Review

Neoadjuvant 177Lutetium-PSMA-617 Radioligand Therapy: A New Frontier in the Management of High-Risk Localized Prostate Cancer

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Neoadjuvant ^{177}Lutetium-PSMA-617 Radioligand Therapy: A New Frontier in the Management of High-Risk Localized Prostate Cancer

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Simple Summary

High-risk localized prostate cancer behaves more like an early systemic disease than a confined lesion, so local therapy alone often fails. Neoadjuvant lutetium-177 PSMA-617 radioligand therapy (RLT) offers a theranostic way to strike both the prostate and occult micrometastases before surgery. Early trials, including the LuTectomy study, show the drug is safe and delivers meaningful PSA drops and partial histologic responses, but a single cycle rarely clears the tumor completely. Ongoing studies now test multi-cycle regimens and combinations with checkpoint blockade or ADT to boost pathologic complete response. Key hurdles are selecting patients, defining surrogate end-points such as metastasis-free survival, and balancing cost, logistics, and long-term safety—especially if potent alpha emitters enter the clinic. If these challenges are met, neoadjuvant RLT could meaningfully raise cure rates for the most aggressive localized disease.

Abstract

Men with high-risk localized prostate cancer (PCa) often experience unfavorable long-term outcomes, highlighting the need for improved neoadjuvant strategies beyond the current standard of care. Radioligand therapy with ^{177}Lutetium-PSMA-617 (^{177}Lu-PSMA-617) has emerged as a promising method to eliminate occult micrometastases while enhancing immune-mediated clearance of the primary tumor. Initial trials have affirmed the treatment's feasibility and safety, yet they consistently report a lack of pathologic complete responses. This absence of profound initial tumor reduction necessitates further therapeutic advancements. The underlying rationale for future strategies is clear, as ^{177}Lu-PSMA-617 promotes immunogenic cell death, potentially sensitizing immunologically "cold" tumors to checkpoint inhibitors. However, caution is warranted. The synergy observed between these therapies in advanced, metastatic castration-resistant PCa arises from a distinctly different biological context, and similar outcomes cannot be assumed in treatment-naïve, localized disease without dedicated validation. Continued progress hinges on developing improved metrics for success and patient selection. Simple PSA reductions have shown minimal correlation with significant pathologic outcomes in this setting, underscoring the critical need for validated surrogate endpoints and predictive biomarkers. Ultimately, large-scale randomized trials are essential to determine whether this investigational approach impacts key clinical outcomes—namely, metastasis-free and overall survival. While the strategy is theoretically sound, its capacity to enhance cure rates for high-risk localized PCa remains an unverified proposition.

Keywords: high-risk localized prostate cancer; immunogenic cell death; Lutetium-177; neoadjuvant radioligand therapy; PSMA; radioimmunotherapy; tumor immune microenvironment

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1. Introduction

Prostate cancer (PCa) persists as the most prevalent non-dermatological malignancy among males and constitutes a significant factor in cancer-related mortality on a global scale [1]. In the year 2024, it is projected that approximately 299,010 novel cases will be identified in the United States, accompanied by an estimated 35,250 fatalities [1]. While the bulk of males get identified with localized disease that tend to be slow and treatable, a considerable fraction shows high-risk features that point to aggressive clinical patterns, metastatic developments, and ultimately, death related to the condition. In cases of high-risk localized PCa, standard localized therapies, while administered with the aim of curing, often do not meet the necessary standards for effective disease control [2].

This therapeutic limitation has engendered an acute and unmet clinical need for innovative strategies that can address the systemic characteristics of high-risk localized PCa from the initial stages. The elevated rates of disease recurrence following even optimally administered local therapies strongly imply that, in numerous instances, high-risk localized PCa is not merely a localized condition but rather an early systemic disease with latent micrometastases already present at the time of diagnosis [1]. This insight reframes the core therapeutic dilemma. The predicament we are dealing with is not fundamentally a shortage of local treatment tactics, like radical prostatectomy (RP) or radiation therapy (RT), but rather a limitation in a conceptual framework that believes the disease is confined to the prostate gland. The focus, therefore, transitions from exclusively enhancing local control to attaining early and effective systemic management [3].

The integration of systemic therapies into the neoadjuvant landscape, preceding the final local treatment, represents an optimistic framework aimed at improving long-term prognoses for this sensitive patient demographic [4]. In the realm of innovative systemic therapies, the 177Lutetium-PSMA-617 (177Lu-PSMA-617) radioligand therapy (RLT) focusing on the prostate-specific membrane antigen (PSMA) has surfaced as a notably captivating option [5]. This model employs a 'theranostic' framework, promoting the accurate administration of radiation focused on tumor cells found within the biological system. This review will investigate the landscape of high-risk localized PCa, elucidate the rationale for a neoadjuvant strategy, delineate the mechanism and evidence supporting 177Lu-PSMA-617 RLT, and scrutinize the emerging clinical data, immunomodulatory potential, and prospective hurdles associated with advancing this potent therapeutic modality into the curative-intent framework.

2. Defining the High-Risk Patient and the Limits of Standard of Care

2.1. A Heterogeneous Definition: Comparing International Guidelines

The contemporary method for managing PCa relies significantly on assessing risks, a tactical approach that influences the diagnosis, chosen therapies, and the advice for ongoing assistance [6]. Three essential global institutions—the National Comprehensive Cancer Network (NCCN) situated in the United States, the European Association of Urology (EAU), and the American Urological Association (AUA)—in conjunction with the American Society for Radiation Oncology (ASTRO) and the Society of Urologic Oncology (SUO)—supply protocols that are based on evidence for this method. Although these guidelines converge on a foundational framework that incorporates serum prostate-specific antigen (PSA) levels, Gleason score stratified by Grade Group, and clinical T-stage, their particular delineations of high-risk disease manifest subtle yet critical divergences, which are encapsulated in Table 1.

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Table 1. Comparison of International Guideline Definitions for High-Risk and Very High-Risk Localized Prostate Cancer.

Guideline	High-Risk Criteria	Very High-Risk Criteria	Key Features & Differences
NCCN (2025) [7]	One or more of the following: • Clinical stage cT3-cT4 • Grade Group 4 or 5 • PSA > 20 ng/mL	Designated as Very High-Risk. Two or more of the following: • cT3-cT4 • Grade Group 4-5 • PSA > 40 ng/mL	• Clearly defines separate "High-Risk" and "Very High-Risk" categories. • Uses a higher PSA threshold (40 ng/mL) for the Very High-Risk definition.
EAU (2025) [8]	Two or more of the following: • cT3-cT4 • Gleason Score 8-10 (GG 4-5) • PSA ≥ 40 ng/mL	Designated as Very High-Risk. • Node-positive (N1) disease • Or meeting the high-risk criteria above (if node-negative)	• The definition of "High-Risk" is much stricter than NCCN's, requiring 2 factors and a higher PSA threshold. • Explicitly includes N1 disease in the Very High-Risk category.
AUA/ASTRO/SUO (2022) [9]	One or more of the following: • cT3a • Grade Group 4-5 • PSA > 20 ng/mL	No separate "Very High-Risk" category. Instead, these are classified as "Locally Advanced Disease": • cT3b-T4 (seminal vesicle invasion or beyond) • Presence of multiple high-risk features • Pelvic node positivity	• Maintains a three-tier risk system and does not use the "Very High-Risk" terminology. • The High-Risk T-stage definition is more specific (cT3a). • The most advanced cases are managed as "Locally Advanced," emphasizing a multimodal approach.

Abbreviations: ASTRO, American Society for Radiation Oncology; AUA, American Urological Association; cT, Clinical T-stage; EAU, European Association of Urology; GG, Grade Group; N1, Node-positive; NCCN, National Comprehensive Cancer Network; PSA, Prostate-Specific Antigen; SUO, Society of Urologic Oncology.

The 2025 NCCN guidelines [7] have been updated to differentiate advanced localized disease into two notable segments: high-risk and very high-risk. A disease is labeled high-risk when it has one or more of the following features: a clinical stage of cT3-cT4, Grade Group 4 or 5, or a PSA level that is above 20 ng/mL. The NCCN further designates a very high-risk subgroup for patients with at least two of the following: a clinical stage of cT3-cT4, Grade Group 4 or 5, or a PSA greater than 40

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ng/mL. This granular stratification acknowledges the notably poor prognosis allied with particularly advanced local tumors or a confluence of detrimental clinical attributes.

The 2025 EAU guidelines [8] define high-risk localized PCa as having at least two of the following: cT3-4, Gleason Score 8-10, or PSA ≥40 ng/mL. Very high-risk PCa includes node-positive disease or, if node-negative, meeting the high-risk criteria mentioned above. The 2025 AUA/ASTRO/SUO guideline (last updated 2022 and still current in 2025) [9] continues to use a three tier risk system and designates localized prostate cancer as high risk when any one of the following is present: clinical stage cT3a, Grade Group 4 or 5 (Gleason 8–10), or a PSA level > 20 ng/mL. Unlike the NCCN, it does not create a separate "very high risk" category; tumors with seminal vesicle invasion (cT3b), adjacent organ involvement (cT4), multiple high risk features, or pelvic node positivity are classified as locally advanced disease and managed with intensified multimodality treatment rather than being labeled very high risk localized cancer.

The nuanced distinctions among these preeminent guidelines, particularly the explicit very high-risk classification posited by the NCCN, illuminate an aspect of clinical ambiguity. This absence of a singular, universally standardized definition may obfuscate the interpretation and comparison of clinical trial outcomes and could engender discrepancies in patient management across disparate healthcare systems. Also, it reveals a pivotal concern: clinical assessments on their own could struggle to convey the extensive biological diversity that exists in aggressive PCa. This incongruity underscores the pressing necessity for more sophisticated prognostic instruments, such as molecular biomarkers or the pathological response to neoadjuvant therapy, to more accurately identify patients necessitating treatment intensification [10].

2.2. The Sobering Reality of Recurrence and Mortality

For men diagnosed with high-risk localized PCa, the standard of care involves definitive local therapy, typically RP with extended pelvic lymph node dissection or external beam radiotherapy (EBRT) combined with long-term androgen deprivation therapy (ADT) [9]. While these treatments can be curative for some, a substantial proportion of patients experience disease recurrence, highlighting the limitations of a purely local approach for a disease that is often systemic at presentation.

The statistics on treatment failure are sobering. Across various studies, between 27% and 53% of all patients undergoing RP or RT will eventually develop a rising PSA, a condition known as biochemical recurrence (BCR) [9]. For patients with the most adverse disease features, the risk of recurrence and subsequent metastasis can exceed 50% [11]. This high rate of failure strongly suggests that at the time of initial diagnosis and treatment, occult micrometastatic disease has already spread beyond the prostate and pelvic region, rendering local therapy alone insufficient for cure. This leads to significant long-term mortality. Even with aggressive local treatment, the 10-year prostate cancer-specific mortality (PCSM) for men in the D'Amico high-risk group treated with RP is approximately 7.4% [8]. Other large series report 10-year PCSM rates for high-grade disease (Gleason score 8-10) ranging from 7% to as high as 15% after surgery [12]. For patients with clinical T3 disease, 10-year cancer-specific survival is approximately 85%, meaning 15% of these men will have died from their cancer within a decade of treatment [13].

2.3. The Rationale for a Neoadjuvant Approach

The neoadjuvant strategy, which involves administering systemic therapy before definitive local treatment, is a well-established paradigm in other solid tumors, such as breast, esophageal, and rectal cancers [14]. Its application in high-risk localized PCa is based on several compelling theoretical advantages. The primary goal is the eradication of micrometastatic disease. By delivering a potent systemic agent before surgery or radiation, there is an opportunity to eliminate the disseminated tumor cells that are responsible for future relapse and mortality. This approach addresses the fundamental limitation of local-only therapy.

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Second, the neoadjuvant setting provides a unique "window of opportunity" for an in vivo assessment of treatment sensitivity. This concept is perhaps best illustrated by the experience in breast cancer, where the response of the primary tumor to neoadjuvant chemotherapy offers a powerful real-time biomarker of therapeutic efficacy [15]. A profound pathologic response, particularly a pathologic complete response (pCR) defined as the absence of any residual invasive tumor in the surgical specimen, is a strong surrogate for improved long-term survival [16]. The ability to observe this response transforms the primary tumor from a liability to be removed into a "living laboratory" for assessing drug efficacy. A poor response could identify patients at very high risk who may benefit from immediate adjuvant therapy or enrollment in clinical trials of novel agents, while a strong response could justify de-escalation of further treatment. This real-time biological feedback is a powerful tool for personalizing therapy and accelerating drug development, a principle that has been adopted by regulatory bodies like the U.S. Food and Drug Administration for expediting drug approvals in breast cancer [17].

Third, neoadjuvant therapy can induce tumor downstaging. By shrinking the primary tumor and treating locoregional lymph node involvement, the therapy may increase the probability of achieving negative surgical margins—a key predictor of recurrence-free survival (RFS)—and potentially facilitate nerve-sparing techniques, thereby improving functional outcomes [18].

Finally, this approach provides an invaluable platform for translational research. Analysis of pre-treatment biopsy tissue and post-treatment surgical tissue allows investigators to study the biological effects of a novel therapy on the tumor and its microenvironment, accelerating the discovery of predictive biomarkers and elucidating mechanisms of response and resistance. It is within this framework of addressing micrometastatic disease and gaining crucial biological insights that neoadjuvant 177Lu-PSMA-617 RLT is being explored as a transformative strategy for high-risk localized PCa [19,20].

Figure 1 provides a clear visual summary contrasting the standard treatment pathway with the proposed neoadjuvant RLT strategy, illustrating the latter's aim to systemically target both the primary tumor and occult micrometastases prior to definitive local therapy.

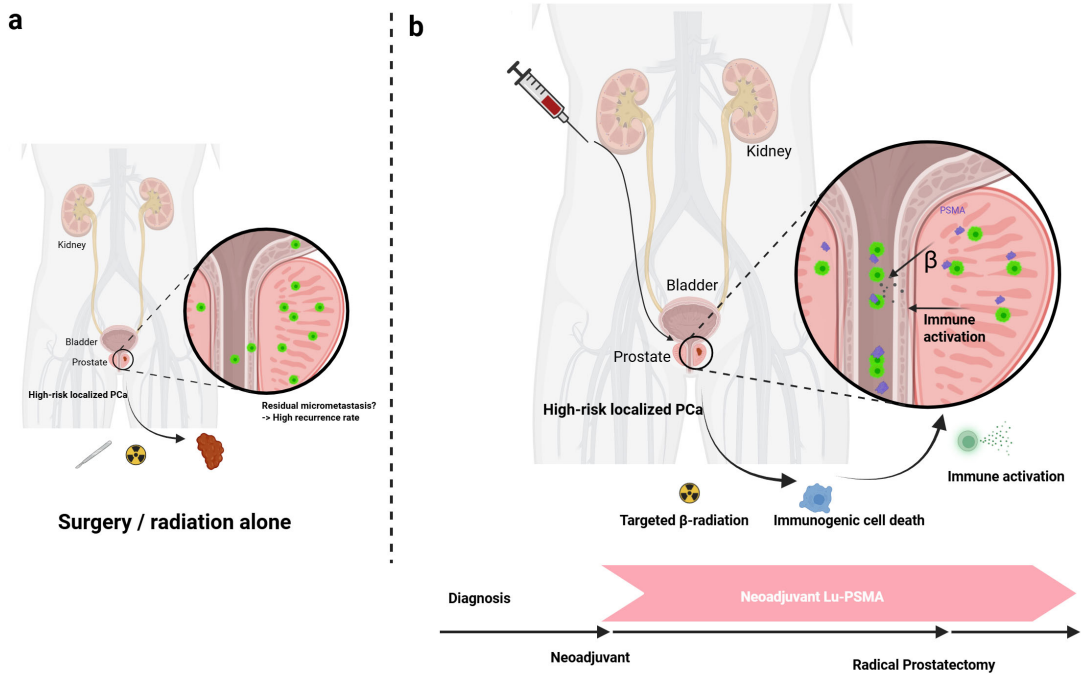

Figure 1. Comparative schematic of treatment strategies for high-risk localized prostate cancer.
(a) Standard radical prostatectomy or radiation therapy alone frequently leaves occult micrometastases, leading to high biochemical-recurrence rates. (b) In the neoadjuvant paradigm, intravenous ^{177}Lu-PSMA-617 radioligand

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selectively targets PSMA-expressing tumor foci in the prostate and potential micrometastatic deposits. β-particle emission induces direct DNA damage and cross-fire effects, debulking disease before surgery while initiating immunogenic cell death that may prime systemic anti-tumor immunity. Therapy is administered during the interval between diagnosis and planned radical prostatectomy. (Figure created with BioRender.com.).

3. The Theranostic Foundation: PSMA-Targeted Radioligand Therapy

The advent of PSMA-targeted RLT signifies a substantial progression in the therapeutic management of PCa [21]. This technique hinges on the 'theranostic' concept—integrating both therapeutic and diagnostic processes—using one specific molecular target for imaging and treatments, thus allowing for a uniquely customized application of radionuclide therapy. The success of 177Lu-PSMA-617 in the most advanced stages of the disease has provided a robust foundation for its investigation in earlier, curative-intent settings.

3.1. Mechanism of Action of 177Lu-PSMA-617

The therapeutic effectiveness of 177Lu-PSMA-617 is contingent upon the intricate interaction of its three fundamental components: the target, the ligand, and the radionuclide [22]. The target, PSMA, is a transmembrane glycoprotein that is found to be overproduced by nearly 1000 times on the surface of PCa cells when compared to benign prostate tissue [23]. Notably, the expression of PSMA tends to escalate with the progression of the disease, attaining particularly high levels in poorly differentiated, metastatic, and castration-resistant tumors, thereby rendering it an optimal target for intervention in aggressive disease states.

The ligand known as PSMA-617 is a uniquely crafted small molecule designed to show remarkable affinity and precision towards the extracellular enzymatic site of the PSMA protein. Once the PSMA-ligand complex connects, the cancer cell swiftly internalizes it, thus isolating the corresponding radionuclide inside. The agent 177Lu serves therapeutically, noted for its radioisotopic nature and the decay process that includes beta particle (β-particle) emission [24]. The β-particles that are released, known as electrons, indicate an average distance of 0.67 mm, with a peak travel distance nearly hitting 2 mm in soft tissues [25]. When these pieces journey through organic entities, they produce energy, damaging the cellular arrangement, particularly influencing DNA. The 177Lu radiation mainly causes single-strand DNA breaks, which could arrest the cell cycle and eventually lead to apoptosis if they are sufficiently numerous or left unrepaired [26]. The millimeter-scale path length of these β-particles engenders a beneficial "cross-fire" effect, whereby radiation emanating from a targeted cell can also compromise adjacent tumor cells that may exhibit lower or absent PSMA expression, thereby aiding in the mitigation of tumor heterogeneity.

This therapeutic agent is one half of a theranostic pair. For patient selection, the diagnostic agent PSMA 11 is marked radioactively with Gallium 68 (68Ga), creating 68Ga PSMA 11. Subsequent to intravenous administration, PET/CT imaging corroborates adequate PSMA expression in the lesions of the patient, suggesting a propensity for these lesions to uptake the therapeutic radioligand 177Lu-PSMA-617. This imaging-centered selection approach guarantees that treatment is exclusively provided to patients most likely to reap therapeutic rewards [27].

3.2. Pivotal Evidence from the Metastatic Setting

The journey of 177Lu-PSMA-617 into clinical practice was solidified by two landmark clinical trials that established its efficacy in the most advanced and difficult-to-treat setting: metastatic castration-resistant prostate cancer (mCRPC) that has progressed after both novel hormonal agents and taxane-based chemotherapy [28]. These studies provide a high level of evidence for the efficacy of 177Lu-PSMA-617 in this patient population.

The VISION trial (NCT03511664) was a global, randomized, phase 3 study that enrolled 831 men with PSMA-positive mCRPC [29]. Patients were randomized 2:1 to receive 177Lu-PSMA-617 plus standard of care or standard of care alone. The results were practice-changing. The addition of 177Lu-

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PSMA-617 led to a significant improvement in the trial's two primary endpoints. Radiographic progression-free survival (rPFS) was more than doubled, with a median of 8.7 months in the RLT arm compared to 3.4 months in the control arm, corresponding to a hazard ratio (HR) of 0.40 (95% CI, 0.29–0.57; p<0.001). More importantly, 177Lu-PSMA-617 conferred a significant overall survival (OS) benefit, extending the median OS from 11.3 months to 15.3 months (HR 0.62; 95% CI, 0.52–0.74; p<0.001).

The TheraP trial (NCT03392428), a randomized phase 2 study conducted in Australia, provided further compelling evidence [30]. This trial compared 177Lu-PSMA-617 directly against an active comparator, the chemotherapy agent cabazitaxel, in men with mCRPC who had progressed after docetaxel. Patients were rigorously selected using both PSMA-PET and FDG-PET to ensure high PSMA expression and exclude tumors with FDG-avid but PSMA-negative disease. The trial met its primary endpoint, demonstrating a significantly higher PSA response rate (a decline of ⩾50%) for 177Lu-PSMA-617 compared to cabazitaxel (66% vs. 37%). The RLT also resulted in a longer PFS (HR 0.63; 95% CI, 0.46–0.86). With longer follow-up, the OS was similar between the two arms. This result was heavily confounded by the high rate of patients in the cabazitaxel arm who crossed over to receive 177Lu-PSMA-617 upon progression, complicating the interpretation of the survival endpoint but not diminishing the clear evidence of superior activity and lower toxicity for the radioligand therapy [30].

The robust and consistent efficacy demonstrated in these trials, conducted in a patient population with very limited options and poor prognosis, provided unequivocal proof of the agent's potent anti-tumor activity. This success in the end-stage, palliative setting serves as the primary justification for investigating its use in earlier disease states. The logical hypothesis is that if 177Lu-PSMA-617 is effective against highly resistant, widespread disease, it may be even more effective, and potentially curative, when applied to the lower-volume, less-treated micrometastatic disease characteristic of the high-risk localized PCa setting [31,32].

3.3. The Radiobiological Imperative: Beta- versus Alpha-Emitters

The therapeutic effect of any RLT is dictated by the physical properties of the radionuclide it carries [33]. Understanding these properties is crucial for appreciating the current state of the field and its future direction, which increasingly involves the exploration of different types of radiation emitters. The two main classes of particles used in RLT are β-particles and α-particles, which have fundamentally different radiobiological characteristics, as detailed in Table 2.

Table 2. Radiobiological Properties of Clinically Relevant Radionuclides.

Radionuclide	Particle Emitted	Half-life	Max Energy (MeV)	Max Range in Tissue	Typical LET (keV/μm)
^{177}Lu [43,44]	Beta (β)	6.7 days	0.497	~2 mm	~0.2
^{90}Y [45]	Beta (β)	2.7 days	2.3	~11 mm	~0.2
^{223}Ra [46]	Alpha (α)	11.4 days	5.0-7.5	40-100 μm	~80
^{225}Ac [47,48]	Alpha (α)	9.9 days	5.0-8.4	40-100 μm	~100

Abbreviations: ^{177}Lu, Lutetium-177; ^{223}Ra, Radium-223; ^{225}Ac, Actinium-225; ^{90}Y, Yttrium-90; keV, kilo-electron volt; LET, Linear Energy Transfer; MeV, Mega-electron Volt; μm, micrometer.

Beta-emitters, such as 177Lu, are electrons or positrons. They are characterized by a relatively low Linear Energy Transfer (LET), which is a measure of the energy deposited per unit of distance traveled through tissue. For β-particles, the LET is approximately 0.2 keV/μm [34]. Because of this

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low energy deposition density, hundreds or even thousands of β-particle tracks, or "hits," are required to pass through a cell's nucleus to induce lethal damage. However, their longer path length in tissue (up to several millimeters for some beta emitters) provides the valuable cross-fire effect, allowing them to treat larger tumors and overcome some degree of target antigen heterogeneity [35].

Alpha-emitters, such as Actinium-225 (225Ac)andRadium−223(223Ra), are helium nuclei (two protons and two neutrons). They are vastly different from β-particles. They possess a very high LET, around 100 keV/μm, which is approximately 500 times greater than that of β-particles [36]. This dense ionization track is incredibly damaging to biological molecules. An alpha particle (α-particle) can cause complex, irreparable double-strand DNA breaks, which are highly cytotoxic [37]. Consequently, as few as one to ten α-particle traversals through a cell nucleus can be sufficient to kill the cell [38]. This high potency is coupled with an extremely short range in tissue—typically less than 100 μm, or the span of just a few cell diameters [39]. This short range minimizes damage to nearby healthy tissues but also eliminates any significant cross-fire effect.

This distinction creates a strategic trade-off in the design of radiopharmaceuticals. There is no single "best" radionuclide; rather, the choice depends on the clinical objective [40]. For the neoadjuvant goal of debulking a macroscopic primary tumor, which is likely to be heterogeneous in its PSMA expression, the longer range and cross-fire effect of a beta-emitter like 177Lu are advantageous [41]. However, for the goal of eradicating disseminated single tumor cells or microscopic clusters of cells—the definition of micrometastatic disease or minimal residual disease (MRD)—the extreme potency and short range of an alpha-emitter may be theoretically superior, delivering a lethal dose to isolated targets while maximally sparing surrounding normal tissue [42]. This understanding frames the evolution of RLT from a single-agent approach to a more sophisticated, tailored strategy where the choice of radionuclide could be matched to the volume of disease and the specific therapeutic intent.

4. Emerging Evidence for Neoadjuvant ^{177}Lu-PSMA Radioligand Therapy

The transition of 177Lu-PSMA RLT from the palliative metastatic setting to the curative-intent neoadjuvant setting is a recent but rapidly advancing field [49]. While large-scale phase 3 data are not yet available, a foundation of preclinical work and a series of pioneering early-phase clinical trials are beginning to provide the first insights into the safety, feasibility, and potential efficacy of this approach.

4.1. Preclinical Rationale and Early Human Experience

The foundational rationale for the application of 177Lu-PSMA agents in the treatment of prostate cancer was predicated on extensive preclinical investigations. In controlled studies employing cellular models that express PSMA, we confirmed the significant binding strength of various PSMA-targeting compounds. Subsequent research utilizing murine xenograft models of prostate cancer revealed a specific and substantial accumulation of radiolabeled PSMA ligands within tumors, resulting in significant, dose-dependent inhibition of tumor growth and the induction of DNA damage [50]. These assessments highlighted the key evidence needed to validate the delivery system for PSMA-targeted radionuclides. The first human applications of 177Lu-PSMA radioligand therapy were initiated through compassionate use efforts, primarily in Germany and Australia [5]. Although these preliminary experiences were not performed under the stringent protocols of a formal clinical trial, they yielded critical initial data indicating that the therapy was generally well-tolerated and capable of eliciting significant PSA responses and tumor regression in patients who had undergone extensive prior treatment. This empirical evidence from real-world scenarios was pivotal in generating momentum and providing the safety justification necessary for the initiation of prospective clinical trials, which ultimately culminated in the landmark VISION and TheraP studies.

4.2. Initial Clinical Trial Data: The LuTectomy Study

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The current landscape of neoadjuvant RLT is defined by a small number of innovative, investigator-initiated trials. The LuTectomy trial (NCT04430192) is a single-arm, phase 1/2 study conducted in Australia, designed as a first-in-human evaluation of neoadjuvant 177Lu-PSMA-617 [51]. The trial enrolled 20 men with high-risk localized PCa or locoregionally advanced PCa who were scheduled for RP and pelvic lymph node dissection. A key inclusion criterion was high PSMA avidity on a screening 68Ga-PSMA PET/CT scan. Participants were administered a solitary intravenous infusion of roughly 5 GBq of 177Lu-PSMA-617 six weeks in advance of their scheduled surgical intervention .

The first results, announced at the 2023 European Association of Urology yearly meeting, have delivered the pioneering prospective information concerning this method [52]. About safety, the treatment intervention was found to reflect a notable degree of tolerability. The characteristics of negative effects were in line with those noted in the metastatic setting, featuring mild xerostomia, temporary nausea, and fatigue as the chief toxicities. The surgeons affirmed that the RP performed afterward was both safe and uncomplicated, reporting no unforeseen intraoperative difficulties or escalated complications tied to the earlier RT. This represents a pivotal discovery, as it confirms the essential viability of the neoadjuvant RLT in conjunction with surgical intervention.

The primary endpoint of dosimetry confirmed that the therapy delivers a high and targeted radiation dose to the sites of disease. The median absorbed dose to the prostate was 19.6 Gy, and even higher to involved pelvic lymph nodes, at 37.9 Gy. While these doses are substantial, they are lower than the curative doses delivered with external beam radiation therapy (typically >70 Gy), and there was significant variability in dose delivery among patients.

The preliminary efficacy data were encouraging. The single cycle of RLT induced a median PSA decline of 49%, with 45% of patients achieving a PSA50 response (a decline of ≥50%). On post-treatment PSMA PET scans, 55% of patients had a partial response, defined as a decline in SUVmax of >30%, while 40% had stable disease. At a median follow-up of nearly 14 months, the biochemical RFS rate was 80%.

However, it was the most pivotal findings that arose from examining the prostatectomy specimens. A significant 80% of the subjects exhibited indications of a partial histologic response, which included aspects like stromal fibrosis, diminished tumor cell density, and cytoplasmic vacuolation, yet not a single patient in the trial accomplished a pathologic complete response (pCR). One individual (5%) was identified as possessing only MRD. This outcome, while indicating a distinct biological activity, holds considerable significance. It strongly implies that a solitary cycle of 177Lu-PSMA-617 monotherapy is inadequate for the complete eradication of macroscopic, high-risk PCa localized within the prostate. This 'negative' result is not indicative of a trial failure but is instead a valuable, hypothesis-generating insight. It delineates the lower threshold of efficacy for this therapeutic approach and offers a compelling rationale for the development of strategies designed to enhance the anti-tumor effect, such as the utilization of multiple RLT cycles, dose escalation, or integrative treatment modalities [51,53].

4.3. The Next Frontier in Trial Design: An Overview of Ongoing Studies

The findings from LuTectomy have directly informed the design of the next wave of clinical trials, which seek to build upon its initial observations. These studies, summarized in Table 3, represent the logical evolution of the research agenda in this space.

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Table 3. Summary of Key Ongoing Trials of Neoadjuvant PSMA-RLT.

Trial Name (Identifier)	Phase	Patient Population	Intervention(s)	Primary Endpoint(s)	Key Secondary Endpoints
LuTectomy (NCT04430192) [51]	I/II	High-risk localized/locoregional PCa (n=20)	Single cycle of ^{177}Lu-PSMA-617 prior to RP	Absorbed radiation dose (dosimetry)	Safety, surgical feasibility, PSA response, imaging response, pathological response
NEPI (EudraCT 2021-004894-30) [54]	I/II	Very high-risk localized PCa (n=46)	ADT + 2 cycles ^{177}Lu-PSMA-617 +/- 4 cycles ipilimumab prior to RP	Feasibility of RP, pCR	Safety, DFS
PSMA-DC [55]	III	Oligometastatic (≤5 lesions) recurrence post-local therapy (n=~450)	SBRT to all lesions, then ^{177}Lu-PSMA-617 vs. Observation	MFS	Time to next hormonal therapy, OS, safety

Abbreviations: ADT, Androgen Deprivation Therapy; DFS, Disease-Free Survival; MFS, Metastasis-Free Survival; OS, Overall Survival; PCa, Prostate Cancer; pCR, pathologic Complete Response; PSA, Prostate-Specific Antigen; PSMA, Prostate-Specific Membrane Antigen; RP, Radical Prostatectomy; SBRT, Stereotactic Body Radiotherapy.

The NEPI trial (EudraCT 2021-004894-30) is a randomized phase 1/2 study being conducted in Germany, targeting patients with very high-risk PCa [54]. This trial takes the next logical step by evaluating a combination therapy strategy. It is designed as a direct response to the LuTectomy finding that monotherapy is insufficient for pCR. Patients are randomized to receive 12 weeks of neoadjuvant therapy consisting of ADT plus two cycles of 177Lu-PSMA-617, either with or without the addition of ipilimumab, an immune checkpoint inhibitor (ICI) that blocks CTLA-4. The co-primary endpoints are the feasibility of performing RP after this intensive neoadjuvant regimen and, critically, the rate of pCR.

While not a neoadjuvant trial in the strictest sense, the PSMA-DC trial is also highly relevant as it represents a move of RLT into an earlier, potentially curative disease space [55]. This international phase 3 trial is evaluating 177Lu-PSMA-617 versus observation in patients who have developed oligometastatic recurrence after initial definitive local therapy. The primary endpoint is metastasis-free survival (MFS). This study will provide valuable data on the ability of RLT to control low-volume metastatic disease and delay the need for systemic hormonal therapy, offering insights that are applicable to the goal of eradicating micrometastases in the neoadjuvant setting.

5. The Immunomodulatory Potential of Neoadjuvant Radioligand Therapy

Beyond direct cytotoxicity, RLT is shown to influence the tumor microenvironment and elicit systemic immune responses. This "in situ vaccine" effect suggests that targeted tumor cell destruction can transform non-responsive tumors into ones that the immune system actively targets. This effect that modulates immunity encourages the merging of RLT alongside immunotherapy [56].

5.1. Inducing an In Situ Vaccine Effect

Radiation, including radionuclide delivery, induces immunogenic cell death (ICD), which activates the immune response [57]. Unlike regular apoptosis, ICD signals the immune system regarding dying tumor cells. Notable aspects of ICD involve the emergence of Damage-Associated Molecular Patterns (DAMPs). Cardinal DAMPs in ICD involve calreticulin (CRT) translocation as an

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"eat me" signal for phagocytosis by dendritic cells (DCs) [58]. In addition, dying cells produce ATP, acting as a signal to draw DCs towards the tumor region [59]. Ultimately, the release of HMGB1 encourages the maturation process of DCs and the showcasing of tumor antigens to T-cells.

Dendritic cell activation within the tumor area can profoundly impact the local microenvironment and promote a widespread anti-tumor T-cell response. Mature DCs engage with naive T-cells in the lymph nodes by presenting tumor-associated antigens, thus priming cytotoxic CD8+ T-cells that are specific to the tumor. Activated T-cells can then journey back to the primary tumor and remote metastases to eliminate any lingering cancer cells. The concept of an in situ vaccine, where the treated tumor provides antigens for vaccination, is a primary objective in combining radiation with immunotherapy [56].

Figure 2 illustrates the detailed mechanistic cascade initiated by RLT, showing how targeted tumor destruction leads to immunogenic cell death, antigen presentation by dendritic cells, and the subsequent activation and trafficking of cytotoxic T cells to enact a systemic anti-tumor response.

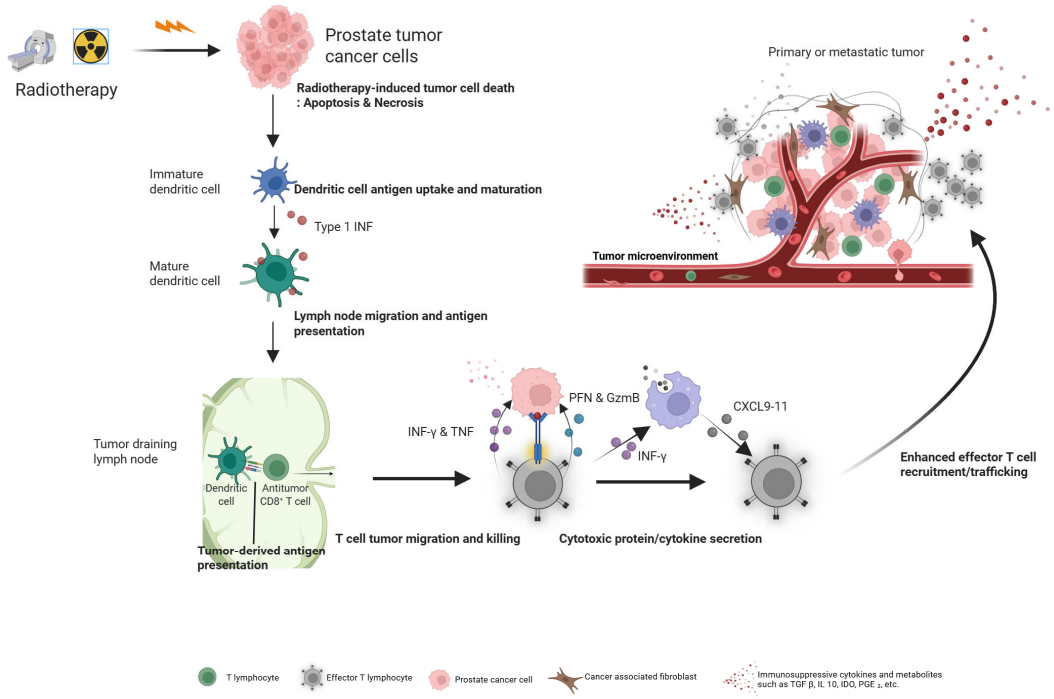

Figure 2. Radio-immunologic modulation of the tumor immune microenvironment after ^{177}Lu-PSMA-617 radioligand therapy. Targeted β-particle irradiation triggers apoptosis and necrosis of PSMA-expressing prostate-cancer cells, driving immunogenic cell death and the release of tumor-associated antigens and damage-associated molecular patterns. Immature dendritic cells capture these signals, mature under type-I-IFN influence and migrate to tumor-draining lymph nodes, where they prime naïve T cells. CXCL9–11-guided effector CD8$^+$ T cells then home back to the tumor, release perforin and granzyme B, and secrete IFN-γ and TNF, collectively reshaping the tumor immune microenvironment toward effective cytotoxicity. (Figure created with BioRender.com.).

5.2. A Hypothesis-Generating Biomarker: The PD-L2 Signature

Identifying which patients are most likely to mount an effective immune response to RLT is a critical step toward personalizing therapy. Recent research has uncovered promising biomarkers rooted in the interferon-gamma (IFN-γ) signaling pathway. A recent and potentially paradigm-shifting exploratory study analyzed the tumor immune microenvironment of patients with mCRPC undergoing 177Lu-PSMA-617 therapy [57,60]. The investigators correlated baseline tumor gene

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expression signatures from archival primary tumor tissue with clinical outcomes. The analysis revealed that a higher baseline expression signature for Programmed Death-Ligand 2 (PD-L2) was strongly and significantly associated with a better response to RLT [57]. Patients with a high PD-L2 signature had a much longer median overall survival compared to those with a low signature (17.2 months vs. 5.7 months), with a HR of 0.46. Furthermore, higher PD-L2 expression correlated with a greater PSA decline. Remarkably, the expression of the more widely studied immune checkpoint, PD-L1, showed no significant association with outcome.

It is critical to frame this finding with appropriate caution. This was a single-center, retrospective, exploratory analysis with a very small sample size for the transcriptomic analysis (n=23) and a long interval between biopsy and RLT. As such, these results are hypothesis-generating and require rigorous validation in larger, prospective cohorts before they can be considered for clinical use.

Nonetheless, the finding has profound implications. The discovery that the PD-L2 signature may be the dominant predictor of response to RLT suggests that radionuclide therapy could induce a distinct immunological phenotype within the tumor microenvironment, one that relies on a different axis of immune regulation than that targeted by most current immunotherapies [61-63]. This challenges the default assumption that anti-PD-1/L1 agents are the automatic choice for combination with RLT and provides a strong biological rationale for designing future clinical trials that incorporate agents targeting the PD-L2 pathway or other immune axes, such as the CTLA-4 pathway targeted by ipilimumab in the NEPI trial.

6. Optimizing Efficacy: Combination Strategies and Sequencing

The inadequacy of neoadjuvant 177Lu-PSMA-617 monotherapy for achieving high pCR rates has prompted the investigation of combinatorial approaches. By integrating RLT with agents exhibiting complementary mechanisms, synergistic anti-tumor effects and resistance mitigation may be attainable [56].

6.1. Synergy with Immunotherapy

The integration of RLT with ICIs represents a highly promising investigational strategy. The biological reasoning is solid: RLT operates as an 'in situ vaccine,' causing ICD, discharging tumor antigens, and prompting a T-cell response [56,64]. However, the activated T-cell response frequently encounters quick suppression by immune checkpoint pathways found in the tumor microenvironment. CTLA-4 inhibitors like ipilimumab and PD-1/PD-L1 inhibitors, part of the ICIs group, strive to 'remove the brakes' on T-cells, avoiding exhaustion and enhancing a more efficient and sustained systemic anti-cancer response. The NEPI trial, which assesses the combination of 177Lu-PSMA-617 and ipilimumab, is the inaugural clinical evaluation of this hypothesis in the neoadjuvant context for PCa [54].

6.2. Interplay with PARP Inhibitors: Evidence of Cross-Resistance

Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) are another class of highly effective agents for a subset of men with mCRPC, specifically those whose tumors harbor mutations in DNA damage repair (DDR) genes, such as BRCA2 [65]. Since both RLT (via radiation) and PARPi (via enzymatic inhibition) ultimately exert their cytotoxic effects by inducing lethal DNA damage, there is a strong biological basis for both potential synergy and cross-resistance [66].

The question of how to best sequence these two potent therapies is a critical and unresolved clinical issue. A recent, important retrospective study investigated this question by comparing outcomes with 177Lu-PSMA-617 in men with DDR-mutated mCRPC who had either previously received a PARPi or were PARPi-naïve [67]. The results were notable. Prior exposure to a PARPi was associated with significantly worse outcomes on subsequent 177Lu-PSMA-617. This effect was most pronounced in the subgroup of patients with BRCA2 mutations. In this group, PARPi-naïve patients had a median PSA PFS of 14.0 months, compared to just 2.9 months for those who had previously

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been treated with a PARPi. The PSA50 response rate was also dramatically lower in the PARPi-exposed group (35% vs. 89%).

This clinical evidence strongly suggests the development of acquired cross-resistance. Treatment with a PARPi appears to exert a powerful selective pressure, enriching the tumor with clones that have developed mechanisms to more efficiently repair DNA damage. These same clones are then, in turn, resistant to the DNA damage induced by radiation from 177Lu-PSMA-617. This creates a crucial clinical dilemma: in a patient eligible for both therapies, which one should be used first? Using the PARPi first might effectively "burn the bridge" for RLT. This finding has immediate clinical implications for the sequencing of therapies in mCRPC and raises urgent questions for future research, including whether prior RLT induces resistance to subsequent PARPi therapy. Answering this will require prospective, randomized sequencing trials and will be essential for designing future neoadjuvant combination trials, as a significant proportion of men with high-risk localized PCa harbor germline DDR mutations [68].

6.3. Modulating the Target: The "PSMA Flare" Phenomenon

A third and highly sophisticated strategy for enhancing RLT efficacy involves manipulating the expression of the target itself. PSMA expression on the surface of PCa cells is not static; it is dynamically regulated by the androgen receptor (AR) signaling pathway. Paradoxically, inhibiting the AR with ADT or potent AR pathway inhibitors (ARPIs) such as enzalutamide has been shown to cause a transient upregulation of PSMA gene and protein expression [69,70].

This phenomenon, termed the "PSMA flare," has been demonstrated in both preclinical xenograft models and in clinical imaging studies [70]. In one notable case report, a patient with castration-sensitive PCa underwent a PSMA PET scan before and four weeks after starting ADT. The post-ADT scan revealed a 7-fold increase in PSMA uptake in known lesions, and, remarkably, 13 new metastatic lesions became visible on the scan that were not detected at baseline [71]. More recent work has shown that a short course of enzalutamide (9-14 days) can induce a significant increase ($\geqslant$20%) in the SUVmax of existing tumor lesions in 56% of cases [69]. This biological insight transforms PSMA from a passive biomarker into a therapeutically modifiable target. It raises the possibility of using a short course of an ARPI to intentionally induce a PSMA flare immediately prior to PSMA-targeted therapy. This could theoretically increase the absorbed radiation dose delivered to tumors, improve the visualization of low-volume disease on diagnostic scans, and potentially convert patients with initially low PSMA expression into eligible candidates for RLT. Clinical trials are now underway to formally test this hypothesis.

7. Navigating the Path to Clinical Implementation

While the scientific rationale for neoadjuvant RLT is strong and early data are promising, several significant hurdles must be overcome before this approach can be integrated into routine clinical practice. These challenges span the domains of clinical trial design, biomarker development, and the practical realities of implementing a novel radiopharmaceutical therapy [52].

7.1. Validating Endpoints for Accelerated Approval: The Role of MFS

A major historical barrier to developing new therapies for localized PCa has been the extremely long time required for clinical trials to mature. Because many men with PCa have a long natural history, demonstrating a statistically significant improvement in the gold-standard endpoint of OS can take more than a decade of follow-up [72]. This timeline is prohibitive for efficient drug development.

To address this, the Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) working group was formed to identify and validate a surrogate endpoint for OS [73]. Through a large-scale, patient-level meta-analysis of randomized trials, ICECaP rigorously evaluated MFS—defined as the time from randomization to the first evidence of distant metastasis or death from any cause—as a

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potential surrogate. The results were definitive. The initial analysis demonstrated a very strong correlation between the effect of a given treatment on MFS and its effect on OS, with a trial-level coefficient of determination (R2) of 0.92 [74]. A subsequent analysis, ICECaP-2, which included data from more contemporary trials where patients had access to modern systemic therapies for metastatic disease, confirmed that MFS remains a robust surrogate for OS (R2=0.83) [74].

The validation of MFS as a surrogate for OS is a landmark achievement that has profound implications for clinical research in localized PCa. It provides regulatory agencies with a statistically sound and clinically meaningful endpoint upon which to base drug approvals, dramatically shortening the required duration of clinical trials. Consequently, MFS is now the accepted primary endpoint for future phase 3 trials of neoadjuvant or adjuvant therapies in high-risk localized PCa and will be the linchpin for the regulatory approval of neoadjuvant RLT.

7.2. Detecting Minimal Residual Disease with Circulating Tumor DNA

While MFS provides a validated pathway for drug approval, researchers are actively seeking even earlier biomarkers of treatment efficacy. One of the most promising is the detection of circulating tumor DNA (ctDNA) to identify MRD [75]. ctDNA consists of small fragments of DNA that are shed from tumor cells into the bloodstream and carry the same somatic mutations as the primary tumor. Using highly sensitive, next-generation sequencing techniques, it is possible to detect these tumor-specific mutations in a patient's plasma [76].

In numerous other solid tumors, the presence of detectable ctDNA in the blood after curative-intent surgery or therapy is a powerful predictor of subsequent disease relapse, often identifying patients at risk months or even years before recurrence is visible on conventional imaging [75]. Early feasibility studies in PCa have shown that tumor-informed, personalized ctDNA assays can detect MRD in patients after RP, and that the persistence of ctDNA after surgery is associated with a higher risk of subsequent PSA relapse [76]. The potential application of ctDNA in the neoadjuvant RLT setting is transformative. Clearance of ctDNA from the blood after neoadjuvant RLT and subsequent surgery could serve as a very early and powerful surrogate for treatment success, potentially predicting long-term MFS. Conversely, the persistence of ctDNA would identify patients at the highest risk of relapse, who could then be immediately triaged to receive adjuvant therapy, creating a truly risk-adapted, personalized post-operative management strategy.

7.3. Key Hurdles in Clinical Adoption

The successful clinical implementation of neoadjuvant RLT will also depend on navigating a complex landscape of practical challenges, which must be addressed concisely. First, ethical considerations are paramount, particularly with the development of next-generation alpha-emitter RLTs. While these agents offer superior potency, their high LET radiation causes complex and largely irreparable DNA damage. The ethical threshold for accepting the risk of potential irreversible off-target toxicity to healthy tissues, such as the salivary glands or kidneys, is substantially higher in the curative-intent neoadjuvant setting compared to the palliative, end-of-life mCRPC setting [47]. Rigorous long-term safety data will be required.

Second, regulatory and logistical disparities pose a significant challenge. Radiation safety regulations differ substantially across the globe, with some countries requiring multi-day inpatient hospital stays while others permit outpatient administration [77]. These differences profoundly impact the cost of care, patient access, and the operational feasibility of conducting harmonized international clinical trials.

Finally, the economic burden of novel cancer therapies is a major societal concern. A formal cost-effectiveness analysis of ^{177}Lu-PSMA-617 in the mCRPC setting, based on the VISION trial data, calculated an incremental cost-effectiveness ratio (ICER) of $200,708 per quality-adjusted life year (QALY) gained [77]. This value is above the commonly cited willingness-to-pay thresholds in the United States. As this therapy moves into the larger, earlier-stage population of high-risk localized PCa, addressing issues of cost and value will be paramount to ensure equitable access.

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8. Conclusion and Future Directions

8.1. Summary of the Potential for Neoadjuvant RLT to Reshape the Treatment Paradigm

Neoadjuvant ^{177}Lu-PSMA-617 RLT represents a potential paradigm shift in the management of high-risk localized PCa. It challenges the traditional approach of relying solely on local therapies for a disease that is frequently systemic from its inception. By delivering a potent, targeted systemic therapy prior to definitive local treatment, this strategy offers the multifaceted potential to eradicate occult micrometastases, provide an in vivo readout of treatment sensitivity through pathological response, and prime a systemic anti-tumor immune response. The early data from trials like LuTectomy are encouraging, demonstrating that the approach is safe, feasible, and biologically active. While monotherapy appears insufficient to achieve complete tumor eradication, these initial findings have paved the way for more advanced combination strategies that hold the promise of significantly improving cure rates for men with the most aggressive forms of localized PCa.

8.2. Key Unanswered Questions and the Roadmap for Future Research

Despite the vast possibilities, the area of neoadjuvant RLT is still developing, and numerous critical questions remain. Future research must clarify these ambiguities through a series of meticulously designed, prospective trials.

First, the the optimal regimen for neoadjuvant RLT needs to be defined. This means investigating the most effective dosage, the treatment interval count, and the timing of administration tied to the surgical intervention. The LuTectomy trial implemented a singular cycle, whereas the NEPI trial is examining a two-cycle regimen, and subsequent studies may delve into further intensification strategies.

Second, the central question of whether a meaningful rate of pCR can be achieved should be addressed. This will likely necessitate transcending monotherapy approaches. The results of the NEPI research, melding RLT with immune treatment techniques, will signify an important preliminary progression. Future investigations should assess alternative combinations, such as those involving PARPi in patients with DDR mutations, or the incorporation of more efficacious alpha-emitting radionuclides like ^{225}Ac-PSMA.

Third, establishing the optimal sequencing of RLT with other potent systemic agents, particularly PARPi, is essential. The preliminary evidence indicating cross-resistance underscores the pressing necessity for randomized trials to ascertain whether RLT should precede or follow PARPi in suitable patient populations to optimize cumulative therapeutic benefits.

Fourth, the role of biomarkers in personalizing neoadjuvant RLT needs to be solidified. This includes the validation of PSMA PET imaging parameters to forecast therapeutic response, the confirmation of the predictive value of immune signatures such as PD-L2 to appropriately select candidates for immunotherapeutic combinations, and the development of ctDNA-based MRD assays to inform post-operative adjuvant treatment decisions.

Finally, the long-term safety and quality-of-life impacts of neoadjuvant RLT in a curative-intent population should be carefully evaluated. While the immediate toxicity may be well-regulated, comprehensive long-term tracking is important to catch any delayed effects, especially concerning kidney and bone marrow function, particularly as more potent alpha-emitters are introduced.

In conclusion, neoadjuvant ^{177}Lu-PSMA-617 RLT is one of the most exciting new frontiers in the treatment of high-risk localized PCa. It offers a scientifically robust strategy to address the fundamental challenge of micrometastatic disease. While the path to establishing this approach as a new standard of care is long and will require rigorous investigation, the potential to substantially increase the cure rate for these high-risk patients makes it a journey of paramount importance for the field of oncology. The success of this endeavor will hinge on the execution of well-designed, prospective, randomized clinical trials that leverage validated surrogate endpoints like MFS to deliver clear answers in a clinically relevant timeframe.

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