PSMA PET–Guided Secondary Radiotherapy: Leveraging Molecular Imaging for Biologically Informed Treatment

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The landscape of secondary radiotherapy (sRT) following radical prostatectomy has undergone a remarkable transformation over the past decade. Historically, the management of biochemically recurrent prostate cancer was guided by conventional imaging modalities with limited sensitivity at low prostate-specific antigen (PSA) levels, often relegating clinicians to empiric treatment decisions based on anatomic risk stratification alone. In 2020, the RADICALS, RAVES, and GETUG-AFU 16 trials established early secondary therapy as the preferred approach over adjuvant radiotherapy (RT) for many post-prostatectomy patients, demonstrating similar oncologic outcomes with reduced toxicity.[1]

These trials showed that early sRT spares approximately half of patients from irradiation while maintaining rates of disease control.[1] However, even in this contemporary era, the inability to visualize recurrent disease at these early PSA levels meant that treatment planning remained largely based on consensus contouring guidelines rather than individualized tumor localization. More recently, prostate-specific membrane antigen (PSMA) PET/CT has further improved our approach to sRT.

PSMA PET as a Superior Staging Tool

The evolution of molecular imaging for prostate cancer has progressed through several iterations, each offering incremental improvements in detection capabilities. The EMPIRE-1 trial provided compelling evidence that molecular imaging with ^{18}F-fluciclovine PET/CT improved 3-year event-free survival compared with conventional imaging alone (75.5% vs 63.0%; $P=.0028$) when used to guide postprostatectomy sRT.[2] This amino acid analog tracer represented a significant advancement over bone scans and conventional cross-sectional imaging, foreshadowing the superior performance of PSMA-targeted imaging.

PSMA PET/CT demonstrates remarkably high detection rates even at very low PSA levels. In one prospective study of patients undergoing initial staging, ^{68}Ga-PSMA-11 PET/CT identified disease in 49% of patients with a PSA level <1.0 ng/mL, with 19% having lesions outside the consensus radiation volumes.[3] In the biochemically recurrent setting, a multicenter Australian study demonstrated detection rates of 65%, with the most common extra-fossa sites involving bone (44%) and perirectal lymph nodes (31%).[4] This ability to identify oligometastatic disease at PSA levels at which conventional imaging remains blind has profound implications for treatment personalization.

PSMA-Based Risk Stratification and Treatment Personalization

In this issue of *JNCCN*, Nikitas et al[5] present 5-year outcomes from a single-center cohort of 113 patients who underwent PSMA PET/CT–guided sRT following radical prostatectomy. With a median follow-up of 59.4 months and median PSA level of 0.4 ng/mL at imaging, this represents one of the most mature datasets examining long-term outcomes of PSMA-guided RT.[5] The results demonstrate favorable oncologic control, with a 5-year progression-free survival (PFS) rate of 48.7%, freedom from distant progression of 72.4%, and overall survival rate of 97.1%.[5] Freedom from initiation of systemic therapy at 5 years was 82.7%.

In this cohort, PSMA PET/CT findings were strongly prognostic, with patients who had negative scans or fossa-confined disease achieving superior outcomes compared with those with extra-fossa disease. This stratification informs more nuanced treatment decisions. For patients with local recurrence only (termed TrN0M0 in the paper), the addition of whole-pelvis RT (WPRT) was associated with significantly improved PFS (adjusted hazard ratio [aHR], 0.12; $P=.035$), supporting consideration of elective nodal coverage even in the absence of radiographically evident nodal disease. Conversely, for patients with N1/M1 disease, the addition of androgen deprivation therapy (ADT) was independently associated with improved PFS (aHR, 0.37; $P=.02$).

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These findings supporting the role of PSMA-guided treatment broadly align with emerging data from other cohorts. A nationwide Danish study of 844 patients demonstrated that use of PSMA PET/CT before sRT was associated with improved 5-year overall survival (98.1% vs 93.8%; $P=.0486$) compared with patients who did not undergo PSMA imaging.[6] The multicenter Australian experience similarly demonstrated 3-year freedom from progression rates of 82% for patients with negative or fossa-confined findings compared with 45% for those with extra-fossa disease.[4]

The ORIOLE trial provided early proof of principle that PSMA-guided therapy improves outcomes in the oligometastatic setting. Patients randomized to stereotactic ablative RT (SABR) for oligometastatic prostate cancer had significantly improved PFS compared with observation, with benefits that may be most pronounced among patients who had consolidation of all PSMA-avid disease.[7] These findings underscore the therapeutic potential of comprehensively addressing all sites of PSMA-avid disease.

Open Questions and Future Directions

Despite these encouraging results, several critical questions remain. First, what is the optimal management for patients with PSMA-negative scans? Nikitas et al[5] found that 41% of patients had no visible disease on PSMA PET/CT, yet this cohort still achieved favorable outcomes with sRT. Whether prostate bed irradiation alone suffices for these patients, or whether elective nodal coverage provides additional benefit, remains uncertain.

Second, for patients with nodal oligorecurrence, is prostate bed treatment necessary? A recent Australian series examined 46 patients with PSMA PET–documented nodal-only relapses who received nodal RT with or without prostate bed irradiation. They found that 4-year biochemical failure-free survival was similar between groups (64% vs 67%); however, only 4% of patients treated with nodal RT alone experienced in-field prostate bed failures.[8] This raises the intriguing possibility that dose de-escalated treatment or omission of prostate bed irradiation might be safely considered in selected patients with isolated nodal disease, potentially reducing treatment-related toxicity; however, this hypothesis merits further evaluation. Furthermore, Nikitas et al[5] found that among patients with N1/M1 disease but no prostatic bed recurrence, those receiving prostate bed irradiation had significantly improved PFS (aHR, 0.25; $P=.005$), suggesting that occult prostatic bed disease may be present even when not visualized by PSMA PET/CT.

Third, how do we optimize systemic therapy integration? The benefit of ADT in patients with N1/M1 disease shown in the study by Nikitas et al[5] aligns with established paradigms from the GETUG-AFU 16 trial, which demonstrated that 6 months of ADT combined with sRT significantly improved 5-year PFS (80% vs 62%; $P<.0001$).[9] However, in the PSMA era, can we further personalize ADT use based on disease burden, location, MMAI (multi-modal AI), or genomic features? Could patients with limited-volume, PSMA-avid oligometastases be spared systemic therapy if complete consolidation is achieved? Data from post-RT recurrences suggest that early PSMA PET/CT (performed at PSA ≤2 ng/mL) identifies oligorecurrent disease amenable to salvage therapy in the majority of patients,[1] supporting an aggressive, metastasis-directed approach in selected cases.

Equity and Global Access Considerations

Although PSMA PET/CT represents a paradigm shift in prostate cancer management, access to this technology remains highly inequitable globally. Analysis of cancer system characteristics across 185 countries demonstrates that factors such as universal health coverage, gross domestic product (GDP) per capita, surgical workforce, and RT capacity are independently associated with improved cancer outcomes.[11] Advanced imaging technologies such as PSMA PET/CT are disproportionately available in high-income countries, potentially widening treatment disparities.[11] Furthermore, significant racial disparities in prostate cancer incidence and mortality persist even within well-resourced health systems.

As we celebrate the advances enabled by PSMA PET/CT, we must simultaneously work to ensure equitable access globally. This includes strategies to improve radiopharmaceutical production and distribution in low- and middle-income countries, regulatory harmonization to accelerate approvals, and consideration of alternative imaging modalities that may serve as bridges where PSMA PET/CT remains unavailable. The promise of precision medicine must not become another vector for health inequity.

Conclusions

The study in this issue by Nikitas et al[5] provides valuable real-world evidence that PSMA PET/CT–guided sRT produces favorable long-term outcomes, with nearly three-quarters of patients remaining free from distant metastasis at 5 years. These results underscore a fundamental evolution in how we approach biochemically recurrent prostate cancer, from anatomically based consensus guidelines to biologically informed, personalized treatment strategies. PSMA PET/CT enables unprecedented risk stratification, informs decisions about treatment intensification with WPRT or ADT, and identifies oligometastatic disease amenable to consolidative therapy. However, improved detection capabilities must ultimately translate into improved patient outcomes, not merely stage migration. The journey from molecular imaging to meaningful clinical benefit continues, guided by prospective trials currently underway (PSMA-SRT, PEACE-V STORM, ADOPT) and tempered by the imperative to ensure equitable global access. As we refine our approach to PSMA-guided therapy, we move ever closer to the promise of precision oncology, where every treatment decision is informed by the unique biology of each patient's disease.

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