Optimizing Care for Patients With Metastatic Castration-Resistant Prostate Cancer

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OVERVIEW

The therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has evolved substantially over the past decade, with androgen receptor pathway inhibitors, taxanes, poly (ADP-ribose) polymerase (PARP) inhibitors, radioisotopes, bone-protecting agents, and emerging targeted therapies improving survival for patients. At the same time, earlier treatment intensification in the hormone-sensitive setting has resulted in heterogeneous clinical presentations at the onset of castration resistance, adding complexity to treatment sequencing and clinical decision making. Here, we propose a pragmatic, patient-centered framework to help guide the management of mCRPC by integrating clinical features, molecular profiling, imaging findings, and supportive care considerations. Confirmation of castration resistance remains a critical first step and requires documented biochemical or radiographic progression in the setting of castrate testosterone levels. Treatment selection should consider prior systemic therapies, disease burden and tempo, symptom profile, comorbidities, and frailty. Molecular characterization, including evaluation for homologous recombination repair alterations and mismatch repair deficiency, is highly important for identifying candidates for PARP inhibitors or immune checkpoint blockade and other emerging biomarker-driven targeted strategies. Prostate-specific membrane antigen (PSMA)–targeted radioligand therapy has emerged as a key treatment. PSMA-positron emission tomography–based selection, incorporating assessment of uptake intensity, tumor heterogeneity, and total tumor volume, may help identify patients who are most likely to benefit from this treatment. Clinical factors such as liver metastases and limited prior response to androgen receptor–directed therapy have been associated with less favorable outcomes. Early on-treatment assessment using prostate-specific antigen response and PSMA-based imaging may support adaptive treatment strategies and earlier recognition of resistance. Given the high prevalence of bone metastases, bone-protecting agents should be considered to reduce skeletal-related events. Early palliative care (EPC) is now widely recognized as a concurrent, patient-centered intervention that improves quality of life, symptom burden, coping, and satisfaction across advanced cancers. Prostate cancer represents an especially compelling setting for EPC because of prolonged advanced disease courses, cumulative symptom burden, repeated treatment transitions, and persistent unmet supportive needs.

FIRST-LINE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: ONE SIZE DOES NOT FIT ALL

Over the past decade, the therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has expanded at an unprecedented pace.[1,2] Androgen receptor pathway inhibitors (ARPIs), taxanes, poly (ADP-ribose) polymerase (PARP) inhibitors, radioisotopes, bone-protecting agents, and emerging targeted agents have collectively transformed outcomes for many patients. Sipuleucel-T is another option. This complex cell therapy is rarely used and, only in the United States, most commonly in patients with early mCRPC.[3] Yet paradoxically, this therapeutic abundance has also exacerbated uncertainties in everyday clinical practice. These uncertainties are partially related to the use of some of these agents in the hormone-sensitive setting, thus creating new clinical situations in mCRPC. The challenge that oncologists are often facing worldwide is no longer whether effective treatments exist, but how to select, sequence, combine, and adapt them for each individual patient.

In this context, a pragmatic and patient-centered approach is needed. Rather than advocating for a rigid treatment algorithm, we propose here a clinically driven checklist designed to mirror real-world practice.

PRACTICAL APPLICATIONS

- The use of next-generation sequencing, performed on tumor tissue or circulating tumor DNA, should be encouraged whenever feasible, as it may increasingly inform biomarker-driven treatment strategies and future therapeutic development.
- The landscape is changing fast with [^{177}Lu]-PSMA moving earlier in the prostate cancer space. Ongoing trials are evaluating combination strategies as well as PSMA targeted alpha therapies.
- Early integration of palliative is now widely recognized as a patient-centered intervention that improves quality of life.

From Definition to Decision Making: A Checklist for mCRPC

Defining Castration Resistance: Beyond a Semantic Exercise

The first and most critical step in managing mCRPC is ensuring that the diagnosis itself is correct. Castration resistance should never be assumed without confirming adequate androgen deprivation. A serum testosterone level below 0.50 ng/mL (=50 ng/dL = 1.7 nmol/L) remains the accepted threshold. Once castrate levels are confirmed, progression must be clearly documented. This may occur biochemically, with a rising prostate-specific antigen (PSA) characterized by three consecutive increases. Alternatively, radiographic progression may be demonstrated by the appearance of two new bone lesions on a bone scan or progression of measurable soft tissue disease according to RECIST 1.1 criteria. This distinction is not trivial; it may shape therapeutic decisions, prognostic discussions, and eligibility for clinical trials. Progression criteria on next-generation imaging such as prostate-specific membrane antigen-positron emission tomography (PSMA-PET) are less well-established.[4]

Patients Come First: Age, Frailty, and Comorbidities

Similar to many other cancers, mCRPC is predominantly a disease of second half of life. Therefore, many patients have vulnerabilities that may inadequately be captured by the performance status alone. Chronologic age should not dictate treatment intensity, but biological age often does. Simple geriatric screening tools, such as the G8 score, can identify patients who may benefit from a more comprehensive geriatric assessment and tailored therapeutic strategies.[5,6]

Comorbidities are equally influential. Cardiovascular disease, metabolic syndrome, and renal impairment may all affect treatment tolerance and safety, particularly with ARPIs or taxanes. Just as importantly, polypharmacy is common, and drug-drug interactions may compromise both efficacy and toxicity profiles.[7] In this context, involving an oncology-trained pharmacist can be relevant, particularly in complex cases, to ensure prescription safety.

Importantly, beyond clinical and geriatric parameters, patients' preferences and goals of care represent a critical determinant of treatment choice. Shared decision making is essential in this setting, ensuring that therapeutic strategies align with what matters most to the patient, with an emphasis on doing more for the patient rather than to the patient.

Never Overlook the Skeleton

Bone metastases are the dominant site of metastatic spread in castration-resistant prostate cancer, affecting more than 80% of patients and contributing substantially to morbidity, impaired quality of life (QOL), and mortality. The complex interaction between prostate cancer cells and the bone microenvironment leads to both osteoblastic and osteolytic activity, resulting in skeletal-related events (SREs) such as pathologic fractures, spinal cord compression, and the need for bone surgery or radiation therapy. Bone-targeted agents such as bisphosphonates or RANK-ligand inhibitors (denosumab) significantly reduce the risk of SREs and should be considered in an early setting.[8-10] Both play a role in maintaining QOL, reducing pain, and preserving functional independence. Denosumab was shown to be superior to zoledronic acid in a large phase III trial.[8]

Effective management of skeletal health in mCRPC requires a multimodal approach that integrates baseline and follow-up bone mineral density assessment and routine calcium and vitamin D supplementation with appropriate monitoring to mitigate hypocalcemia. Evidence from meta-analyses suggests that calcium and vitamin D supplementation can reduce fracture risk by approximately 7%-20% in at-risk populations, supporting their systematic use.[11] Preventive measures should also include a baseline dental assessment and the maintenance of good oral hygiene throughout treatment to reduce the risk of osteonecrosis of the jaw, a well-known side effect of bone-protecting agents.

In addition to pharmacologic interventions, adapted physical activity plays a critical role in maintaining bone health, reducing risk of falling, and preserving functional status in men with mCRPC. Structured exercise programs have been shown to enhance bone mineral density, improve muscle strength, and reduce the incidence of falls and fractures in patients undergoing androgen deprivation therapy, which itself accelerates bone loss.[12]

Bone-targeted agents should be considered standard care for patients with mCRPC and bone metastases to reduce the risk of SREs.

One Disease Name, Many Clinical Scenarios

mCRPC Is Not a Single Clinical Entity

Prior treatments now vary widely as many patients enter the castration-resistant phase after intensified therapy in the hormone-sensitive setting, including triplet and doublet systemic regimens. Whether a patient has received androgen deprivation alone, combined androgen receptor inhibition, or combined androgen receptor inhibition plus docetaxel profoundly influences subsequent therapeutic choices. In addition, cabazitaxel, Lu-PSMA, and PARP inhibitors (for *BRCA* patients) have all shown improvements in overall survival in mCRPC patients with prior ARPI and docetaxel and therefore shall be regarded as standard options in patients with mCRPC post-triplet for hormone-sensitive prostate cancer.[13–15]

Similarly, clinical presentation matters. At one end of the spectrum is the frail older patient with indolent, minimally symptomatic disease, and at the other, the young, fit patient with rapidly progressive bone and, sometimes, visceral metastases. Applying identical treatment strategies to these fundamentally different situations is neither rational nor patient-centered.

Molecular Profiling: From Optional to Essential

Molecular characterization plays an increasingly important role in the management of mCRPC although it is not yet universally accessible in routine clinical practice. Next-generation sequencing (performed on tumor tissue or circulating tumor DNA) should be strongly encouraged whenever feasible. While actionable alterations are by far not present in every patient, their identification can help guide therapy and support personalized management.

Alterations in homologous recombination repair genes, particularly *BRCA1* and *BRCA2*, represent one of the most clinically impactful molecular subsets. PARP inhibitors have demonstrated meaningful benefit in this population.[15–19] and platinum-based chemotherapy remains an area of active investigation supported by biological and clinical data.[20]

Mismatch repair deficiency or microsatellite instability-high status, although rare, identifies patients who may benefit from immune checkpoint inhibition. Access to immunotherapy remains heterogeneous worldwide, but testing remains essential to identify eligible patients.[21]

Other alterations, including androgen receptor mutations or amplifications, are being actively explored, with multiple investigational agents targeting androgen biosynthesis or receptor signaling which are currently in development (ClinicalTrials.gov identifiers: NCT03436485, NCT06764485, NCT05067140).

Recognizing Aggressive Biology

Certain molecular and clinical features indicate a poor prognosis and require increased vigilance. Loss of *TP53*, *PTEN*, or *RB1* is frequently associated with aggressive tumor behavior, early visceral involvement (particularly liver metastases), and lower sensitivity to androgen receptor–directed therapies. In these cases, closer imaging surveillance and earlier consideration of taxanes may be warranted.

Taxanes remain a standard of care in the mCRPC setting. Docetaxel retains substantial activity post-ARPI, and cabazitaxel provides a valid option after docetaxel failure.[13]

In about 20% of cases, tumors may undergo neuroendocrine differentiation, which is typically characterized by rapid progression, low PSA levels, and visceral disease (often on top of bone metastases). Histologic confirmation should be sought whenever possible. Evidence guiding treatment is limited, and platinum-based regimens are commonly used despite the absence of phase III evidence.

Sequencing Therapies in mCRPC: Matching Disease Biology and Clinical Trajectory

Therapeutic sequencing after progression on an ARPI currently is a central challenge in the management of mCRPC. Beyond molecularly driven strategies, clinical practice increasingly converges toward two distinct therapeutic pathways after ARPI failure.

In patients who are fit and candidates for a taxane, accumulating evidence suggests that early use of docetaxel may confer a survival advantage when administered immediately after ARPI failure, compared with immediate Lu-PSMA and deferred chemotherapy strategies. This benefit appears to be most pronounced in carefully selected populations, typically characterized by preserved performance status, symptomatic disease, and a higher burden of aggressive features, including rapidly evolving bone metastases and/or visceral metastases.[22]

In patients with an indolent disease course, limited symptoms, and demonstrable PSMA expression, PSMA-targeted radioligand therapy represents an emerging alternative, with not only better radiographic progression-free survival but also better QOL outcomes.[22–24]

Selective Radiotherapy in the Era of Systemic Therapy for mCRPC ?

Radiotherapy continues to play a role in selected patients with mCRPC. Metastasis-directed radiotherapy may delay systemic treatment modification in cases of oligoprogression, and local treatment of the primary tumor may provide meaningful control. Although supported mainly by phase II data,[25,26] these approaches reflect a growing

recognition of spatial and temporal heterogeneity in advanced disease.

Conclusion

In an era of rapidly expanding therapeutic options, the management of mCRPC demands more than guideline adherence. It requires thoughtful integration of clinical judgment, molecular insight, patient vulnerability, and treatment history.

HOW TO BETTER PERSONALIZE TREATMENT WITH [^{177}Lu]Lu-PSMA RADIOLIGAND THERAPY

Aim

To understand how to best select patients for [^{177}Lu]-PSMA therapy including which criteria to use on PSMA-PET and other imaging. What patient and tumor characteristics best predict response. To understand in which line patients profit most from radioligand therapy and how to prevent side effects. To understand how many cycles should be given and how to decide on the optimal number of cycles for a specific patient (dose adaption). To understand how to best monitor patients on treatment (evaluating tumor response and progression).

Before Treatment

Identifying patients who will respond well to PSMA-radioligand therapies (RLT) is important in determining optimal sequencing choices to better personalize the therapeutic journey. With PSMA-RLT, this is best done through a combination of PSMA-PET parameters including both PSMA expression and tumor volume, diagnostic computed tomography (CT), or fluorodeoxyglucose (FDG)-PET to evaluate for metastatic sites that do not express PSMA, clinical features such as prior response to ARPI, the presence of hepatic metastases, and, potentially in the future, circulating tumor DNA (ctDNA) fraction.

PSMA-PET/CT to screen for [^{177}Lu]-PSMA suitability enables measuring both PSMA expression (both lesional and whole body) measured as standardized uptake value (SUV) and total tumor volume. To select patients, trials have used varying PSMA expression criteria. All phase III trials have used a liver-based threshold requiring PSMA expression above liver at a single site with no PSMA-negative soft tissue metastases on CT, an inclusive criterion developed to maximize the number of eligible patients with just a 13% screen failure rate in the VISION trial.[14,23] By contrast, the TheraP trial required an SUVmax (≥20) at one site and SUVmax ≥10 at all sites with no FDG-PET discordance, a more stringent approach that excluded 28% of patients.[27] This approach improved depth of PSA response in TheraP compared with VISION (66% *v* 46%), but not overall survival. At a clinical level, a PSMA-PET criterion that ensures relatively homogenous PSMA expression across all larger metastatic deposits is likely to select patients who will better respond to PSMA-targeted treatment, minimizing the number of men with primary treatment resistance. ENZA-p used middle ground criteria, SUVmax ≥15 at a single site and ≥10 at all larger sites of disease with no soft tissue mismatch on diagnostic CT (particularly in liver), a criterion now adopted in Australia for funded [^{177}Lu]-PSMA selection.[28]

Patient selection may be optimized with PSMA SUVmean, if clinically available. SUVmean gives the average PSMA expression within the total tumor volume and is reflective of

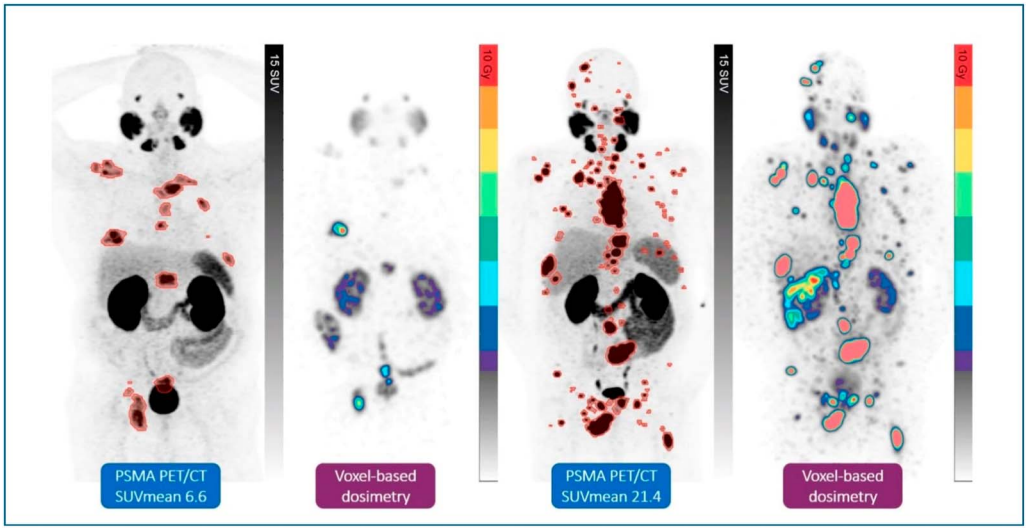

FIG 1. (A) A patient with low PSMA SUVmean in the total tumor burden, segmented in red. (B) On his cycle 1 [^{177}Lu]-PSMA SPECT/CT, there is low radiation-absorbed dose in most metastases (<2 Gy). By contrast, (C) another patient with high PSMA SUVmean has (D) very high radiation-absorbed dose at cycle 1, most 60-80 Gy. CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; SPECT, single photon emission computed tomography.

PSMA intensity and heterogeneity. High SUVmean ≥10 is positively associated with treatment response and radiation absorbed dose from [^{177}Lu]-PSMA and prognostic for overall survival (Fig 1).[29,30] In the TheraP trial, PSMA-SUVmean was predictive of PSA response to [^{177}Lu]-PSMA versus cabazitaxel for the top three quartiles (SUVmean ≥6.9). By contrast, patients with SUVmean <6.9 had a PSA 50% response rate of 29% (6 of 21) with [^{177}Lu]-PSMA versus 43% (12 of 28) with cabazitaxel. This may be a reasonable clinical cutoff below which to consider chemotherapy versus [^{177}Lu]-PSMA or [^{177}Lu]-PSMA in combination with other treatments, such as ARPI. As SUVmean is clinically unavailable for most clinicians, alternative visual methods that derive similar response information have been developed including the HIT score and the PSMA PET tumor-to-salivary glands ratio.[31,32] Automated quantitation of PET including SUVmean is also getting closer to being clinically available.[33-35]

Total tumor volume is another PET parameter that has demonstrated potential for patient selection. Higher baseline PSMA total tumor volume is predictive for overall survival, improving from 20 to 36 months with the addition of [^{177}Lu]-PSMA to enzalutamide in men with high-volume disease in the ENZAp trial (>230 mL).[36] PSMA total tumor volume also demonstrated prognostic benefit with [^{177}Lu]-PSMA monotherapy, with improved overall survival in low- versus high-volume disease.[37,38] Similarly, high pretreatment FDG PET-CT tumor volume (≥200 mL) was prognostic for OS after adjusting for conventional biomarkers in TheraP and may play a future role in identifying patients who would better benefit from combination strategies.[29]

Ultimately, although PSMA-PET screening can identify patients more likely to respond, it cannot identify all nonresponders to [^{177}Lu]-PSMA as this is also dependent on the radiation sensitivity of individual tumoral clones. For this reason, other clinical parameters and early on-treatment response evaluation with [^{177}Lu]-PSMA are clinically valuable.

Other important predictors of poor response include the presence of hepatic metastases and prior limited response to ARPI (<12 months).[37] Patients with liver metastases have a poorer prognosis with [^{177}Lu]-PSMA therapy, and careful evaluation of the diagnostic CT before commencing treatment to ensure that all hepatic lesions are PSMA-avid is important to ensure that patient benefit.[39] A nomogram that incorporates both clinical and imaging parameters has previously been published. ctDNA fraction, when clinically available, has potential as a predictor of treatment response with [^{177}Lu]-PSMA.[40] A baseline low ctDNA fraction (<2% or not detected) is associated with better overall survival in a number of trials.[41-43]

Identifying Patients at Risk of Adverse Events

Low glomerular filtration rate (GFR) is not a specific contraindication for [^{177}Lu]-PSMA therapy although care must be taken to ensure the that cause is not related to renal outflow obstruction before therapy.[44] While a median 20% reduction in GFR is known to occur at 2 years in patients receiving [^{177}Lu]-PSMA, impaired GFR at baseline does not make deterioration in GFR more likely and the treatment appears to be safe even in the presence of baseline renal dysfunction.[45,46]

Patients with baseline high-volume symptomatic disease are at higher risk of significant toxicities related to [^{177}Lu]-PSMA therapy compared with those with lower-volume disease or without baseline pain. The most prominent symptoms are marked fatigue, pain flare, and nausea around the time of treatment. All patients experiencing pain before [^{177}Lu]-PSMA therapy should have a discussion around pain flare and have a pain control plan before their first dose of treatment. Similarly, oral dexamethasone (4-8 mg once daily) with as-required ondansetron on days 1-3 in patients with high-volume disease on PSMA PET (>250 mL) or baseline pain significantly reduces the risk of fatigue, nausea, and pain, particularly at the first dose of treatment.

High-volume metastatic bone disease before [^{177}Lu]-PSMA therapy presents a significant risk of marrow compromise as [^{177}Lu]-PSMA will also affect a small region of marrow surrounding each tumor deposit.[47] Ensuring adequate PSMA expression in the majority of bone deposits and maximizing (not reducing) the first [^{177}Lu]-PSMA dose administered are important in this situation. Improving marrow function in these men requires significant treatment response at involved sites of marrow infiltration. High-volume low-PSMA expression bone involvement may be better treated with a PSMA-targeted alpha radionuclide or Radium-223, where adjacent marrow may be less compromised because of the shorter radionuclide pathlength.[48]

During Treatment

On-treatment biomarkers offer the potential to clinically personalize treatments based on response. The phase III trials of [^{177}Lu]-PSMA have all treated six-cycles, 6-weekly until radiographic progression without allowing treatment pauses or on-treatment biomarkers to evaluate for treatment response or progression.[14,23] ENZA-p evaluated the concept of adaptive dosing using an on-treatment PSMA-PET combined with PSA response. Those patients who had complete metabolic/biochemical responses on a 3-month PSMA-PET/PSA were given two doses rather than 4, continuing on enzalutamide alone.[28] The TheraP and EVOLUTION trials used a single photon emission computed tomography (SPECT)/CT and PSA response to identify marked responders who qualified a treatment pause, with retreatment commencing again at first confirmed PSA rise (ClinicalTrials.gov identifier: NCT05150236). [^{177}Lu]-PSMA SPECT/CT is a whole-body 3D image derived from the [^{177}Lu] emissions that can be undertaken between 4 and 72 hours after each treatment, generally taking around 20 minutes to acquire using a standard gamma camera. A SPECT/CT

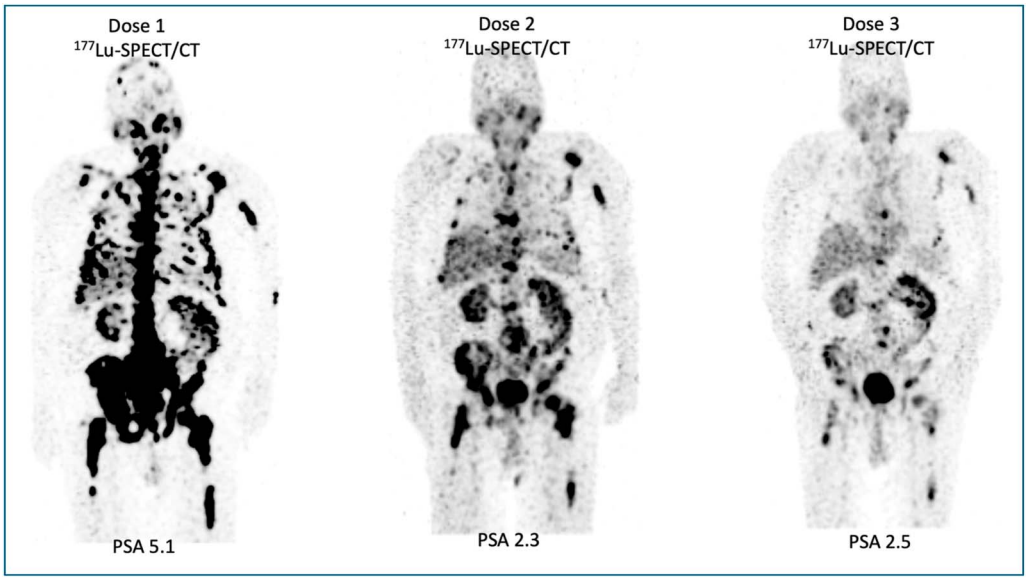

FIG 2. [^{177}Lu]-PSMA SPECT/CT is an additional tool in evaluating treatment response. This is a patient with high-volume metastatic disease in bone with PSA underexpression (PSA 5.1). Measuring PSA in this patient has clinical limitations. However, the SPECT/CT images help confirm that the patient has had a marked response to treatment at all sites of disease involvement despite no measurable soft tissue involvement and an unchanged bone scan. CT, computed tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SPECT, Single photon emission computed tomography.

undertaken after each therapy dose in conjunction with PSA response allows a dynamic assessment of response/progression that can help decide best ongoing patient management, with both PSA and PSMA response providing independent data (Fig 2).[49-52] Patients with increased PSMA tumor volume and/or new lesions on 177Lu-SPECT/CT at 6 weeks after commencing treatment have significantly shorter progression-free and overall survival than those patients with any reduction in PSMA tumor volume/no new lesions.[49] The 6-week (dose 2) time point SPECT/CT appears to be effective at identifying patients with primary treatment resistance who may benefit from treatment intensification, such as with PSMA-targeted alpha therapy or change to chemotherapy in those with new sites of PSMA-low-expression disease. Conversely, a marked PSMA (and PSA) response on interim PSMA SPECT or PET identifies patients who can safely pause treatment for up to 2 years before responding again at rechallenge. Clinical registries have reported that these patients have repeat PSA50% response rates of between 50% and 80% with [^{177}Lu]-PSMA rechallenge.[53,54] A number of trials are also evaluating dose intensification, using shorter interval induction dosing to deepen and prolong responses (ClinicalTrials.gov identifier: NCT06526299).

While prospective trials have evaluated up to six doses of [^{177}Lu]-PSMA, retrospective studies have reported ongoing treatment responses with a higher number of doses with no significant toxicities.[55] The Flex-MRT trial is evaluating up to 12 doses of [^{177}Lu]-PSMA given using an adaptive dosing schedule (ClinicalTrials.gov identifier: NCT06216249). Ultimately, however, a minority of patients require more than six doses, with early treatment failure before a significant issue with [^{177}Lu]-PSMA therapy, particularly when used in metastatic castration-resistant prostate cancer as a monotherapy.

The landscape is changing fast with [^{177}Lu]-PSMA moving earlier in the prostate cancer space because of the positive findings from the PSMAddition trial, which administered [^{177}Lu]-PSMA in combination with ARPI in metastatic hormone-sensitive prostate cancer (mHSPC).[56] Similarly, the ENZA-p trial found that [^{177}Lu]-PSMA added to first-line enzalutamide therapy in early mCRPC improved overall survival by over 8 months compared with enzalutamide alone.[57] Further trials are evaluating other combinations including cabazitaxel chemotherapy (ClinicalTrials.gov identifier: NCT05340474), PARP inhibitors (ClinicalTrials.gov identifier: NCT03874884), and immune modulators (ClinicalTrials.gov identifier: NCT05150236). Where to fit [^{177}Lu]-PSMA and PSMA-targeted alpha therapies in prostate cancer sequencing is under evaluation (ClinicalTrials.gov identifiers: NCT06855277, NCT06780670).

EARLY INTEGRATION OF PALLIATIVE CARE IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: EVIDENCE, RATIONALE, AND A PRACTICAL FRAMEWORK

Early palliative care (EPC) refers to specialist palliative care integrated alongside disease-directed oncology treatment early in the course of advanced cancer. EPC is typically delivered by an interdisciplinary team that focuses on four longitudinal domains: symptom management, coping and psychosocial support, communication and shared decision

making, and future planning including advance care planning (ACP). The team may consist of doctors, advance care providers, nurses, spiritual care providers, social workers, and other supportive care providers.

This model of early integration is consistent both the ASCO Clinical Practice Guideline Update and European guidelines, which recommend that patients with advanced solid tumors and hematologic malignancies receive early integrated specialist palliative care concurrent with active cancer therapy, based on patient needs such as symptom burden, quality-of-life concerns, or psychosocial distress rather than prognosis alone.[58,59]

Evidence of EPC Benefits

EPC improves outcomes that matter most to patients and caregivers while patients continue cancer-directed treatment. The Cochrane review of randomized trials found improved QOL with EPC and lower symptom intensity without consistent survival benefit.[60,61] Additional meta-analyses report better QOL, fewer symptoms, and improved mood.[62]

The landmark randomized trial in metastatic non–small cell lung cancer demonstrated that early outpatient palliative care significantly improved QOL and mood while reducing aggressive end-of-life care.[63] Several other landmark trials reinforce that benefit depends on the intervention structure and intensity. The ENABLE II trial demonstrated that a nurse-led palliative intervention improved QOL and mood.[64] ENABLE III further compared early versus delayed initiation and found improved one-year survival in the early group.[60] Studies of EPC in different cancers showed that QOL improvements differed by cancer type, suggesting that EPC may need tailoring to disease trajectory.[65]

Benefit of EPC in GU Cancers

GU-focused reviews describe low uptake of palliative and supportive care services despite substantial symptom burden and propose structured frameworks for earlier referral.[66] A national survey of individuals living with prostate cancer and their caregivers demonstrated significant unmet needs in communication, symptom management, and care coordination—domains directly targeted by EPC.[67]

Conceptual work further argues that prostate cancer's long disease trajectory and cumulative treatment-related morbidity make it especially amenable to early palliative involvement.[68]

More recent synthesis suggests that palliative and hospice care in prostate cancer is associated with improved QOL, fewer hospitalizations, and reduced high-intensity interventions near the end of life, yet referrals remain delayed.[69]

Taken together, EPC in GU oncology should be viewed as guideline-concordant supportive comanagement rather than a late-stage alternative to therapy.

How Should EPC Be Integrated?

A practical implementation model distinguishes primary palliative care, delivered by oncology clinicians, from secondary or tertiary specialist palliative care, supported by trigger-based workflows consistent with ASCO guidance.[58]

Primary Palliative Care (oncology-led)

Primary palliative care refers to core supportive skills that should occur during routine oncology visits:

- Symptom screening and first-line symptom management
- Serious illness communication
- Medication safety and supportive care planning
- Identification of caregiver needs

ASCO explicitly recognizes that oncology clinicians share responsibility with specialist teams for delivering palliative care across the cancer continuum.[58]

Embedding these skills into routine GU practice is critical given frequent patient contact with the oncology team and palliative care workforce limitations. Primary palliative care can be provided by any member of the primary oncology team, including physicians, advanced care providers, nurses, social workers, pharmacists, and financial counselors. When the primary team is unable to address symptoms and need additional expertise, a referral to a specialist palliative care team is warranted.

Secondary or Specialist Palliative Care

Specialist palliative care should be engaged when needs exceed routine oncology workflows, including

- Refractory or complex symptoms
- Significant psychological or existential distress
- Complex treatment decision making
- Recurrent hospitalizations or ICU consideration.

Trials demonstrating the greatest benefit typically used structured, longitudinal follow-up, underscoring that palliative care should function as comanagement rather than a one-time consultation.[70,71]

Trigger-Based Referral: A Prostate Cancer–Focused Referral Approach

Recent studies have shown trigger-based referral systems to standardize workflow to be better than individual clinician discretion in patient outcomes.[58] Potential triggers are listed below (Table 1). Depending on the expertise and comfort of the primary oncology team's ability to address the four domains of palliative care needs and availability of the

specialist palliative care team, each institution can establish one or more of the following triggers.

Triggers in Metastatic Castration-Resistant Prostate Cancer

As highlighted above, there are several possible triggers to consider referral for EPC. Disease-based triggers include a new diagnosis of metastatic castration-resistant prostate cancer (mCRPC). Patients developed mCRPC because they had failure of therapies for either mHSPC or nonmetastatic hormone-sensitive or castration-resistant prostate cancer (nmHSPC or nmCRPC). Regardless of how the patient developed mCRPC, the fact that cancer has progressed to mCRPC implies the change in disease status and it has implications for prognosis and therapy choices.

These patients might also have physical symptoms from their disease, such as pain from bone metastasis. The change in disease status and symptoms can be distressing to both patients and caregivers. Routine evaluation for psychosocial symptoms with tools such as patient health questionnaire-9 and National Comprehensive Cancer Network's Distress Thermometer can help identify patients who may benefit from primary or secondary EPC 17. Rarely, the diagnosis of mCRPC occurs when the patient presents to the hospital with severe symptoms of disease progression.

From an oncologic perspective, patients with mCRPC are offered palliative-intent interventions such as RLT, chemotherapies, ARPI, and novel therapies including bispecific antibodies and antibody-drug conjugates (ADC), presenting overwhelming choices with different side effect profiles. Management of side effects can be accomplished by the primary oncologic teams (medical oncology, radiation oncology, or nuclear medicine radiologist) depending on the interventions used. Depending on the therapy used, the symptoms can include dry mouth, neuropathy, hot flashes, fatigue, nausea, vomiting, and immune-mediated toxicities. Primary oncologic providers typically manage these symptoms although collaboration with secondary PC team can be helpful in cases where additional support is needed.

Additional Benefits of Integration of EPC in mCRPC

Scientific advances in finding better targets and treatments such as bispecific antibodies, ADC, radioligands, and immunotherapy will help advance cancer-specific outcomes. There is an opportunity to improve the same cancer-specific outcomes by improving supportive care by advancing science of symptom management and palliative care.

TABLE 1. Potential Triggers for Early Palliative Care Referral

Disease-based triggers
New diagnosis of metastatic prostate cancer, hormone-sensitive or castration-resistant
Progression to castration-resistant prostate cancer
Enrollment in early-phase clinical trials[1]
Symptom and functional triggers
Moderate-to-severe symptoms despite primary palliative care interventions
Escalating opioid requirements
Functional decline (eg, ECOG ≥2)
Psychosocial triggers
Reports of depression, anxiety, demoralization
Caregiver distress
Difficulty in coping with illness trajectory as coping-focused mechanisms likely contribute to improved outcomes[5]
Health system triggers
Emergency department visits
Unplanned hospitalizations
Complex discharge needs

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Integration of EPC has the potential to collaborate on advancing supportive care. Research has focused on symptoms such as fatigue, immune reactions, neurologic toxicities, and other system-based toxicities.

CONCLUSION

EPC is now widely recognized as a concurrent, patient-centered intervention that improves QOL, symptom burden, coping, and satisfaction across advanced cancers.[58,60,61,63]

Prostate cancer represents an especially compelling setting for EPC because of prolonged advanced disease courses, cumulative symptom burden, repeated treatment transitions, and persistent unmet supportive needs.[66,67]

For oncology teams, integrating EPC requires three core strategies:

1. Deliver primary palliative care at every visit.
2. Refer early to specialist palliative care for advanced disease, if such expertise exists and the primary team needs assistance
3. Use trigger-based workflows at major clinical transitions.

When systematically embedded into GU oncology practice, EPC can function as a practical quality standard that optimizes patient-centered care.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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