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From PSMA PET to Molecularly Guided Surgery: A Target-Readiness Framework for the Molecular Surgical Index

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Perspective

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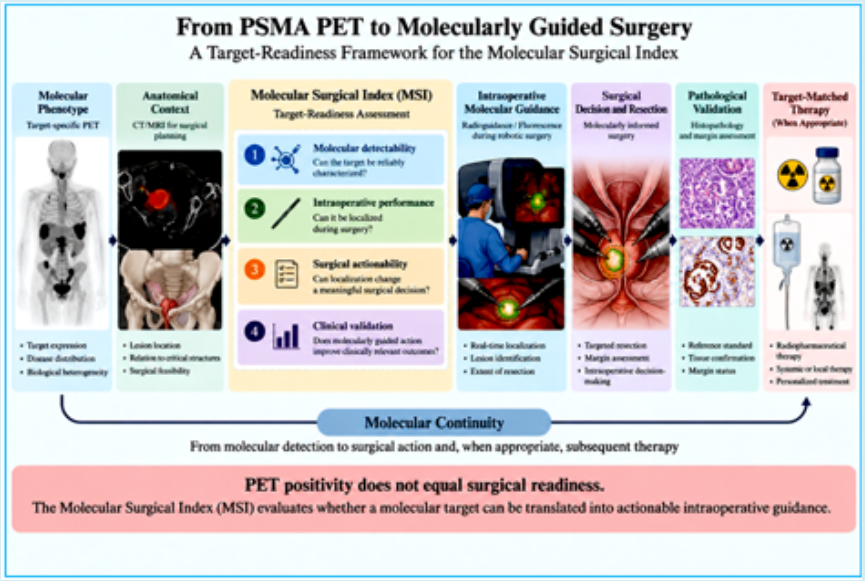
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Abstract

Precision oncology is increasingly moving beyond anatomy-based treatment toward surgical decisions informed by tumor biology. Positron emission tomography (PET) provides molecular information on target expression, disease distribution, and biological heterogeneity, yet this information is not consistently translated into intraoperative decision-making, where anatomical assessment and surgical judgment remain dominant. Existing approaches, including PET imaging, radioguidance, fluorescence, and robotic surgery, address individual components of molecularly guided intervention but lack a unified framework for determining when a molecular target is sufficiently ready to influence surgical action. We propose a PET-to-surgical-console framework based on molecular continuity, in which PET-derived molecular phenotyping informs surgical planning, intraoperative localization, residual-disease assessment, pathological correlation, and, when appropriate, subsequent target-matched therapy. Central to this framework is the proposed Molecular Surgical Index (MSI), which organizes target readiness across four domains: molecular detectability, intraoperative performance, surgical actionability, and clinical validation. The MSI is intended to distinguish PET positivity from true surgical readiness and to provide a structured basis for prioritizing targets and technologies for clinical translation. PSMA-directed prostate cancer represents the most mature clinical model, while somatostatin receptors, FAP, and HER2 illustrate different stages of translational development. The proposed framework is a conceptual and testable model, not a validated clinical index or established standard of care. Prospective and multicentre studies are required to define thresholds, establish reproducibility, assess concordance with pathology, determine effects on surgical decision-making and residual-disease detection, and ultimately establish whether molecular continuity improves patient-centred outcomes.

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Keywords: PET; Molecularly Guided Surgery; Molecular Surgical Index; Robotic Surgery; Radioguided Surgery; Precision Oncology

Introduction

Precision oncology is increasingly moving beyond anatomy-based assessment toward treatment decisions informed by tumor biology. Target-specific positron emission tomography (PET) has contributed substantially to this transition by visualizing the molecular distribution of disease, characterizing biological heterogeneity, and supporting treatment selection. In theranostic oncology, PET can therefore provide information that extends beyond diagnosis and staging by defining a molecular phenotype that may inform subsequent therapeutic strategies [1]. However, the clinical value of this molecular information depends not only on its ability to identify disease, but also on whether it can be translated into a clinically meaningful action.

A clinically important translational gap persists between molecular information obtained before surgery and decisions made within the operating room. PET can identify molecularly active lesions and define their distribution, but intraoperative management remains largely dependent on anatomical landmarks, visual assessment, and surgical judgment. Emerging PSMA-directed approaches demonstrate that molecular information can be carried further into surgery. Prospective radioguided robotic procedures have enabled intraoperative localization of molecularly positive lesions, while dual-modality PSMA probes have linked preoperative PET/CT with intraoperative fluorescence imaging [2]. These studies establish the feasibility of molecularly guided surgical intervention, but they do not yet establish that integration of PET, intraoperative guidance, and robotic surgery improves long-term oncological outcomes.

The central challenge is therefore not simply whether molecular technologies can be incorporated into robotic surgery, but whether molecular information is sufficiently reliable and actionable to support a specific surgical decision. This distinction is critical because PET positivity does not necessarily imply intraoperative detectability, intraoperative detectability does not necessarily imply surgical actionability, and technical actionability does not by itself establish clinical benefit. Target expression may be heterogeneous, lesion detectability may vary with depth and signal-to-background characteristics, and the ability to identify molecularly positive tissue does not necessarily mean that its removal will improve patient outcomes [3]. Consequently, a molecular target requires assessment across the continuum from biological detection to operative use and clinical validation rather than evaluation on the basis of PET uptake alone.

We therefore propose a PET-to-surgical-console framework based on molecular continuity, in which PET-derived molecular phenotyping is carried forward into surgical planning, intraoperative target localization, residual-disease assessment, pathological correlation, and, when clinically appropriate, subsequent molecularly matched therapy. The framework is intended to connect existing technologies rather than introduce another independent imaging or surgical platform. Central to this approach is the proposed Molecular Surgical Index (MSI),

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a structured framework for assessing target readiness across four domains: molecular detectability, intraoperative performance, surgical actionability, and clinical validation [4]. The MSI is designed to distinguish molecular targets that are merely detectable on PET from those sufficiently mature to influence surgical decision-making.

This Perspective therefore presents the PET-to-console framework and MSI as a testable translational model rather than an established clinical pathway or validated clinical score. The proposed architecture is intended to support systematic evaluation of whether molecular information can change operative decisions, improve detection or removal of target-positive disease, complement pathological assessment of residual disease, and inform subsequent treatment selection. Prospective and multicentre studies will be required to establish disease- and technology-specific thresholds, assess pathological concordance and reproducibility, determine clinical utility, and ultimately establish whether molecular continuity across imaging, surgery, and therapy provides meaningful patient benefit.

From Molecular Imaging to Surgical Action: The PET-To-Console Framework

The central translational challenge in molecularly guided surgery is converting molecular information into a reliable and actionable intraoperative decision. PET defines the distribution and biological characteristics of molecularly active disease, whereas surgery requires precise localization within a changing anatomical environment. PSMA-directed radioguided robotic procedures and dual-modality molecular probes demonstrate the feasibility of extending preoperative molecular information into the operating room [5]. We therefore propose a three-stage PET-to-console framework that maintains molecular continuity from preoperative characterization to intraoperative action while complementing conventional imaging, surgical judgment, and histopathology [6] (Figure 1).

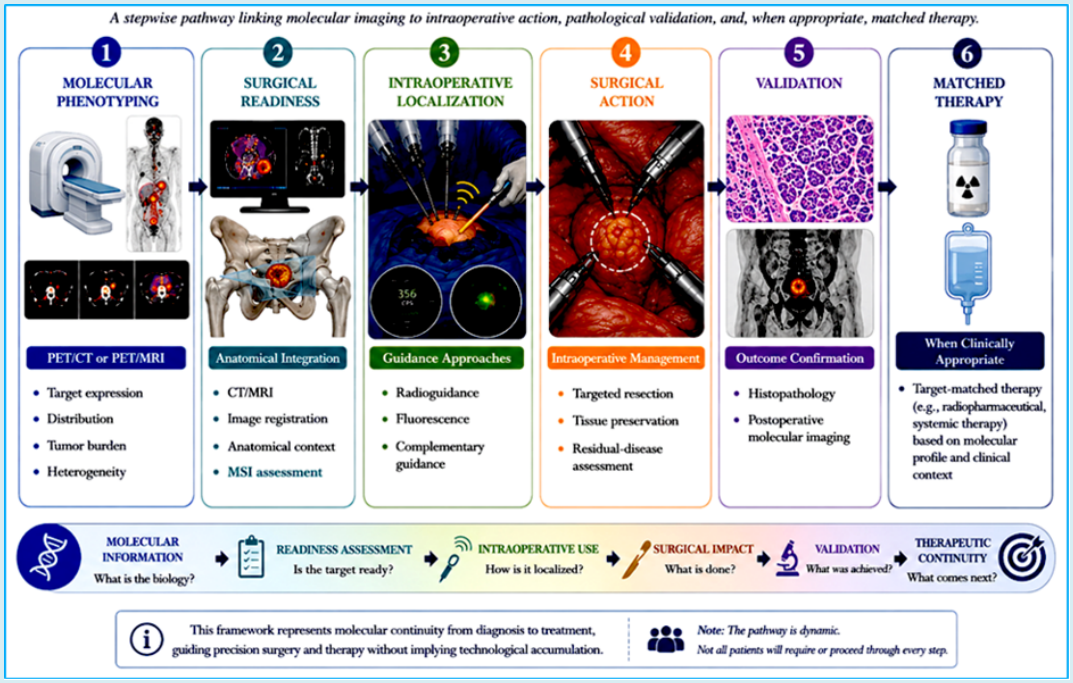


Figure 1: PET-to-Console Molecular Continuity Framework(Conceptual pathway linking PET-based molecular phenotyping with surgical readiness, intraoperative target localization, surgical action, pathological validation, and, when appropriate, molecularly matched therapy).

Stage 1. Molecular Phenotyping

Target-specific PET establishes the biological phenotype and distribution of disease, including target expression, lesion location, disease burden, and, where measurable, molecular heterogeneity. PET/CT or PET/MRI provides the initial map for identifying and prioritizing lesions for potential surgical management. In theranostic settings, the same phenotype may also inform subsequent target-matched therapy [7].

PET positivity, however, should not be considered equivalent to surgical suitability. Uptake may vary with lesion size, target density, biological specificity, and anatomical context. Molecular phenotyping therefore defines the

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biological starting point but should not independently determine operative intervention.

Stage 2. Surgical Readiness

The molecular phenotype must next be integrated with its anatomical and operative context. PET findings are correlated with CT, MRI, or other anatomical information to establish relationships between target-positive lesions, vessels, organs, surgical planes, and critical structures. Registration accuracy and tissue deformation are particularly relevant because preoperative imaging may not precisely reflect the anatomy encountered during surgery [8].

The proposed Molecular Surgical Index (MSI) provides a conceptual bridge at this stage. Rather than treating PET positivity as sufficient justification for intervention, MSI considers four dimensions: molecular detectability, intraoperative performance, surgical actionability, and clinical validation. A target would progress toward operative use only when molecular information supports a defined surgical purpose. MSI remains a research construct and has not been clinically validated.

Stage 3. Intraoperative Molecular Action

Once surgical readiness is established, the intraoperative modality should be selected according to target biology, lesion depth, accessibility, signal characteristics, and the intended surgical task. Radioguidance may support localization of deep or occult targets, whereas fluorescence may provide high-resolution visualization of accessible molecularly labelled tissue. Complementary modalities can further connect preoperative PET characterization with intraoperative localization [9].

The robotic platform provides the operative interface through which molecular information may guide localization, dissection, and resection. Its potential value is particularly relevant for small, occult, recurrent, multifocal, or anatomically challenging lesions. Nevertheless, robotic capability alone does not demonstrate molecular benefit [10]. Clinical utility should instead be assessed by whether molecular guidance changes operative decisions, improves target-positive tissue removal or residual-disease assessment, or facilitates preservation of non-target structures.

Thus, the framework follows:
Molecular phenotype → Surgical readiness → Intraoperative molecular action

This three-stage sequence is illustrated in Figure 1, while the principal clinical tasks and corresponding molecular guidance modalities are summarized in Table 1.

Clinical Requirement	Preferred Approach	Translational Status
Whole-body molecular mapping	Target-specific PET/CT or PET/MRI	Established
Preoperative surgical localization	PET integrated with anatomical imaging	Emerging
Deep or occult target detection	Intraoperative radioguidance	Clinically emerging
High-resolution visualization	Targeted fluorescence	Clinically emerging
Precise minimally invasive manipulation	Robotic surgery	Established
Residual-disease assessment	Intraoperative molecular assessment with pathological correlation and postoperative PET	Emerging
Treatment of disseminated target-positive disease	Matched radiopharmaceutical therapy	Established for selected targets

Table 1: Task-Based Selection Of Molecular Guidance Modalities Within The PET-To-Console Framework.

Progression between stages should remain evidence-dependent rather than automatic. PET establishes the biological target, anatomical imaging defines its surgical context, MSI assesses readiness, and validated intraoperative guidance supports localization. Histopathology remains the reference standard for tissue and margin assessment, while postoperative molecular imaging may provide complementary information when clinically appropriate [11].

The framework's principal contribution is therefore molecular continuity rather than technological accumulation. It establishes a structured pathway for determining when molecular information can progress from detection to readiness and ultimately to surgical action. Prospective studies are required to establish whether this approach changes surgical decision-making and improves pathological, functional, or patient-centred outcomes.

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Molecular Surgical Index: from PET Positivity to Surgical Readiness

A major translational challenge in molecularly guided surgery is determining whether a PET-defined target has sufficient biological validity, intraoperative detectability, and clinical relevance to justify surgical action. PET positivity establishes a molecular phenotype but does not demonstrate that the target can be reliably localized during surgery, alter operative strategy, or improve patient outcomes. Evidence addressing these requirements is distributed across nuclear medicine, molecular imaging, surgery, pathology, and theranostics. We therefore propose the Molecular Surgical Index (MSI) as a target-readiness framework linking four sequential domains:
Molecular detectability → Intraoperative performance → Surgical actionability → Clinical validation

The MSI complements established imaging, pathological assessment, and multidisciplinary clinical judgment. Its central principle is that PET positivity represents the starting point for surgical evaluation, not evidence of surgical readiness.

Molecular Detectability

This domain establishes whether the target can be reliably characterized before surgery. Relevant parameters include target expression, lesion visualization, target-to-background characteristics, lesion size, distribution, and biological heterogeneity. PET/CT or PET/MRI provides the molecular map for identifying potential surgical targets [12]. However, uptake may be influenced by biological heterogeneity, nonspecific accumulation, lesion size, partial-volume effects, and other imaging limitations. The output is therefore a credible molecular phenotype rather than an indication for intervention.

Intraoperative Performance

The second domain determines whether the PET-defined target can be reliably localized within the operative field. Assessment may include sensitivity, specificity, signal-to-background ratio, lesion depth, spatial resolution, localization accuracy, detection thresholds, and reproducibility. Tissue deformation, organ motion, altered anatomy after dissection, lesion depth, and differences between preoperative imaging and operative conditions can impair this translation [13]. Radioguidance may facilitate detection of deep or occult targets, whereas fluorescence can provide high-resolution visualization of accessible lesions. Modality selection should therefore reflect validated performance and the specific surgical task. The output is a target that can be reproducibly localized intraoperatively.

Surgical Actionability

The third domain determines whether molecular localization supports a defined operative decision. Potential applications include identifying occult target-positive tissue, modifying resection, directing targeted sampling, assessing suspected residual disease, or preserving non-target structures [14].

A detectable target may still have limited surgical value if its identification does not change management or provide a demonstrated clinical advantage. Actionability should therefore be evaluated against predefined questions, including whether molecular guidance identifies additional pathological disease, changes the operative plan, improves target-positive resection, or provides information unavailable from conventional imaging and surgical assessment.

The output is a molecular signal linked to a clinically meaningful surgical purpose.

Clinical Validation

The final domain evaluates whether molecularly guided decisions are supported by pathological and patient-level evidence. Intraoperative findings should be correlated with histopathology, the reference standard for tissue characterization and margin assessment. Relevant outcomes include pathological concordance, false-positive and false-negative findings, residual disease, margin status, recurrence, complications, functional outcomes, and patient-centred measures [15]. Technical performance alone cannot establish clinical benefit. Additional molecularly positive tissue may be detected without demonstrating improved disease control, while a negative intraoperative signal cannot necessarily exclude microscopic disease.

MSI as a Target-Readiness Continuum

The MSI integrates these domains into a progressive evidence pathway (Figure 2). It addresses four sequential questions: Can the target be reliably characterized? Can it be localized during surgery? Can localization change a meaningful surgical decision? Does molecularly guided action improve clinically relevant outcomes? This structure distinguishes translational maturity from simple PET positivity. PSMA represents a relatively advanced example because molecular imaging and intraoperative radioguidance have demonstrated clinical feasibility, although a fully integrated PET-to-surgery-to-therapy pathway remains insufficiently validated. SSTR, FAP/FAPI, and HER2 require target-specific evaluation [16].

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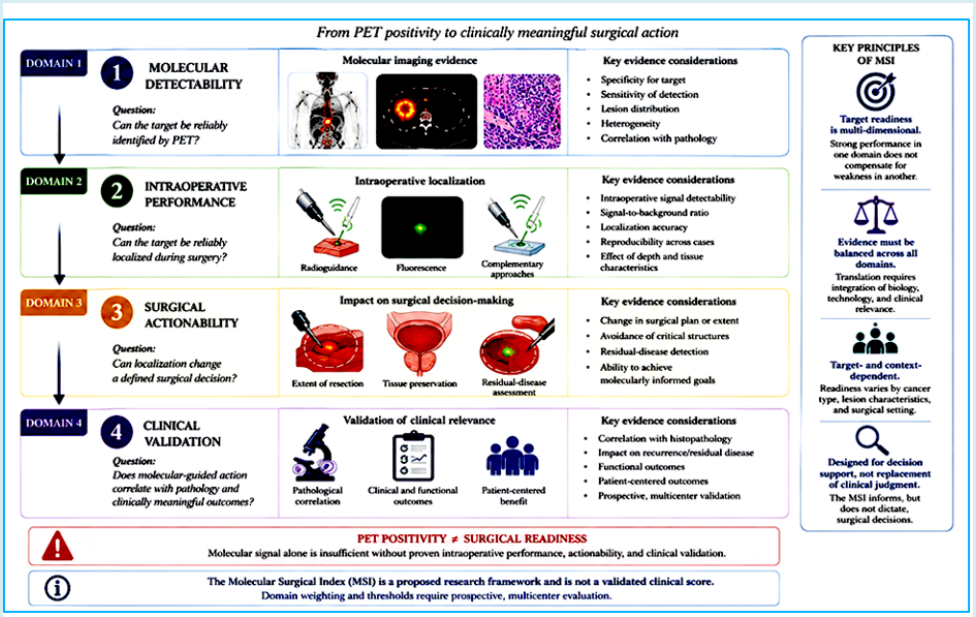


Figure 2: Molecular Surgical Index for Target Readiness (Proposed four-domain framework assessing molecular detectability, intraoperative performance, surgical actionability, and clinical validation to distinguish PET positivity from surgical readiness.

Contribution of the MSI

The MSI does not introduce a new biomarker or favor a particular intraoperative technology. Its contribution is a decision architecture for assessing molecular readiness before surgical implementation. By separating detectability, intraoperative performance, actionability, and clinical validation, it provides a structured basis for comparing molecular targets and identifying evidence gaps. The MSI remains a research framework, not a validated clinical index. Its operational definitions, thresholds, weighting, reproducibility, and association with pathological and patient-centred outcomes require prospective, disease-specific, multicentre evaluation. Its ultimate value will depend on whether it can distinguish targets genuinely ready for surgical translation from those that remain technically promising but clinically investigational.

Intraoperative Molecular Guidance and Robotic Theranostic Integration

PET provides the preoperative molecular map, whereas surgery requires reliable target localization within a dynamic anatomical field. The translational challenge is to convert molecular information into an intraoperative signal that supports a defined surgical decision. Modality selection should therefore reflect target biology, lesion depth, accessibility, signal characteristics, and clinical task, rather than technological complexity.

From PET-defined Targets to Intraoperative Localization

Target-specific PET identifies molecularly active lesions, while CT or MRI establishes their anatomical relationships for operative planning. During surgery, tissue deformation, organ motion, lesion depth, and changing anatomy may reduce correspondence between the preoperative molecular map and the operative field.

Radioguidance can facilitate localization of deep or occult targets, whereas fluorescence provides high-resolution visualization of accessible lesions. Complementary approaches may be appropriate when both depth sensitivity and surface visualization are required. PSMA-directed studies demonstrate the feasibility of radioguided localization, while dual-modality probes have linked preoperative PET/CT with intraoperative fluorescence imaging [17]. The preferred approach should remain task-specific and evidence-based. β-particle guidance, Cerenkov imaging, augmented reality, and automated navigation remain investigational and require prospective evaluation.

Robotic Surgery as the Operative Interface

Robotic surgery provides a platform through which molecular localization can potentially support precise tissue manipulation, particularly for small, occult, recurrent,

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multifocal, or anatomically challenging targets. However, displaying molecular information at the console does not establish clinical benefit. Its value should be determined by whether molecular guidance changes operative strategy, improves localization or resection accuracy, facilitates preservation of non-target tissue, or strengthens residual-disease assessment and functional outcomes [18]. Molecularly guided robotic surgery should therefore be regarded as a translational strategy requiring clinical validation, rather than inherently superior to conventional surgery.

Extending Molecular Information Beyond Surgery

Molecular information may potentially extend across the treatment pathway:

PET characterization → intraoperative localization → surgical action → pathological assessment → postoperative molecular assessment → matched therapy

PSMA-directed prostate cancer provides the most mature example. PSMA PET can characterize target-positive disease, while PSMA-radioguided robotic procedures demonstrate intraoperative localization [19]. The same target may subsequently support PSMA-directed radiopharmaceutical therapy in selected patients. However, these established components do not yet constitute a prospectively validated closed-loop surgical-theranostic pathway.

Somatostatin-receptor imaging and peptide receptor radionuclide therapy represent an established theranostic paradigm in selected neuroendocrine tumors, whereas FAPI/FAP- and HER2-directed approaches remain less mature for surgical applications [20]. Their potential surgical roles should therefore be evaluated independently according to molecular detectability, intraoperative performance, surgical actionability, and clinical evidence.

Task-Based Selection of Molecular Guidance

The framework prioritizes clinical requirement over technological accumulation. This hierarchy defines a clinical rather than technological pathway: PET establishes the molecular phenotype, anatomical imaging provides surgical context, and the least complex validated intraoperative modality is selected according to the intended task. When the same molecular target remains clinically relevant after surgery, molecular information may subsequently contribute to treatment selection [21]. Importantly, the presence of a molecular signal does not by itself establish surgical readiness. Within the MSI framework, intraoperative guidance must demonstrate sufficient performance to support surgical action, while subsequent therapeutic use requires independent clinical evidence. Thus, radioguidance, fluorescence, robotics, and theranostics function as enabling components of molecular continuity rather than separate innovations.

The proposed pathway can therefore be summarized as:

Molecular phenotype → target readiness → intraoperative localization → surgical action → pathological validation → matched treatment

Its clinical value remains an empirical question. Prospective and multicentre studies should determine whether maintaining molecular information across these stages improves target-positive resection, residual-disease assessment, tissue preservation, functional outcomes, treatment selection, or long-term disease control [22].

Molecular Residual-Disease Assessment

Surgical completeness is ultimately established by histopathology, but pathological margin assessment occurs after tissue removal. Molecular imaging and intraoperative guidance may provide complementary information during resection by identifying target-positive tissue that remains in the operative field or by highlighting suspicious areas requiring further evaluation. Their role is therefore not to replace pathology, but to provide an earlier molecular signal that may permit corrective action while surgery is still underway [23].

This approach may be particularly valuable for small, multifocal, recurrent, nodal, or anatomically indistinct disease. In PSMA-directed surgery, intraoperative radioguidance has demonstrated the feasibility of identifying molecularly suspicious tissue with subsequent pathological correlation in selected cases. Similarly, intraoperative specimen PET/CT has shown potential for identifying PSMA-avid lesions and areas associated with positive or close histopathological margins [24]. These findings support further evaluation of molecular assessment as an adjunct to conventional margin assessment.

The clinical value, however, depends on actionability rather than signal detection alone. A molecular signal may prompt targeted inspection, additional sampling, or selective resection when interpreted alongside anatomy and operative findings. Conversely, a negative signal cannot exclude microscopic residual disease because detection may be limited by lesion size, heterogeneous target expression, or insufficient tracer uptake. Molecular uptake may also occur in non-malignant or biologically inactive tissue. Histopathological confirmation therefore remains essential.

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We propose molecular residual-disease assessment as an integrated endpoint linking preoperative molecular imaging, intraoperative detection, surgical findings, and postoperative pathology. Its value should be judged by whether it improves residual-disease or margin assessment while avoiding unnecessary tissue removal and procedural morbidity [25].

Prospective, disease- and target-specific studies should establish detection thresholds and evaluate concordance with histopathology. Further research should determine whether molecular guidance changes resection decisions, improves margin assessment, preserves non-target tissue, and ultimately affects recurrence, functional outcomes, or long-term disease control. Until such evidence is established, molecular residual-disease assessment should remain an adjunctive decision-support approach, with histopathology retained as the definitive reference standard.

Artificial Intelligence as an Enabling Layer

Artificial intelligence (AI) may support the integration of molecular, anatomical, and intraoperative information within the PET-to-console framework. Its near-term role should be considered primarily as decision support rather than autonomous surgical control. By integrating PET, CT/MRI, and intraoperative imaging data, AI may assist with lesion segmentation, molecular target mapping, image registration, and interpretation of radioguided or fluorescence signals [26].

The potential value of AI should be assessed by its ability to improve clinically relevant tasks, including target localization, registration accuracy, residual-disease assessment, tissue preservation, or operative efficiency, rather than by algorithmic complexity alone. Continuously updated multimodal or "digital molecular" models remain investigational and should not be presented as established clinical capabilities.

Before integration into routine molecularly guided surgery, AI-assisted approaches require prospective evaluation, external validation, standardized datasets, transparent performance assessment, and systematic evaluation of automation-related errors [27]. Accordingly, AI is positioned in this framework as an enabling layer between molecular imaging and surgical judgment, while responsibility for interpretation and operative action remains with the surgeon.

Target-Specific Translational Maturity and Near-Term Clinical Potential

The potential for PET-informed molecular surgery is unlikely to be uniform across targets or cancer types. Rather than assuming that every PET-visible lesion is suitable for intraoperative translation, the proposed framework evaluates targets according to molecular characterization, intraoperative detectability, surgical actionability, therapeutic compatibility, and clinical evidence. This target-centred approach applies the Molecular Surgical Index (MSI) while distinguishing established theranostic pathways from emerging surgical opportunities.

PSMA: The Most Mature Model

Prostate-specific membrane antigen (PSMA) currently provides the strongest clinical model for the PET-to-console concept. PSMA PET is established for molecular characterization of prostate cancer, while PSMA-radioguided surgery has demonstrated intraoperative localization during robotic procedures. PSMA-targeted fluorescence further illustrates the potential to connect preoperative molecular imaging with intraoperative visualization, while PSMA-directed radiopharmaceutical therapy provides an established therapeutic application in appropriately selected patients [28].

These components should not, however, be interpreted as evidence of a fully validated PET-to-surgery-to-therapy pathway. Rather, PSMA represents the most suitable near-term model for prospective MSI evaluation because multiple stages of the molecular-to-surgical continuum already have supporting clinical evidence.

Somatostatin Receptors: Mature Theranostics, Limited Surgical Translation

Somatostatin-receptor (SSTR) imaging and peptide receptor radionuclide therapy are established in selected patients with neuroendocrine tumors. However, established imaging-therapy integration does not automatically establish readiness for receptor-guided surgery. Intraoperative SSTR-directed applications remain considerably less developed than PSMA-based approaches. SSTR therefore illustrates a target with high molecular and therapeutic maturity but limited surgical maturity [29]. The MSI can help distinguish these stages and prevent established theranostic capability from being equated with surgical readiness.

FAP/FAPI: Promising but translational

Fibroblast activation protein (FAP) is an attractive target because its expression in cancer-associated fibroblasts occurs across several solid tumors. FAPI PET can characterize FAP-associated disease and contribute to staging and treatment planning, while FAP-directed radioligand therapy remains under investigation [30]. Translation to molecularly guided surgery is less mature,

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with limitations including heterogeneous target expression, tracer variability, limited intraoperative evidence, incomplete pathological correlation, and insufficient long-term outcome data. Moreover, FAP uptake may reflect stromal biology rather than viable malignant cells. Consequently, high FAPI uptake should not independently justify molecularly guided resection. Prospective studies must establish reproducible intraoperative detection and demonstrate that acting on the signal improves a defined surgical outcome [31,32].

HER2 and Other Emerging Targets

HER2, integrins, and hypoxia-related targets remain at earlier or heterogeneous stages of development. Their surgical potential depends on target specificity, tracer performance, lesion-to-background characteristics, intraoperative detectability, therapeutic compatibility, and clinical validation. HER2 demonstrates this distinction: molecular imaging can characterize target expression, but evidence for routine HER2-guided robotic surgery remains insufficient [33,34].

These targets should therefore be considered investigational candidates for MSI evaluation, rather than established components of the PET-to-console pathway.

Translational Prioritization

The current evidence supports a staged, target-specific approach to molecularly guided surgery rather than assuming that all PET-defined targets have equivalent surgical readiness (Table 2). PSMA represents the most advanced translational model within the framework, with established molecular imaging, demonstrated intraoperative radioguidance, emerging integration with robotic surgery, and an established therapeutic application in selected patients. In contrast, SSTR illustrates a target with established imaging and theranostic applications but comparatively limited intraoperative surgical evidence. FAP/FAPI and HER2 remain at earlier stages of surgical translation, with evidence gaps involving intraoperative localization, target heterogeneity or specificity, pathological correlation, and clinical validation. These differences emphasize that PET-based target detection alone is insufficient to establish surgical readiness. Instead, progression toward molecularly guided surgery should require evidence across the MSI domains of molecular detectability, intraoperative performance, surgical actionability, and clinical validation. This target-specific approach provides a structured basis for identifying evidence gaps and prioritizing prospective evaluation while avoiding premature translation of molecular imaging signals into unvalidated surgical practice [35,36].

Molecular target	Molecular imaging maturity	Intraoperative surgical evidence	Theranostic maturity	Overall translational position
PSMA	Established	Demonstrated/clinically emerging	Established for selected patients	Most mature
SSTR	Established	Limited	Established for selected patients	Theranostic mature; surgical translation limited
FAP/FAPI	Emerging	Limited	Emerging	Translational
HER2	Emerging	Limited/investigational	Developing	Investigational
Other targets	Variable	Limited	Variable	Target-specific evaluation required

Table 2: Target-Specific Translational Readiness For Molecularly Guided Surgery Within The MSI Framework.

What this Framework Adds Beyond Existing Approaches

The proposed framework does not claim novelty from PET, radioguidance, fluorescence, robotic surgery, image registration, artificial intelligence, or radiopharmaceutical therapy individually. These technologies have each been investigated in molecular imaging, image-guided surgery, or theranostic oncology. The contribution lies instead in organizing these components within a target-readiness architecture that defines how molecular information can progress from imaging to surgical action [37].

Three distinctions are central. First, molecular detectability is not equivalent to surgical readiness; a PET-positive target may not be suitable for intraoperative intervention. Second, intraoperative localization is not equivalent to surgical actionability; detecting a target does not demonstrate that acting on it will alter management. Third, technical feasibility is not clinical validation; successful localization does not establish improved resection, residual-disease control, functional preservation, or patient outcomes.

The PET-to-console framework therefore provides a molecular continuity architecture linking preoperative

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phenotyping, anatomical planning, intraoperative localization, pathological assessment, and, where appropriate, target-matched therapy. Within this pathway, radioguidance, fluorescence, robotics, and AI function as enabling technologies selected according to the clinical task rather than as independent indicators of innovation [37,38].

The principal conceptual contribution is the Molecular Surgical Index (MSI), which organizes target readiness across four sequential domains:

Molecular detectability → Intraoperative performance → Surgical actionability → Clinical validation

This structure addresses a fundamental translational question: when is a molecular target sufficiently mature to influence a surgical decision? The MSI is therefore proposed as a research framework for comparing targets, identifying evidence gaps, and prioritizing prospective validation rather than as a validated clinical score.

A complementary task-based principle guides technology selection. PET may establish molecular phenotype, radioguidance or fluorescence may enable intraoperative localization, robotics may provide the operative interface, and histopathology remains the reference standard for definitive tissue assessment [39].

Accordingly, the innovation is conceptual and translational rather than technological. Its value lies in providing a structured pathway for evaluating molecular information before surgical use while separating detection, intraoperative performance, actionability, and clinical benefit. Whether this architecture improves surgical decision-making or patient outcomes remains unproven and requires prospective, disease-specific, multicentre validation [40].

Major Barriers to Clinical Translation

Despite its potential, PET-informed robotic theranostic surgery faces several barriers before molecular guidance can become a reliable clinical strategy. The principal challenge is not any single technology, but the coordinated integration of target biology, molecular imaging, intraoperative detection, surgical workflow, and clinical validation.

Biological heterogeneity is a fundamental limitation. Target expression may vary between primary and metastatic lesions or change with disease progression and treatment. Moreover, non-malignant uptake, including inflammation, can produce PET-positive findings. Molecular uptake should therefore be interpreted alongside anatomical and pathological evidence rather than assumed to represent surgically actionable tumor [41].

Translating molecular information into the operative field presents a second challenge. PET provides whole-body molecular mapping, but spatial resolution, partial-volume effects, tissue deformation, organ motion, and changes after tissue removal can compromise PET-to-operative registration. Reliable registration and calibration will therefore be essential for accurate navigation [42].

Intraoperative signal interpretation also requires standardization. Fluorescence is influenced by tissue penetration and background signal, whereas radioguidance depends on detector characteristics, counting statistics, background activity, and lesion depth. Disease- and device-specific thresholds will therefore need prospective validation.

Finally, technical feasibility does not establish clinical benefit. Current evidence remains concentrated in selected cancers and early-stage studies. Prospective multicentre evaluation should use predefined molecular thresholds, standardized pathological reference standards, and clinically meaningful endpoints. Workflow, safety, regulatory, and implementation requirements must also be addressed through multidisciplinary collaboration involving nuclear medicine, surgery, radiopharmacy, pathology, engineering, and radiation safety [43,44].

Ultimately, the critical question is whether molecular guidance changes surgical decisions and improves patient outcomes, rather than whether multiple technologies can be technically combined.

Conclusion

The next step in precision oncology may be to connect, rather than further expand, molecular imaging, robotic surgery, intraoperative guidance, pathology, and theranostics around a shared target. We propose PET-to-console precision robotic theranostic surgery as a translational framework in which PET defines tumor biology, molecular guidance supports intraoperative localization, and pathology provides definitive validation, with matched therapy considered when clinically appropriate. The central premise is that molecular information should remain actionable across the treatment pathway while preserving surgical judgment and human oversight. The immediate priority is therefore clinical validation, not technological accumulation. Prospective studies should determine whether this approach improves target detection, resection completeness, residual-disease assessment, tissue preservation, treatment selection, and patient outcomes. Technical feasibility alone cannot establish clinical benefit. The framework should consequently be regarded as a testable hypothesis that, if validated, could

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move precision surgery from molecularly informed planning toward molecularly guided decision-making.

Credit Authorship Contribution Statement

Mohammad Nadeem Khan: - Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Resources, Visualization, Validation, Writing - original draft, Writing - review & editing, Project administration, Supervision.
Mahak Bhandari: - Conceptualization, Clinical interpretation, Surgical interpretation, Writing - review & editing, Validation, Supervision.
Ashok Kumar: - Conceptualization, Visualization, Supervision, Validation, Writing - review & editing.

Ethics Approval and Consent to Participate

This study is a perspective review based on the analysis and synthesis of previously published clinical and preclinical research. No new experiments involving human participants or animals were conducted. Therefore, ethical approval and informed consent were not required.

Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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