remain the two primary treatment modalities, serving as the standard of care and commonly utilized options. Additionally, the combination of flutamide and finasteride can be used to manage both early and advanced prostate cancer while preserving potency [34]. Dutasteride alone has been shown to help delay biochemical failure in the Avodart After Radical Therapy for Prostate Cancer Study (ARTS) trial [35]. High-intensity focused ultrasound (HIFU) and cryotherapy are focal treatment alternatives that heavily rely on PSMA PET; however, these approaches lack the extensive track record of current standard-of-care treatments [36–45].

Prostatectomy: recent advances

Advances in nerve-sparing techniques not only improve sexual function but also enhance urinary continence. A significant large randomized study, NeuroSAFE PROOF, involving 407 patients, confirmed the benefits of NeuroSAFE with standardized frozen section analysis [44]. Prostatectomy nowadays is indeed more precise with the use of the Da Vinci system, which features remote control capabilities [46, 47]. The Senhance Surgical System, on the other hand, utilizes reusable instruments [48]. Safety and short-term outcomes are comparable between the two systems. However, experienced surgeons find the Senhance system more straightforward and cost-effective for performing radical prostatectomy.

Radiotherapy: recent advances

Modern *external beam radiotherapy* options include intensity-modulated RT, volumetric modulated arc therapy, and stereotactic body RT targeting primary and/or metastatic sites. Proton therapy is also

available, though it is likely the least accessible method due to location and cost constraints. Additionally, radiotherapy can be delivered internally through brachytherapy, which is more invasive as compared to external beam radiotherapy. It is commonly administered at either low- or high-dose rates. Pulsed dose rate machines are currently being phased out in Canada. Radioactive sources, such as iodine-125 (I-125) and palladium-103 seeds are less commonly used today due to safety concerns. Instead, remote iridium-192 after-loading machines are widely installed in cancer centers worldwide to provide brachytherapy. However, prostate gland brachytherapy requires significant experience and expertise, is invasive, and is therefore less desirable for patients with a large prostate or those who have difficulty discontinuing anticoagulants. It requires dedicated staff and a specialized suite, making it expensive and leading to waiting lists in most countries. A practical reminder is to administer hormonal therapy for cytoreduction prior to brachytherapy if the prostate volume is too large to achieve optimal geometry [49].

Proton therapy is not yet available in Canada or many other countries. In the United States, patients must obtain insurance approval and travel to proton centers, requiring them to stay at the treatment location. This poses a financial burden, particularly for seniors on fixed incomes. Additionally, arranging a stay in an unfamiliar place can be challenging for patients with cognitive impairments or poor social support.

Radiotherapy boost, guided by PSMA PET to localize the dominant intra-prostatic lesion, can be delivered via external beam radiotherapy or brachytherapy [50]. According to the **A**ndrogen **S**uppression **C**ombined with **E**lective **N**odal and **D**ose **E**scalated **R**adiation **T**herapy (ASCENDE-RT) trial [51], brachytherapy yields better outcomes as a boost compared to external beam radiotherapy for high-risk patients. The 9-year relapse-free survival rate was 85% in the arm of I-125 seed brachytherapy combined with external beam RT and ADT—21% higher than that achieved with external beam radiotherapy at 78 Gy combined with ADT [51].

In high-risk patients, triple or tri-modality treatment allows ADT to be shortened from the previous standard of 30 months to 6 months. For high-dose brachytherapy, common regimens include 27 Gy/2 f or 38 Gy/4 f as monotherapy, and 18–20 Gy/2 f or 15 Gy/1 f as a boost following external beam radiotherapy for improved disease control [52, 53]. High-dose rate brachytherapy monotherapy with 38 Gy/4 f demonstrated better long-term freedom from biochemical failure compared to 24 Gy or 27 Gy/2 f, without an increase in complication rates [53]. Another recent development originated from the Canadian Quebec group of radiation oncologists, who have been particularly active in prostate cancer research. The group proposed an 18-month duration of ADT for high-risk patients, which has now been widely adopted in select cases across Canada [54].

The *target volume* for the prostate varies depending on the volume of the seminal vesicles, the extent of pelvic nodal coverage, and the cranial extent of the coverage. Previously, the upper border was set at the junction of the lumbar (L5) and sacral (S1) vertebrae, but patterns-of-failure studies recently recommend extending it to the aortic bifurcation [55]. The survival benefit of pelvic nodal radiotherapy coverage was equivocal in the definitive radiotherapy study **R**adiation **T**herapy **O**ncology **G**roup (RTOG) 9413 [56, 57]. However, more recent studies, such as **P**rostate-only **O**r whole-**P**elvic **R**adiation **T**herapy (POP-RT) in high-risk prostate cancer and RTOG 0534/SPPORT, support pelvic nodal coverage [58, 59]. An easy way to remember SPPORT might be: **S**tudy of addition of ADT and **P**elvic lymph node treatment to **P**rostate bed **O**nly salvage **R**adiation **T**herapy. However, we could not find the exact full term for the acronym SPPORT as such.

The exact fractionation of external beam radiotherapy has been the subject of research for decades [60]. In Canada, 60 Gy/20 f is currently one of the standard care options [61] (Table 1). In the United States, doses of 1.8 Gy per fraction (1.8 Gy/f) to over 74 Gy are more commonly used. In Europe and Canada, conventional fractionation typically involves 74–78 Gy delivered in 2 Gy fractions (2 Gy/f). Hypofractionation for pelvic nodal volumes has been studied in recent years and has been found to be safe [62].

Table 1. Selected key radiotherapy trials addressing contemporary controversies

Controversy	Trial	Eligibility (PSA in ng/mL)	Arms	Outcomes
RT dose	MRC RT01 [63]	T1b-3a, N0, M0	**64 Gy/32 f vs. 74 Gy/37 f**	Improved bPFS, PFS
		PSA < 50	Conformal RT + neoadjuvant ADT	Increased late bladder and bowel toxicities
Dose fractionation	CHiPP [64]	T1b-3a, N0, M0	**60 Gy/20 f vs. 74 Gy/37 f**	Non-inferior results
		PSA < 100	Conformal RT + neoadjuvant ADT	
RT dose & ADT	Quebec randomized study, PCS III [54]	Favorable intermediate risk: only 1 risk factor, not GS 4 + 3/biopsy core ≥ 50%. The rest are unfavorable cases	**ADT + 70 Gy + 6 m ADT**	Favorable group: n.s. between the arms
			ADT + 76 Gy + 6 m ADT	
			76 Gy alone	Unfavorable group: less biochemical failure with addition of ADT. Low cancer mortalities for all arms
		PSA > 10		
RT pelvic coverage	RTOG 9413 [56]	T1c-4 and estimated 15% nodal risk	**WP RT + NCHT**	4-year PFS:
			PO RT + NCHT	60%*
		PSA > 100	**WP RT + AHT**	44%
			PO RT + AHT	49%
			Neoadjuvant ADT or AHT. RT to pelvis: 50.4 Gy/28 f, prostate only: 70.2 Gy/39 f	50%
				P = 0.008

ADT: androgen deprivation therapy; AE: adverse effect; AHT: adjuvant hormonal therapy; bPFS: biochemical progression-free survival; f: fraction; MRC: Medical Research Council; NCHT: neoadjuvant and concurrent hormonal therapy; n.s.: non-significant; PFS: progression-free survival; PO: prostate only; PSA: prostate-specific antigen; RT: radiation therapy; RTOG: **R**adiation **T**herapy **O**ncology **G**roup; WP: whole pelvis; Gy: Gray is a unit of absorbed dose; m: months. * This arm has more grade 3 gastrointestinal complications

The three Prostate Advances in Comparative Evidence (PACE) studies have helped resolve the long-standing debate between radiotherapy and surgery [65–70]. The key findings are summarized in Table 2. In summary, as observed in many studies, including the PACE study, the primary side effects of prostatectomy are sexual impotence and urinary incontinence. For patients not considered for surgery, stereotactic body radiation therapy (SBRT) demonstrated non-inferior efficacy vs. conventional RT in intermediate-risk prostate cancer and a similar toxicity profile in both intermediate and high-risk prostate cancer. The main complications of radiotherapy include second malignancies in surrounding organs such as the bladder and rectum [67], rectal bleeding due to radiation proctitis, and sexual impotence. The side effects of ADT primarily include hot flashes, insomnia, depression, and sexual impotence, all of which can significantly impact quality of life [68–71]. To prevent misunderstandings and preserve the doctor-patient relationship, patients should receive both written information along with a thorough discussion of potential side effects to avoid unexpected surprises (**a practical caution**).

Table 2. Summary of the three Prostate Advances in Comparative Evidence (PACE) studies [67–70]

Study name	PACE-A	PACE-B	PACE-C
Treatment	SBRT (36.25 Gy/5 f) vs. surgery	SBRT (36.25 Gy/5 f) vs. conventional moderate hypofractionated EBRT (62 Gy/20 f or 78 Gy/39 f)	SBRT (36.25 Gy/5 f) vs. moderate hypofractionation (60 Gy/20 f)
Risk group	8% low	9% low	35% high
	92% intermediate	91% favorable intermediate	65% intermediate
ADT	No	No	6-month ADT
Key results	GU/GI toxicity (see below). Sexual score by EPIC sexual domain, 62.3 (32.0–87.5) vs. 18 (13.8–40.3) at 24 m	Biochemical or clinical-failure-free rate 95.8% vs. 94.6%	*Accrual completed, results pending*
GU toxicity	6.5% vs. 50% reported use of urinary pads (P < 0.001)	26.9% vs. 18.3% (P < 0.001)	RTOG scale: 28% vs. 27%, P = 0.83
			CTCAE scale: 34% vs. 28%, P = 0.038 (n.s.)

Table 2. Summary of the three Prostate Advances in Comparative Evidence (PACE) studies [67–70] (*continued*)

Study name	PACE-A	PACE-B	PACE-C
GI toxicity	Bowel scores by EPIC bowel domain [87.5 (79.2–100) vs. 100 (100–100)]	10.7% vs. 10.2% Grade 2+ in both arms (P = 0.94)	RTOG scale: 13% vs. 11%, P = 0.47 CTCAE scale: 17% vs. 10%, P = 0.0008
Conclusion	SBRT: less urinary incontinence, sexual bother, but slightly more bowel bother than prostatectomy	SBRT: non-inferior to conventional RT for intermediate-risk prostate cancer	GU and GI toxicities were comparable to the PACE-B trial, despite the larger prostate volume

ADT: androgen deprivation therapy; CTCAE: common terminology criteria for adverse events; EPIC: The Expanded Prostate Cancer Index Composite; GI: gastrointestinal; GU: genitourinary; m: months; n.s.: non-significant; RT: radiation therapy; RTOG: **R**adiation **T**herapy **O**ncology **G**roup; SBRT: stereotactic body radiation therapy; Gy: Gray is a unit of absorbed dose; m: months

Recent updates on combination local treatment

The value of routine postoperative adjuvant radiotherapy in cases of positive resection margins, seminal vesicle involvement, or extracapsular extension has been questioned in the ARTISTIC meta-analysis of trials [72]. This meta-analysis included 2,153 patients from three studies (RADICALS-RT [73, 74], RAVES [75], and GETUG-AFU17 [76]), which predominantly represented low- and intermediate-risk patients, with 77.6% having a Gleason score of 7. Biochemical progression-free survival (bPFS) was defined by the researchers as PSA level > 0.4 ng/mL following radiotherapy, PSA > 2.0 ng/mL at any time, clinical progression, initiation of salvage ADT, or death from prostate cancer [71]. The 5-year bPFS rates were 85% for the adjuvant radiotherapy group vs. 88% for the salvage radiotherapy group (hazard ratio: 1.10; 95% confidence interval: 0.81–1.49; P = 0.56) [72]. This meta-analysis concluded that adjuvant radiotherapy does not improve event-free survival. Consequently, early salvage treatment is now recommended in treatment guidelines, as it appears preferable for avoiding long-term side effects and reducing healthcare costs.

Systemic treatment options for localized prostate cancer

Studies on gonadotropin-releasing hormone antagonists have shown that they offer better responses, lower relapse and recurrence rates, and reduced cardiovascular mortality compared to the agonists [77, 78]. Transitioning to antagonists remains an option even after initiating treatments with agonist [79]. Monthly degarelix injections, however, can be inconvenient for patients who frequently travel or require extended stays away, and they also place greater demands on the space and staffing resources of cancer clinics. Oral relugolix, though more convenient, is significantly more expensive than most agonists, costing around US$2,834 for a 30-tablet supply. From the authors' experience, systemic treatment costs for prostate cancer are increasing in Canada, affecting both patients and cancer clinics. Anti-androgens are often combined with agonists to achieve total androgen blockade, with bicalutamide, flutamide and nilutamide being the most commonly used options. The addition of two years of abiraterone acetate and prednisolone to hormonal therapy plus radiotherapy in high-risk patients significantly delayed metastasis and improved survival, as demonstrated in the landmark STAMPEDE study [27]. However, **caution** is advised for patients with cardiovascular, liver or metabolic comorbidities, as they may not be suitable candidates for abiraterone. Among the various drugs used in prostate cancer treatment, docetaxel is potentially the most cost-effective option. However, patients on docetaxel may experience declines in their quality of life, including pain, physical functioning, role functioning, and social functioning. These adverse effects have been documented to persist for up to two years following the completion of the 24-week docetaxel treatment, significantly impacting quality of life [80].

Best sequence(s) for multimodality treatment

Different sequences of the aforementioned therapies can be adjusted for therapeutic advantage, such as neoadjuvant enzalutamide [81]. According to preliminary trials and reviews [2], PSMA radioligand therapy may serve as an alternative systemic treatment. Further research into androgen resistance, including potential drugs or regimen modifications to delay its onset, will greatly benefit patients [82]. The

RADICALS-HD trial (A Randomized Controlled Trial of ADT Duration with Postoperative Radiotherapy for Prostate Cancer) aimed to assess the efficacy of different ADT durations combined with postoperative radiotherapy. Patients with PSA levels below 5 ng/mL were eligible. The trial found that adding 24 months of **adjuvant** ADT to postoperative adjuvant radiotherapy significantly improved metastasis-free survival compared to 6 months (P = 0.029) [83]. However, when comparing 6 months of adjuvant ADT to no ADT, no significant benefit was observed [84]. Historically, the RTOG employed 2 months of neoadjuvant ADT alongside the initiation of radiotherapy, followed by concurrent and adjuvant ADT [85]. However, an analysis of two trials by Spratt et al. [86] concluded that **adjuvant ADT is preferable** to neoadjuvant ADT.

ADT has many side effects. Cardiac, peripheral vascular disease, thrombosis, and cerebrovascular toxicities, along with excess cardiovascular mortality, do not appear to increase mortality in randomized controlled trials. However, retrospective series have frequently documented these side effects [87]. The discrepancy arises because trial participants are typically younger, healthier, and have a better performance status. Additionally, these trials only account for fatal cardiac disease, whereas retrospective series include all cardiovascular and cerebrovascular events. It should be noted that even androgen receptor pathway inhibitors can exhibit cardiotoxicities when used in combination with ADT, as shown in a meta-analysis by El-Taji et al. [88]. This analysis evaluated risk ratios for all-grade and grade 3 or higher cardiovascular events (primary outcomes), as well as secondary outcomes such as hypertension, acute coronary syndrome, cardiac dysrhythmia, cardiovascular death, cerebrovascular events, and venous thromboembolism. Cardiac toxicities can, however, be mitigated as suggested by Crawford et al. [89]. Treatment should be tailored to each patient, considering factors like the necessity to shrink the prostate gland before radiotherapy to reduce the irradiation volume, baseline urinary symptoms, and existing comorbidities. **A practical caution** is to limit the duration of ADT as much as possible while still maintaining optimal outcomes as supported by literature. This is particularly relevant for patients with diabetes, cardiovascular or liver diseases, cognitive impairment, sexual dysfunction and osteoporosis. As a result, high-risk patients are now commonly treated with 18–24 months of ADT, whereas previously, 24–36 months were recommended [89].

The preservation of sexual function varies in importance among patients and requires an open dialogue between the doctor and patient. Older patients may prioritize overall survival rather than sexual function. Conversely, lonely widowers may lean toward more conservative or non-curative treatments due to limited family support and the challenges of managing treatment side effects alone.

Different clinical scenarios

(1) *For early-stage and low-risk disease*, ongoing debates persist about the optimal timing to transition from active surveillance to radical treatment [2]. The **P**rostate cancer **I**ntervention **V**ersus **O**bservation **T**rial (PIVOT) study raised questions about the benefits of surgery for certain men with early-stage disease [90, 91]. However, the study's accrual was significantly lower than originally planned, leading to a lack of statistical power in some of its findings.

(2) *For the intermediate-risk group*, the use of ADT has been controversial for quite some time. The DART01/05 study concluded that intermediate-risk patients treated with high-dose radiotherapy do not benefit from 24 months of androgen blockade compared to 4 months [92]. RTOG 9408 demonstrated a reduction in 10-year disease-specific mortality from 8% to 4% (hazard ratio for radiotherapy alone: 1.87; P = 0.001) when 4 months of ADT was administered before and during radiotherapy [93]. However, it is **important to note** that few patients succumb to intermediate-risk prostate cancer. Subsequent studies have focused on distinguishing the unfavorable subgroup from the favorable subgroup. In a study of 600 intermediate-risk patients from Quebec, Canada, participants were randomized into three arms: escalated radiotherapy dose of 76 Gy with or without ADT and 76 Gy alone [94, 95]. The study concluded that 76 Gy alone is sufficient for patients with only one risk factor, excluding Gleason pattern 4 + 3 and prostate biopsy cores ≥ 50% (favorable intermediate risk). Conversely, all other unfavorable intermediate-risk patients appear to benefit from the combination of ADT and 76 Gy. Therefore, patient counseling is essential to guide decision-making for unfavorable intermediate-risk patients.

(3) *For high-risk prostate cancer*, triple therapy comprising ADT, brachytherapy boost, and external beam radiotherapy increases bPFS, as discussed above in the context of brachytherapy. D'Amico et al. [71] stratified high-risk patients by cardiac risk groups to determine the optimal duration of hormonal therapy: 0, 6, or 36 months. They concluded that men with a history of heart attack who received radiotherapy for high-risk prostate cancer experienced net harm, with a decrease of 0.1–0.2 and 0.5–0.6 **Q**uality-**A**djusted **L**ife **Y**ears (QALY) for 6 months and 36 months of ADT, respectively. Conversely, men without a history of heart attack gained a quality-adjusted life expectancy benefit from both short- and long-term hormonal therapy, even if they had up to four cardiac risk factors.

What supportive therapies are available?

All patients should receive general health advice to manage treatment-related adverse effects, including those affecting sexual life, mood, diet, and bone health, along with guidance on exercise to enhance their quality of life, as recommended in RTOG 0126 [96, 97]. Hot flashes, a common adverse effect, can disrupt sleep and significantly impact quality of life, potentially leading to treatment discontinuation. Non-hormonal pharmacological treatments (e.g., antidepressants, antiepileptics, antihypertensives), physical and behavioral interventions (e.g., acupuncture, yoga/exercise, relaxation techniques, cognitive behavioral therapy), and natural health products (e.g., black cohosh, flax, vitamin E, ginseng) have all been studied for their effectiveness in managing hot flashes [98].

Supervised exercise has been shown to improve both quality of life and survival. For instance, Tai Chi, a Chinese martial art, has demonstrated benefits in alleviating fatigue, improving balance and preventing falls, as supported by the literature [99–103]. To prevent osteoporosis, patients should undergo monitoring with bone mineral densitometry [104]. Additionally, patients with a history of myocardial infarction or stroke may require a referral to a cardiologist for evaluation before starting hormonal therapy. The use of gonadotropin releasing hormone antagonists may be a better alternative for men with a prior history of myocardial infarction or stroke [79].

How to monitor disease?

For monitoring disease progression, both serum PSA and testosterone levels are currently utilized. In most Canadian centers, family doctors and nurses assist with follow-up for stable patients after two years, as blood tests are relatively simple to perform. Digital examinations are no longer necessary, making telehealth visits increasingly **practical** for rural patients [105]. The question of whether PSMA PET can be used more frequently while maintaining a sustainable healthcare budget remains unanswered and requires further research [106]. The NCCN has established a standardized monitoring protocol [3]. The PSA threshold for relapse or recurrence is defined by the Phoenix criteria after radiotherapy (nadir PSA + 2 ng/mL) [107] and a value of 0.2 ng/mL for post-prostatectomy patients [108]. However, with the advancement of ultrasensitive assays, these standard nadir values may evolve as more research becomes available [109, 110]. Additionally, circulating tumor cell detection as an early indicator of relapse is an emerging technology that holds significant promise for the future [111].

Conclusions

In summary, due to its increased sensitivity and specificity for detecting micro-metastatic disease compared to conventional imaging at both initial staging and biochemical relapse, conventional imaging is not a necessary prerequisite for PSMA PET. PSMA PET/CT or PSMA PET/MRI can serve as an equally effective, if not more effective, frontline imaging tool and can also be used for re-staging during recurrence. Contemporary curative and radical treatment options include surgery, RT (external beam radiotherapy with or without brachytherapy and the emerging neoadjuvant lutetium PSMA), hormonal therapy (gonadotropin-releasing hormone agonists/antagonists with or without androgen receptor pathway inhibitors), and systemic therapy (hormonal therapy, chemotherapy, immunotherapy, and miscellaneous inhibitors). Details of treatment sequences and alternatives have been summarized above.

To choose the best treatment, whether conservative or aggressive, start with a digital rectal exam and a thorough history that includes health, comorbidities, psychosocial factors (especially sexual function), and the baseline International Prostate Symptom Score (I-PSS). The physician then estimates the prognosis using tools such as the NCCN website and considers genomic biomarkers for risk assessment and treatment planning, while also accounting for drug interactions and prioritizing the preferences of the patient and caregiver. Several new agents introduced in the past decade, such as abiraterone, are associated with side effects like fatigue, hypertension, diabetes mellitus, and hepatotoxicity. For monitoring disease during and after treatment, both serum PSA and testosterone levels are essential.

Future research should focus on the sustainability and cost-effectiveness of routine PSMA PET for initial diagnosis, treatment monitoring, and follow-up. While the Australian ProPSMA study indicated that PSMA PET is cost-effective in Australia, research from the United States and Europe has yielded conflicting results. Further investigations into the cost-effectiveness of PSMA PET are necessary to maximize patient benefits while managing healthcare costs. A randomized study on the survival benefit of PSMA PET is unlikely to be feasible, as nonrandomized studies have already demonstrated improved survival following staging with PSMA PET instead of conventional imaging.

Abbreviations

55 Gy/20 f: 55 Gy in 20 fractions

ADT: androgen deprivation therapy

ASCENDE-RT: Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy

CT: computerized tomography

CTCAE: common terminology criteria for adverse events

EPIC: The Expanded Prostate Cancer Index Composite

FDG: fluorodeoxyglucose

GI: gastrointestinal

GU: genitourinary

Gy: Gray is a unit of absorbed dose

MRI: magnetic resonance imaging

NCCN: National Comprehensive Cancer Network

PACE: Prostate Advances in Comparative Evidence

PET: positron-emission tomography

PIVOT: Prostate cancer Intervention Versus Observation Trial

POP-RT: Prostate-only Or whole-Pelvic Radiation Therapy

ProPSMA: Prostate-specific membrane antigen positron-emission tomography-computerized tomography in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy

PSA: prostate-specific antigen

PSMA: prostate-specific membrane antigen

RT: radiation therapy

RTOG: Radiation Therapy Oncology Group

SBRT: stereotactic body radiation therapy

STAMPEDE: Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy

Declarations

Author contributions

PT, KW, EY, and DL: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. ES, KJ, GO, AJT, PM, AD, and RK: Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

Kelvin Wong is a full-time employee of Astellas Pharma Canada, Inc. He was invited to assist with the literature review and drafting of this paper based on his scientific knowledge and experience in the therapeutic area. He does not have any conflicts to disclose aside from his employment with Astellas. No funding was received from Astellas for the drafting or publication of this paper. The assistance of Kelvin Wong in the drafting of this paper is solely in his individual capacity and is not a reflection of Astellas' endorsement or approval of the paper's content. Patricia Tai who is the Editorial Board Member and Guest Editor of *Exploration of Medicine* had no involvement in the decision-making or the review process of this manuscript. The remaining authors declare that they have no conflicts of interest.

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