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Shen B, Wang F

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Review Article

Precision Nodal Staging in Intermediate-Risk Prostate Cancer: A Narrative Review of Molecular Imaging

Banchao Shen[a, b], Fuli Wang[a]

[a] Department of Urology, Xijing Hospital, Air Force Medical University, Xi'an, Shaanxi, 710032, China
[b] Department of Urology, No.988 Hospital of Joint Logistic Support Force, Zhengzhou, Henan, 450042, China

Short Title: Precision Nodal Staging for Intermediate-Risk Prostate Cancer

Corresponding Author:
Fuli Wang
E-mail address: wangfuli98@163.com

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Abstract

Background

Lymph node (LN) staging remains critical for risk stratification and treatment selection in intermediate-risk prostate cancer. Conventional imaging modalities have limited sensitivity, and extended pelvic LN dissection (ePLND) is associated with considerable morbidity.

Summary

This narrative review evaluates conventional imaging, molecular imaging, and intraoperative technologies for LN staging in intermediate-risk prostate cancer. Conventional computed tomography and magnetic resonance imaging demonstrate low sensitivity for detecting lymph node metastasis. Prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography shows substantially improved diagnostic performance; however, it may still underestimate micrometastatic disease. Intraoperative approaches, including PSMA-targeted fluorescence imaging and sentinel lymph node biopsy, enable real-time detection and may reduce morbidity while maintaining high diagnostic accuracy in experienced centers. However, these techniques are limited by technical complexity, lack of standardized protocols, and restricted availability in routine clinical practice.

Key Messages

A multimodal, risk-adapted strategy combining preoperative molecular imaging and intraoperative targeted techniques may improve the precision of LN staging. This integrated approach can help minimize unnecessary ePLND and reduce procedure-related morbidity in patients with intermediate-risk prostate cancer.

Introduction

Prostate cancer (PCa) is the second most common cancer among men worldwide [1, 2], and accurate nodal staging is critical for prognosis and treatment planning [3]. Pelvic lymph node (LN) dissection (PLND) remains the gold standard for detecting LN metastasis (LNM) [4], although its use varies according to risk stratification. Current guidelines recommend omitting PLND in low-risk patients [5, 6], in whom nodal involvement is rare and active surveillance is often appropriate. Conversely, extended PLND (ePLND) is for high-risk patients despite its considerable morbidity rate of 19.8% [4, 7].

However, this risk-adapted approach leaves the intermediate-risk subgroup (International Society of Urological Pathology [ISUP] Grade Group 2–3, prostate-specific antigen [PSA] 10–20 ng/mL, and clinical Stage cT1–2b) in a therapeutic gray zone [8, 9]. Intermediate-risk prostate cancer (IR-PCa) is the most biologically heterogeneous category and is further classified into favorable (ISUP Grade Group 2, PSA <10 ng/mL, cT1–2a) and unfavorable (ISUP Grade Group 3 or PSA 10–20 ng/mL with cT1–2b) subgroups [7, 10]. Favorable cases resemble low-risk disease, with <10% nodal involvement, whereas unfavorable cases exhibit 15%–20% LNM rates and often harbor occult high-grade disease [9]. This marked heterogeneity within a single risk category creates a critical clinical dilemma: the "intermediate-risk" label encompasses both indolent tumors amenable to active surveillance and aggressive disease requiring multimodal therapy, thereby risking overtreatment in favorable subgroups and undertreatment in unfavorable ones. Risk stratification nomograms suggest a 7% LNM threshold; patients with favorable IR-PCa below this threshold may safely omit dissection, whereas those with unfavorable IR-PCa typically exceed it and warrant definitive staging [11]. However, accurate differentiation between these subgroups depends on reliable detection of nodal metastases, which remains challenging with current imaging modalities.

Conventional imaging techniques have notable limitations. Computed tomography (CT) and magnetic resonance imaging (MRI) demonstrate limited sensitivity for LNM (typically <40% for sub-centimeter disease) [12, 13], as they rely on size-based criteria that fail to detect micrometastases in morphologically normal nodes. Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA-PET/CT) improves detection, with size-dependent sensitivity ranging from 50% to 90%; however, it still misses a substantial proportion of micrometastases within standard dissection fields (up to 63%) [14, 15]. These limitations have driven the development of next-generation molecular imaging approaches, ranging from preoperative PSMA-PET/CT to intraoperative fluorescence guidance and sentinel lymph node (SLN) mapping.

Therefore, this narrative review aims to synthesize current evidence addressing the following key questions: How can molecular imaging improve the detection accuracy of pelvic LNM in IR-PCa? What are the complementary roles of preoperative and intraoperative modalities? How can these technologies be integrated to enable precision nodal staging while minimizing overtreatment? We first examine the limitations of conventional imaging, then assess advances in PSMA-targeted diagnostics and intraoperative guidance, and finally propose a multimodal framework for risk-adapted nodal staging while identifying priorities for future research.

Literature Selection Strategy

This narrative review employed purposive sampling to identify pivotal advances in PCa nodal staging, prioritizing clinical impact over exhaustive enumeration [16].

A systematic search was conducted in PubMed and the Web of Science Core Collection using combinations of the following keywords: ("prostate cancer" OR "prostatic neoplasm") AND ("lymph node metastasis" OR "lymph nodal staging") AND ("PSMA-PET" OR "fluorescence imaging" OR "sentinel" OR "CT" OR "MRI" OR "molecular imaging"). The search was restricted to studies published between January 2015 and December 2025, corresponding to the clinical implementation of PSMA-targeted imaging.

We included original research that: (1) evaluated the diagnostic accuracy of novel imaging modalities using histopathology as the reference standard; (2) introduced intraoperative molecular guidance technologies with clinical validation; or (3) provided head-to-head comparisons of staging strategies. Eligible study designs included diagnostic accuracy trials, prospective cohort studies, and key clinical investigations assessing nodal staging performance. We excluded non-human studies, non-English publications, and studies focused on biochemical recurrence or treatment of PCa. Details of the screening process are presented in **Figure 1**.

This selection process yielded a core set of 61 key studies that form the evidentiary foundation of this review. Collectively, these studies delineate the evolution of the clinical workflow for nodal staging, which structures our discussion into three domains: (1) the diagnostic limitations of conventional imaging; (2) the paradigm shift in preoperative molecular staging; and (3) the emergence of intraoperative navigational guidance for targeted dissection.

Limitations of Conventional Imaging Modalities

Traditional imaging modalities, such as CT, are routinely used for whole-body staging in PCa and provide preliminary morphological assessment of LNs. However, they rely solely on morphometric criteria—typically a short-axis diameter of more than 8–10 mm—to define pathological LNs [17]. This size-based approach fundamentally limits the detection of micrometastases in normal-sized LNs, resulting in insufficient sensitivity for accurate LNM detection. Notably, CT cannot reliably distinguish between enlarged benign hyperplastic nodes and malignant metastatic nodes, a limitation that is particularly pronounced in patients with small, low-aggressiveness prostate tumors. Consequently, the sensitivity of CT alone for identifying LNM is consistently reported to be below 40% in clinical studies [12].

Compared with CT, MRI offers superior soft-tissue contrast, enabling clearer visualization of the anatomical relationship between the prostate and surrounding LNs, as well as more accurate assessment of locoregional tumor spread [17]. This represents a significant advantage of MRI over CT in PCa staging. Despite this improvement, MRI remains limited by its reliance on morphological criteria, and its diagnostic accuracy for nodal staging is not substantially better than that of CT. A systematic review of five studies (*n* = 228) demonstrated that MRI detected only 25% of pathologically confirmed LNMs, corresponding to a 75% false-negative rate for nodal disease [18]. Multiparametric MRI is primarily used for local tumor staging, evaluation of extraprostatic extension, and assessment of adjacent structures, as well as detection of distant metastases [19]. Nevertheless, these advances have not translated into improved sensitivity for LNM detection, as nodal assessment continues to depend on size-based evaluation. These persistent limitations indicate that even advanced conventional imaging techniques cannot achieve the diagnostic precision required for reliable nodal staging of PCa.

To address the inherent limitations of morphology-based imaging, radiomics—a computational approach that extracts quantitative texture features from multiparametric MRI images has been explored to improve nodal assessment. However, current evidence demonstrates variability in diagnostic performance, with sensitivity ranging from 50% to 93% and specificity ranging from 29% to 86% for detecting metastases in normal-sized LNs [20]. This heterogeneity is largely attributable to the lack of standardized imaging acquisition and feature extraction protocols, as well as the limited availability of high-quality clinical studies, which restricts its clinical applicability. Collectively, these limitations indicate that even advanced conventional and computational imaging techniques cannot overcome the fundamental constraints of morphology-based assessment, underscoring the need for molecular imaging approaches. To overcome these limitations, next-generation imaging (NGI) techniques, particularly molecular imaging, offer a more sensitive and less invasive strategy for detecting LNM.

Molecular Imaging for Preoperative Staging

NGI, represented by molecular imaging, has triggered a paradigm shift in preoperative nodal staging. Among various NGI techniques, PET/CT using novel tracers has significantly improved the accuracy of LNM detection, with PSMA-based PET imaging being the most extensively studied and widely applied [21]. As the most sensitive method currently available for identifying metastatic spread, PSMA-PET is primarily used for preoperative nodal staging and the detection of postoperative recurrence in patients with PCa [22]. Clinically, the use of PSMA-PET has been progressively standardized. Between 2020 and 2021, the US Food and Drug Administration approved two PSMA-based tracers for clinical use, namely gallium-68 PSMA-11 (^{68}Ga-PSMA-11) [14] and Piflufolastat F-18 (^{18}F-DCFPyL) [23], establishing a foundation for broader clinical adoption.

The superior diagnostic performance of PSMA-PET/CT in pelvic LNM staging is attributed to its molecular targeting capability, which enables specific recognition of PSMA-expressing metastatic lesions. This approach significantly enhances detection efficiency, offering higher sensitivity and specificity compared with conventional imaging meodalities. A prior study demonstrated that PSMA-PET/CT outperformed conventional imaging, achieving an accuracy of 92% versus 65% [24]. Additionally, pooled analyses from multiple studies have reported sensitivity ranging from 47.7% to 95.2% and specificity ranging from 89.9% to 100% [14, 24], reflecting considerable heterogeneity across study designs and patient populations. Conversely, a prospective multicenter Phase III trial reported a sensitivity of 40% (95% confidence interval: 34–46%) in intermediate- and high-risk patients [25], highlighting the discrepancy between optimized single-center results and real-world multicenter performance. This variability is influenced by multiple factors that have been further clarified in subsequent studies and clinical guidelines.

To address this heterogeneity and improve diagnostic consistency, four key influencing factors have been identified: (1) tracer type—^{68}Ga-PSMA-11, ^{18}F-DCFPyL, and ^{18}F-PSMA-1007 differ in diagnostic performance [14, 26, 27]; (2) imaging protocol— reconstruction algorithms, delayed imaging, and administration parameters significantly affect lesion detectability [27]; (3) patient selection—unfavourable disease status and higher tumor burden are associated with increased likelihood of metastasis and improved detection rates [14, 24]; and (4)

lesion biology—PSMA expression correlates with tumor grade, while nonspecific uptake in benign conditions may reduce specificity [26-29]. As these factors are largely related to nonstandardized practices and biological variability, clinical standardization represents the primary strategy to reduce heterogeneity [25, 30]. Standardization should follow established guidelines (e.g., European Association of Urology [EAU] recommendations), including standardized tracer production, clearly defined patient selection criteria, and incorporation of biological context into image interpretation to minimize interinstitutional variability [25, 27, 30]. Beyond these standardization-related challenges, PSMA-PET/CT has inherent clinical limitations that constrain its widespread adoption.

Practical barriers—an important aspect of clinical limitations—significantly limit the accessibility of PSMA imaging. The high cost of PSMA tracers, along with the uneven distribution of technical resources, limits their availability in non-specialized regions with limited medical infrastructure [30]. In addition, false-positive findings may occur due to nonspecific PSMA uptake in benign conditions such as inflammatory LNs, complicating clinical interpretation and reducing overall diagnostic reliability [28, 29].

In summary, despite its limitations, PSMA-PET/CT is a valuable tool for preoperative pelvic LNM staging in PCa, improving staging accuracy and supporting individualized treatment planning [22, 30]. However, as a preoperative modality, it does not fully address discrepancies between preoperative imaging findings and intraoperative pathological assessment, leaving an important unmet clinical need. To bridge this gap, intraoperative navigation techniques have been developed.

Molecular Imaging for Intraoperative Staging: Navigational Guidance

NGI, extending from preoperative molecular imaging to the intraoperative setting, has driven the development of navigational guidance for real-time LNM targeting. Fluorescence-based molecular probe technology serves as the core translational tool in this domain.

Near-Infrared-I Fluorescence Agents (700–1000 nm)

Fluorescence-guided surgery (FGS) enables real-time intraoperative visualization through the detection of target-specific fluorescent agents within the surgical field. Near-Infrared-I (NIR-I) fluorescence imaging is currently the most clinically advanced modality. It provides real-time intraoperative imaging that complements preoperative radionuclide NGI, reduces tissue autofluorescence interference, and improves the tumor-to-background ratio [31]. Specifically, it enables intraoperative real-time visualization of LNMs, facilitates precise resection, and helps address discrepancies between preoperative imaging and intraoperative findings—a key limitation of preoperative PSMA-PET/CT. The diagnostic performance of intraoperative fluorescence guidance depends on the selective accumulation and effective concentration of fluorescent dyes within metastatic LNs [31].

Indocyanine green (ICG), with an absorption peak at 780 nm and an emission peak at 820 nm, is one of the few US Food and Drug Administration-approved optical agents with clinical utility [31]. ICG-based imaging systems can achieve micron-scale spatial resolution (<10 μm) [32], enabling potential differentiation between malignant and benign LNs and providing value for intraoperative margin assessment [33]. However, as a nonspecific fluorescent agent, ICG lacks standardized preoperative and intraoperative dosing protocols. Moreover, its diagnostic performance for PCa LNM detection remains suboptimal, with a reported sensitivity of 62%, specificity of 50%, positive predictive value (PPV) of 45%, and negative predictive value (NPV) of 97% [34].

To overcome the low specificity of non-targeted agents such as ICG and improve the accuracy of LNM detection, PSMA-targeted fluorescent probes have been developed for PCa. (1) IS-002, a NIR fluorophore-labeled PSMA-targeting peptide, is among the first NIR tracers translated into human application. It can identify PCa lesions undetectable by conventional white-light imaging and demonstrates a 90% concordance rate with histopathological findings [35]. (2) OTL78 exhibits high diagnostic accuracy for PSMA-positive lesions due to its strong affinity for PSMA and has shown reliable performance in confirming negative surgical margins [36]. Despite these advantages, clinical studies of PSMA-targeted fluorescent agents have reported inconsistent diagnostic sensitivity [32, 37-40].

To address these limitations, dual-modality probes combining radioactive and fluorescent targeting have been developed, integrating the advantages of preoperative nuclear NGI with intraoperative fluorescence imaging [41]. These probes enable preoperative lesion localization *via* nuclear imaging and real-time intraoperative identification of diseased LNs, facilitating a seamless workflow from staging to surgical guidance. For example, the dual-targeting probe Cy-KUE-OA [42] demonstrates a 13.2-fold increase in fluorescence intensity compared with single-modality probes, enabling precise localization of PCa foci and metastatic LNs and improving intraoperative staging accuracy. In a first-in-human study of a dual-modality PSMA-targeted probe (^{68}Ga-P3), intraoperative fluorescence imaging achieved a maximum accuracy of 92.3% at a dose of 40 μg/kg, with an NPV of 100% for

tumor localization [43]. Notably, preoperative risk stratification can guide the application of these probes to suspicious nodal regions, representing a shift from anatomy-based to biologically guided PLND.

However, single-modality PSMA-targeted fluorescent agents and dual-modality probes share several clinical and technical limitations. Clinically, their use is constrained by the lack of standardized dosing protocols, variability in intraoperative visualization and operator technique, high development and implementation costs, limited patient acceptance, and insufficient high-quality clinical evidence [32, 36, 37, 40]. Technically, as NIR-I agents, both types of probes are limited by shallow tissue penetration (<10 mm) [41], restricting visualization of deep pelvic LNs and limiting their utility for LNM staging. This limitation has motivated the development of NIR-II fluorescence agents.

Near-infrared-II Fluorescence Agents (1000–1700 nm)

NIR-II fluorescence imaging has gained increasing attention in biomedical research, with significant potential for clinical translation due to its unique advantages, including reduced light scattering, deeper tissue penetration, higher spatial resolution, and superior signal-to-noise ratio [44, 45]. Photoluminescent nanomaterials (PLNs) emit light without continuous external excitation. When combined with multimodal imaging strategies, NIR-II PLNs enable the development of high-performance targeted probes. Multimodal imaging integrates the complementary strengths of different imaging modalities to achieve high sensitivity and high spatial resolution for lesion detection [46].

Preclinical proof-of-concept studies in animal models have demonstrated the translational potential of NIR-II probes, enabling detection of submillimeter tumors (<2 mm) that are not visible to the naked eye and suggesting their potential utility for intraoperative navigation [48]. However, clinical translation remains in its early stages. At present, NIR-II probes for PCa LNM are largely confined to preclinical research, with no large-scale clinical trials or regulatory approvals to date [47]. In contrast, most clinical intraoperative fluorescence studies in PCa continue to rely on NIR-I agents [32, 34]. Nevertheless, the high-precision targeted imaging paradigm established by current fluorescence-guided approaches provides a valuable translational framework for the future development of NIR-II probes for LNM detection and intraoperative FGS in PCa.

In summary, NIR-II fluorescence probes have demonstrated significant advantages in preclinical studies and show great potential for intraoperative navigational guidance. However, they still share many of the limitations of NIR-I agents. Overcoming these challenges, conducting high-quality clinical studies, and establishing clinical consensus remain key priorities for realizing the full clinical value of NIR-II fluorescence imaging in PCa LNM.

Sentinel Lymph Node Biopsy Integrated with Molecular Imaging

In PCa, SLN biopsy (SLNB) is used to improve staging accuracy and enable resection of metastatic lesions, including micrometastases. Studies have shown that SLNB can achieve diagnostic accuracy comparable to ePLND in selected cohorts [40, 48]. However, these findings require further validation in larger, standardized studies before SLNB can be considered an equivalent alternative in routine clinical practice. When combined with molecular imaging, SLNB offers a targeted, minimally invasive approach for nodal staging in PCa, with distinct advantages over traditional intraoperative navigation techniques. Technically, it enables precise localization of the first-echelon LNs draining the primary tumor through molecular imaging-based lymphatic mapping, thereby avoiding blind pelvic LN exploration and improving surgical targeting [49]. Clinically, SLNB reduces the extent of surgical dissection while ensuring detection of metastatic LNs, thereby lowering the risk of complications such as lymphocele and lower limb lymphedema associated with ePLND [50].

These advantages support the clinical value of SLNB combined with molecular imaging, as reflected in international guidelines and emerging clinical evidence. The 2025 EAU Prostate Cancer Guidelines (Section 5.8.2.6.3) recognize SLNB as a clinically validated, minimally invasive option for intermediate- and high-risk patients, citing high diagnostic performance (sensitivity 95.2%, NPV 98.0% in a systematic review [40]; sensitivity 95.4%, specificity 100% in the prospective SENTINELLE trial [7]). This reflects its transition from investigational use toward broader clinical adoption in specialized centers with appropriate expertise, while ePLND remains the recommended standard.

Notably, SLNB occupies different positions across clinical guidelines. While it is no longer considered experimental in centers following EAU recommendations, it remains investigational in other settings. The National Comprehensive Cancer Network Prostate Cancer Guidelines (2026.V4) [10] continue to regard ePLND as the reference standard and have not yet incorporated SLNB into routine recommendations. This discrepancy contributes to regional variations in clinical practice: SLNB is routinely performed in selected specialized centers in Europe and Australia, remains largely confined to research protocols in North America, and shows variable adoption in Asia and Oceania depending on local expertise. Inconsistent guideline recommendations hinder the development of unified training standards and limit widespread implementation. Although SLNB has

demonstrated high sensitivity for LNM detection in selected studies (up to 95.2%), with comparable accuracy to ePLND in these cohorts [40, 48], the lack of standardized protocols means that expert consensus still recommends ePLND as the clinical first standard, with SLNB used as an adjunct to improve staging accuracy [51, 52].

SLNB detection typically involves two complementary techniques, which may be used individually or in combination. Gamma probes enable detection *via* radioactive signals but have limited sensitivity, whereas fluorescent tracers allow real-time intraoperative visualization but are constrained by shallow tissue penetration [51]. Hybrid imaging, which combines these two modalities, leverages their respective advantages to overcome existing limitations. Recent hybrid imaging integrates SLN mapping with molecular techniques. For example, hybrid tracers such as ICG-^{99m}Tc-nanocolloid integrate the advantages of nuclear and fluorescence imaging, providing a minimally invasive and reliable method [53]. In addition, portable gamma cameras and single-photon emission CT/CT enable intraoperative mapping and real-time confirmation of complete SLN removal [39]. Robotic-assisted systems further enhance access to deep pelvic nodes [54]. PSMA-PET/CT-guided SLNB has also been proposed for selected patients [55, 56], and the SENSEI gamma probe has demonstrated the ability to detect SLNs beyond standard ePLND templates, enabling more precise staging [57].

Despite these advances, SLNB has notable limitations, particularly variable sensitivity. While the prospective SENTINELLE trial reported high sensitivity (95.4%) [7], gamma probe-assisted SLNB without hybrid tracers achieves sensitivity ranging from 67% to 76%, with high specificity (96%–100%) [58]. The main manifestation of this variability is the missed detection of micrometastases (<2 mm) [15, 59], which can be attributed to three main factors: (1) disrupted lymphatic drainage due to tumor obstruction or prior surgical intervention, reducing tracer accumulation in sentinel LNs; (2) the “shine-through” effect caused by high radioactivity of the primary tumor site, which obscures adjacent nodes; and (3) the absence of standardized tracer dosing and injection protocols, leading to variability in lymphatic mapping results [60].

To address these challenges, several optimization strategies have been proposed: (1) the development of highly sensitive PSMA-targeted dual-modality tracers to improve micrometastasis detection and mitigate the "shine-through" effect; (2) integration of SLNB with intraoperative frozen section analysis to provide real-time pathological assessment [61]; (3) establishment of unified international guidelines and standardized technical protocols; and (4) incorporation of NIR-II fluorescent probes to enhance visualization of deep pelvic sentinel nodes.

Discussion

This narrative review systematically summarizes the clinical applications, diagnostic performance, and limitations of various imaging modalities for pelvic LNs staging in IR-PCa, focusing on both traditional anatomical imaging and molecular imaging approaches. As shown in **Table 1**, the diagnostic accuracy of imaging modalities for nodal staging in IR-PCa has progressively improved with the transition from conventional anatomical imaging to molecular imaging. This evolution underscores that precise identification of metastatic LNs is a critical determinant of accurate staging and individualized management in IR-PCa. Notably, molecular imaging modalities—particularly PSMA-PET—and intraoperative techniques, such as FGS and SLNB, demonstrate superior diagnostic performance due to their molecular targeting capabilities. However, SLNB and FGS currently exhibit considerable inter-institutional variability in procedural protocols and lack standardized technical implementation; therefore, considering them equivalent alternatives to ePLND remains premature. These findings not only confirm the potential of molecular imaging to overcome the limitations of traditional imaging but also provide important technical support for addressing the clinical challenges of nodal staging in IR-PCa. Collectively, they establish the foundation for the multimodal staging strategy proposed in this review and support optimization of clinical decision-making.

Based on a review of existing evidence, we propose a multimodal nodal staging strategy integrating three key components, closely aligned with clinical practice and forming a closed-loop feedback system targeting the heterogeneous IR-PCa population: (1) preoperative risk stratification of patients with IR-PCa using traditional imaging combined with PSMA-PET/CT to distinguish favorable and unfavorable subgroups, with active surveillance recommended for the favorable subgroup and intraoperative intervention for the unfavorable subgroup; (2) intraoperative real-time targeting using FGS and hybrid-tracer SLNB to achieve precise localization and dissection of LNM in the unfavorable IR-PCa subgroup; and (3) intraoperative re-evaluation and real-time feedback to establish a closed-loop treatment strategy—adjusting intraoperative FGS as needed to ensure precise localization, determining whether to perform PLND based on intraoperative findings to enable individualized treatment, and supporting postoperative active surveillance (**Fig. 2**).

This multimodal strategy supports effective risk management by reducing unnecessary ePLND while maintaining diagnostic accuracy. Consequently, it may decrease surgical morbidity without compromising oncologic outcomes. It is particularly well suited to IR-PCa, where distinguishing between favorable and unfavorable subgroups is essential for appropriate treatment selection [7, 10, 11].

In summary, the proposed multimodal strategy for clinical application in IR-PCa includes the following: (1) Target population: patients with IR-PCa; (2) Economic impact: potential reduction in long-term costs by avoiding complications associated with overtreatment and unnecessary ePLND; (3) Advantages: addresses IR-PCa heterogeneity and integrates into routine clinical workflows; (4) Limitations: dependence on specialized equipment, lack of standardized multicenter protocols, operator variability, challenges in multidisciplinary intraoperative coordination, and limited long-term outcome data; and (5) Clinical implementation: feasible in well-equipped centers, but widespread adoption requires standardized protocols and multicenter validation.

Limitations and Future Directions

Limitations

This review has several limitations. First, the pathological gold standard for pelvic LN staging in IR-PCa remains ePLND. However, this review primarily focuses on molecular imaging-based staging techniques and does not provide an in-depth discussion of the synergistic use of ePLND with molecular imaging, nor does it comprehensively address other staging approaches not covered here. Second, as a narrative review, it summarizes a selected subset of relevant literature to highlight advances in molecular imaging rather than attempting an exhaustive synthesis; therefore, subtle differences among all available studies may not be fully captured. Third, molecular imaging techniques are rapidly evolving, and some ongoing or unpublished studies may not be included. Fourth, this review focuses on diagnostic accuracy by design; given limited evidence, clinical outcomes including survival, quality of life, and patient-reported outcomes are not addressed.

Future Directions

While this review focuses on the diagnostic accuracy of multimodal nodal staging, its broader clinical utility requires validation in terms of oncologic outcomes, quality of life, and patient-reported outcomes. Current evidence directly linking multimodal staging strategies to these endpoints remains limited, and well-designed prospective studies are needed to establish these associations. To advance the clinical translation and technological development of molecular imaging in IR-PCa nodal staging, the key future priorities for relevant technologies are summarized as follows: (1) Probe Engineering: Development of next-generation molecular probes for improved intraoperative micrometastasis detection; (2) Integrated Strategy Validation: Prospective multicenter trials evaluating PSMA-PET/CT-guided SLNB to standardize lymphadenectomy approaches; (3) FGS Protocol quantification: Establishment of diagnostic accuracy benchmarks through large-cohort comparisons of FGS and ePLND outcomes; (4) Health economics evaluation: Comparative analyses of costs and long-term benefits between imaging-guided surgery and standard ePLND; (5) Multimodal Data Integration Systems: Development of real-time surgical guidance platforms integrating preoperative risk assessment, intraoperative fluorescence quantification, and robotic instrument tracking to enable adaptive surgical decision-making; and (6) Training and Standardization: Establishment of standardized protocols and structured training programs for surgeons and radiologists to ensure consistent implementation across institutions.

Conclusion

In conclusion, this narrative review summarizes the diagnostic performance of various imaging modalities for pelvic LN staging in IR-PCa. Molecular imaging techniques demonstrate superior accuracy compared with traditional anatomical imaging. The proposed multimodal nodal staging strategy effectively addresses the challenges posed by the heterogeneity of IR-PCa and provides a framework to support individualized clinical decision-making. However, widespread clinical adoption of this strategy will require standardized protocols and validation through multicenter studies.

Statements

Conflict of Interest Statement

The authors have no competing interests

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Author Contributions

Banchao Shen conceived the idea of this review, conducted the literature search and formal analysis, and drafted the original manuscript; Fuli Wang provided supervision and resources, and critically revised the manuscript for important intellectual content. Both authors read and approved the final manuscript.

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Figure Legends

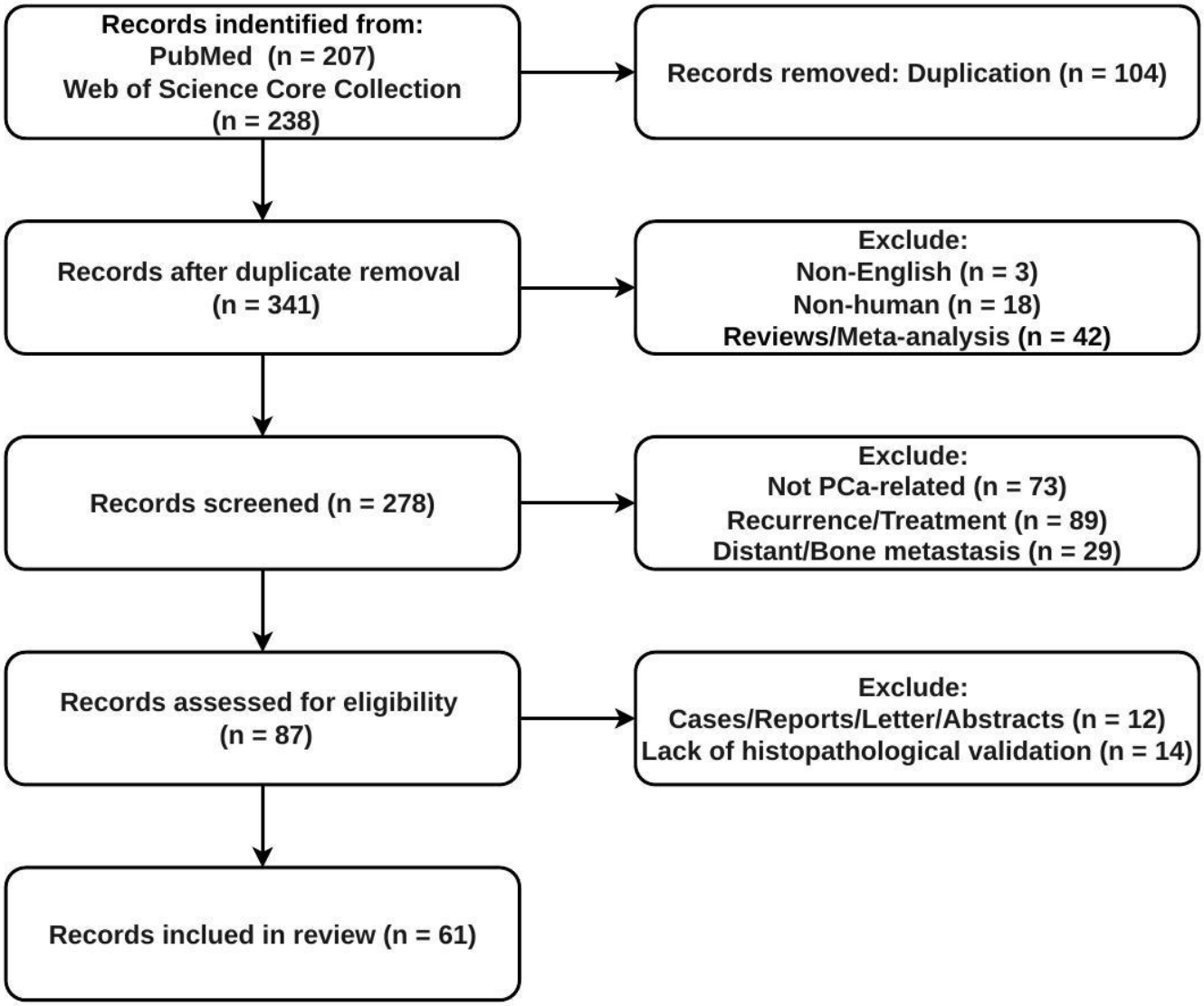
Fig. 1. Flow diagram of literature search and selection

A comprehensive search of PubMed and the Web of Science Core Collection databases (2015–2025) yielded 445 records. After duplicate removal and sequential screening based on language, study species, study type, thematic relevance, and methodological quality, 61 studies were included in this narrative review.

Fig. 2. Integrative multimodal workflow for lymph node staging in intermediate-risk prostate cancer

Preoperative risk stratification combines conventional imaging and PSMA-PET/CT to identify candidates for intraoperative LN assessment. Intraoperative guidance integrates fluorescence imaging using (NIR-I/II probes) , along with robotic SLNB using gamma probes and/or hybrid tracers, to enable real-time LN targeting. The multimodal decision system incorporates intraoperative feedback to reconcile preoperative and intraoperative findings, thereby optimizing individualized pelvic lymph node dissection.

Note: LN = lymph node; NIR = Near-infrared; PSMA-PET/CT = prostate-specific membrane antigen positron emission tomography/computed tomography; SLNB = sentinel lymph node biopsy.



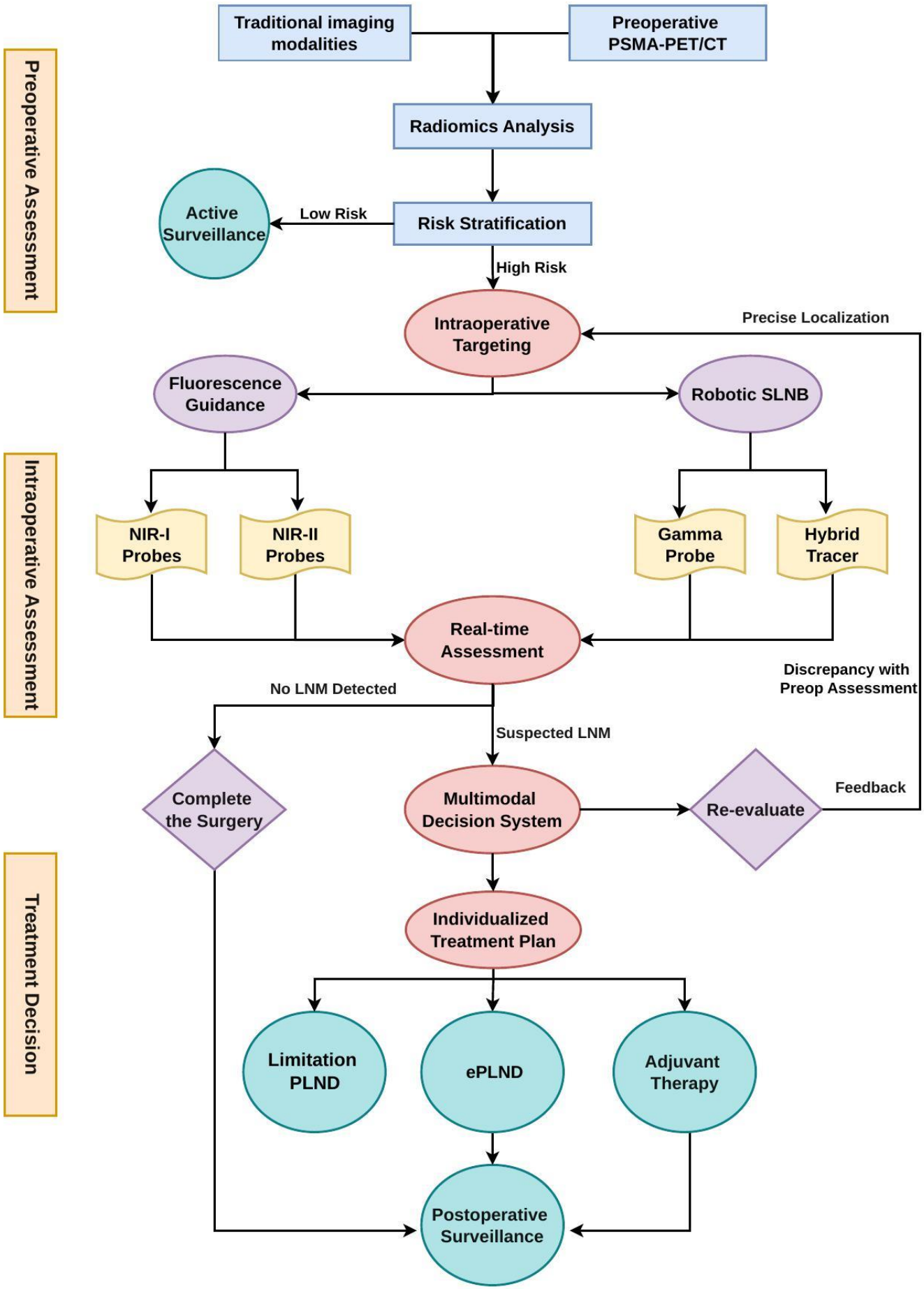


Table 1 Diagnostic performance characteristics of imaging modalities for lymph node staging in prostate cancer

Imaging Modality	Specific Technique	Sensitivity (%)	Specificity (%)	Core Advantages	Main Limitations	Evidence Stage	Key References
Conventional Imaging	CT	8.0–33.0	97.0–100.0	Low cost, suitable for whole-body staging.	Very low sensitivity; inability to detect micrometastases.	Established clinical practice	[12, 13, 17]
	MRI	34.0–61.0	90.0–99.0	Excellent soft tissue contrast; delineates local tumor extent.	Moderate sensitivity; limited specificity for nodal metastasis.	Established clinical practice	[18, 62, 63]
	mpMRI	37.0–81.0	78.9–100.0	Multiparametric approach improves lesion characterization.	Morphology-dependent; misses small-volume disease.	Established clinical practice	[64, 65, 66]
Preoperative Molecular Imaging	PSMA-PET	47.7–95.2	84.2–100.0	Strong molecular targeting; higher sensitivity; facilitates accurate preoperative staging.	Cost-prohibitive; discordance between preoperative and intraoperative findings; inter-study variability.	High-level clinical evidence	[23, 28, 29, 65, 66, 67, 68, 69, 70]
	FGS, NIR-I	62.0–100.0	50.0–100.0	Real-time intraoperative guidance; enhances surgical precision.	Limited penetration (<10 mm); lack of standardization; operator-dependent.	Moderate clinical evidence	[31, 36, 37, 38, 39, 40]
Intraoperative Molecular Imaging	Dual-modality Probes	NR	NR	Bridging preoperative and intraoperative execution; quantitative and real-time guidance.	Complex probe manufacturing; radiation safety; limited clinical validation.	Exploratory Clinical/Translational Research	N/A
	FGS, NIR-II	NR[a]	NR[a]	Enhanced tissue penetration (>10 mm); reduced scatter; improved deep lesion detection.	Preclinical stage; lacks clinical validation and standardization.	Preclinical	N/A
	SLNB	34.1–100.0	64.8–100.0	Minimally invasive; may offer accuracy comparable to ePLND in selected patients; reduces surgical morbidity.	Highly variable sensitivity; limited research data; lacks unified clinical standards.	Emerging/Investigational	[55, 71, 72, 73, 74]

Note: Ranges represent minimum and maximum values reported across studies.
NR = Not Reported; N/A = Not Applicable (no dedicated references for lymph node staging in prostate cancer); CT = computed tomography; MRI = magnetic resonance imaging; PSMA-PET = prostate-specific membrane antigen positron emission tomography; SLNB = sentinel lymph node biopsy; FGS = Fluorescence-guided surgery; NIR-I = Near-infrared-I; NIR-II = Near-infrared-II.
[a] Preclinical studies demonstrate advantages; no clinical data available.