JNM State of the art:

Prostate-specific membrane antigen guided surgery

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Noteworthy:

- The superior predictive diagnostic accuracy of PSMA-ligand PET for metastatic prostate cancer lesions (e.g. lymph nodes) has provided a basis of PSMA-targeted surgical resections
- For nodal staging or management of local lymphatic metastases currently extended pelvic lymph node dissection is considered the standard approach
- Radioactive labelling of sentinel lymph nodes in primary prostate cancer and PSMA-based targeting of metastases in recurrent prostate cancer intend to increase diagnostic and therapeutic results
- Technical developments in tracer design (e.g. fluorescent PSMA ligands and hybrid $^{99m}$Tc/fluorescent PSMA ligands combining both approaches) as well as hardware developments (e.g. drop-in gamma probes for minimal-invasive robotic surgery) are likely to advance the field of image guided urology
- Oncological benefit of and indication for PSMA-targeted approaches still have to be more precisely defined
ABSTRACT:
Since its introduction in the diagnostic pathway of prostate cancer management, prostate-specific membrane antigen (PSMA)-ligand positron-emission tomography (PET) has demonstrated great potential. PSMA-ligand imaging is increasingly influencing therapeutic decision making although its impact on patient outcomes still needs to be defined. One relatively new application, enabled through chemical and engineering efforts, is PSMA guided surgery. In this review, the potential of PSMA guided surgery is highlighted and its implications on lymph node dissection in primary and recurrent prostate cancer are discussed.
PROSTATE CANCER, LOCO-REGIONAL LYMPHATIC SPREAD AND OLIGOMETASTASES

Lymph nodes represent one of the most frequently affected sites by recurrent prostate cancer (PC). Recognizing the exact state and extent of lymphatic spread represents a complex challenge. Beside the application of several clinical variables such as histology from biopsy or previous surgery, prostate-specific antigen (PSA) value and PSA velocity and nomograms, sensitive molecular imaging can substantially move the field forward.

Nodal tumor infiltration can be considered as locoregional progressive disease or as a state between localized disease on one side and oligometastatic disease where a few (commonly less than 3 to 5) metastatic lesions are located outside the pelvic lymph nodes and systemic metastatic disease on the other side. Patients with early locoregional lymphatic metastatic disease exhibit a better prognosis. As a result, locoregional lymphatic metastatic disease should be distinguished from the oligometastatic disease at other sites (e.g. bone), which is more closely related with systemic metastatic disease (1). Thus, localized treatment in this early state of metastasis might yield even better oncological control than local treatment of oligometastatic disease.

Upon progression of local PC, cancer cells hijack the lymphatics originating from the prostate itself or surrounding tissues. In the lymphatics these cells travel to draining lymph nodes. Within the lymphatic sinus cancer cells can reside, multiply and form tumor satellites that progress from micro- to macrometastases (usually defined as tumor deposits > 2mm) (2). In primary PC natural local lymphatic drainage is preserved. Nevertheless, lymphatic drainage may vary substantially between individuals. As a result, in a significant proportion of patients, also metastatic lymph nodes are found outside the classical template of an extended pelvic lymph node dissection (ePLND) (3). Additionally, there are reports about tumor-based blockages in lymphatic ducts or lymph nodes, which could induce a diversion of conventional lymphatic dissemination pathways (4). Therapeutic interventions like radical prostatectomy or radiation therapy may significantly impact lymphatic drainage pathways. For this reason, in recurrent PC metastases may occur in unexpected locations. These metastases are thought to rise from cancer cells that escaped the tumor prior to radical prostatectomy and have resided in the surrounding tissue or lymphatics or, in case of primary radiation therapy, might also spread from the prostate itself. To recognize the exact state and extent of disease in recurrent PC represents a great challenge and remains complex, but significantly impacts proposed treatment (Figure 1). Beside the use of several clinical variables such as primary histology, serum PSA and PSA kinetics, molecular positron-emission tomography (PET) imaging with the use choline-based tracers and especially of tracers directed against the prostate-specific membrane antigen (PSMA) has helped to move the field forward substantially (5-7).
PSMA-LIGAND PET IMAGING

PSMA, albeit not as specific as its name suggests, shows a significant overexpression (100- to 1000-fold) on most PC cells (>90%) (8,9). Within the last decade several small-molecular radiotracers have been developed for PET imaging for staging and restaging of PC (10). Today, there is no clear evidence of the superiority of one of the clinically available radiotracers. PSMA-ligand PET is able to visualize metastatic lesions both at low PSA values (11-15) and at small size (16). Similar to other imaging techniques, detection efficacy decreases with lesions size in PSMA-ligand PET. It should be noted that additionally detection is directly linked to the magnitude of PSMA overexpression in a metastasis. In a meticulous analysis in recurrent PC patients undergoing salvage lymph node dissection (sLND) PSMA-ligand PET detection rates for metastases were >50% and >90% when the short axis diameter of the metastatic lesion was >2.3 and >4.5mm (17). It can be expected that the same holds true also for primary lymph node metastases. Also, the travel pathway of positron emissions in tissue limits the intrinsic spatial resolution of clinical PET-imaging and is dependent on the nuclide used (e.g. $^{68}$Ga, $^{18}$F). As a result, micrometastases (< 2mm) cannot be accurately detected by PSMA-ligand PET. Nevertheless, PSMA-ligand PET clearly outperforms conventional computed tomography (CT) or magnetic resonance imaging (MRI) where lymph node (LN) metastasis are only detected if the size exceeds 8-10mm (18,19). Only lymphatic surgical mapping technologies provide an alternative for the identification of < 2mm micrometastases.

Currently, there is still no evidence that clinical decisions based on PSMA-ligand PET improves oncological outcomes in the management of PC (20). As a result, several guidelines like the guideline of the European Association of Urology do not explicitly recommend nor disregard PSMA-ligand PET in the primary staging setting. Despite this, PSMA-ligand PET is increasingly being used and evaluated in primary high-risk PC patients. In patients with recurrent PC, however, several guidelines changed recently and the most recent European Association of Urology guideline advocates the use of PSMA-ligand PET after radical prostatectomy when the PSA level is > 0.2 ng/mL and when the results will influence subsequent treatment decisions (Level IIb evidence, weak recommendation) (20). In addition, it is recommended as the primary imaging modality in biochemical recurrence after primary curative radiation therapy (Level IIb evidence, strong recommendation).

PSMA GUIDED SURGERY AS MOLECULAR TARGETED PRECISION SURGERY

In patients with biochemical recurrence after primary curative-intended radical prostatectomy salvage external beam radiotherapy is recommended when a local recurrence is suspected in the absence of detectable distant metastases. Equally, salvage prostatectomy might be considered for local recurrences after primary radiotherapy or ablative treatment in selected cases as a potentially curative therapy option. In case of distant recurrence, or failure after salvage procedures, the conventional approach is to use systemic treatment with androgen deprivation, or chemo-hormonal therapy, usually considered as palliative treatment (20). However, with increasing advances in molecular
imaging, such as choline-based and more recently PSMA-ligand PET-CT, small volume metastatic
disease to lymph nodes can be detected with great accuracy, prompting clinicians to undertake local
salvage treatments using radiation or sLND. When selecting surgery for nodal recurrence, a bilateral
ePLND adhering to the standard primary ePLND templates is most commonly advised (20).

Molecular imaging can provide localization of lymph node metastases prior to surgery and as
such a road-map to guide sLND or salvage radiotherapy. Several series mainly based on choline
PET have suggested an oncological benefit in selected patients (21-31). The increasing
implementation of sLND have raised intense discussions on the extent of the template that should be
treated locally. It clearly depends on the extent of prior PLND as well as the accessibility of anatomical
areas and last but not least on the localization of suspected lymph node metastases on preoperative
imaging.

Even with having a detailed surgical road-map provided by PSMA-ligand PET, reliable
intraoperative identification and removal of metastatic lymph nodes is challenging as these lesions
might be atypically located, small-sized, and/or morphologically unrecognizable. Here, intraoperative
guidance is of great value. To cover applications in image guided surgery new PSMA tracer
compounds have been and are still being developed. The first clinical implementation of such tracers
can be found in PSMA radioguided surgery (Figure 2a) (32-34). On the basis of PSMA-directed
DOTA-conjugated EuK(=Glu-urea-Lys)-based inhibitors the DOTAGA-conjugate PSMA-I&T (imaging
& therapy) has been developed and optimized for increased PSMA affinity as well as in vivo stability
(33,35). In this respect, this DOTAGA-based ligand proofed advantageous as it forms stable
complexes with a broad variety of radiometals (36). Initially $^{111}$In ($t_{0.5} = 2.8$ d, $E(\gamma) = 173, 245$ keV)
was chosen in previously developed PSMA-I&T ligands as $\gamma$-emitter for radioguided surgery (33). In
biodistribution studies in LNCaP xenograft-bearing mice $^{111}$In-PSMA-I&T showed further reduction of
hepatobiliary excretion and almost exclusive renal excretion due to its reduced lipophilicity,
demonstrated slightly reduced background signal, but comparable tumor uptake translating in
superior tumor/background ratios (33). Further refinement in PSMA-targeting tracers for radioguided
surgery were triggered due to the high radiation exposure and restricted availability of $^{111}$InCl$_3$ as well
as its high costs. Thus, the concept was adapted to allow for $^{99m}$Tc-labeling as it represents a cheap,
readily available alternative radionuclide used as standard radionuclide in nuclear medicine and
radioguided surgery (34). Compared with $^{111}$In-PSMA-I&T, newly developed $^{99m}$Tc-mas3-γ-nal-k(Sub-
KuE) ($^{99m}$Tc-PSMA-I&S, imaging & surgery) showed delayed clearance kinetics due to high plasma
protein binding (94%) but identical uptake in PSMA-positive tissues 1 h after injection in a LNCaP
xenograft model. After at least 5h or more after injection excellent lesion-to-background ratios were
observed due to the synergistic effect of persistent $^{99m}$Tc-PSMA-I&S uptake and continuing clearance
of background activity that compared favorably with the performance of $^{111}$In-PSMA-I&T. These
characteristics led to a replacement of earlier $^{111}$In- PSMA-I&T (used in 31 patients) with currently
used $^{99m}$Tc-PSMA-I&S as tracer in PSMA radioguided surgery procedures (now used in over 250
patients) (37). Following staging via PSMA-ligand PET, patients have been selected for PSMA guided surgery in the setting of salvage surgery. Those patients that were thought to benefit from PSMA guided surgery mainly based on low PSA value and only few lesions on PSMA-ligand PET received a second intravenous injection of $^{111}$In-PSMA-I&T or $^{99m}$Tc-PSMA-I&S to facilitate intraoperative lesion identification (33,34). Following the administration of the $\gamma$-emitting PSMA tracers, single-photon emission computed tomography (SPECT)/CT imaging was performed to confirm concordance in tracer accumulation with preoperative PSMA-ligand PET. Here it has to be noted that due to the difference in sensitivity and spatial resolution, PSMA-ligand SPECT had the tendency to miss small lesions (Figure 3) (38). Intraoperatively, however, the use of a conventional gamma probe – similar to the ones used during sentinel node procedures (39) – allowed for accurate intraoperative detection of PSMA-positive lesions (Figure 4) that can be confirmed by autoradiographic studies (40). This concept was even compatible with the forward-thinking freehand SPECT technology (32).

Recently, the introduction of a so-called DROP-IN gamma probe (41) has allowed for PSMA guided surgery during robot-assisted laparoscopic surgery (Figure 2b) (42). Intraoperatively, gamma probes not only facilitate intraoperative in vivo guidance, but also enable ex vivo gamma probe measurements to confirm successful resection of these metastatic PC lesions with a specificity >95% for $^{99m}$Tc-PSMA-I&S (32,37). In case of positive identification, defined as measurements exceeding at least twice the background level of the patient’s non-cancerous fatty tissue, intraoperative frozen section histopathological analysis is no longer required to confirm successful resection of a PET positive lesion (37,43). Furthermore, adjacent resected tissues that were part of the LND can be examined for tumor presence by gamma probe measurements. If additional lesions are detected, the planned field of dissection can be extended to increase the probability of complete resection of all tumor-bearing tissue.

In the field of image guided surgery, next to radioguidance there is an increasing interest in fluorescence guidance approaches. The strength of having fluorescent tracers would be their ability to provide the operating surgeon with real-time optical lesion identification (Figure 5a,b). The value of such optical guidance is, however, somewhat limited as a result of light attenuation by tissue; light attenuation limits detectability to < 1cm deep in tissue, and impacts the detection sensitivity (44). While most of the fluorescence-based PSMA-targeting concepts are still confined to the preclinical stage, there is an ongoing clinical trial in the United Kingdom using a fluorophore conjugated reagent (45). Preliminary data suggests the fluorescence approach is feasible and highly likely to impact future care, with the increasing compatibility of multicolor fluorescence imaging with state-of-the-art laparoscopic and robotic surgical platforms (46,47). In order to combine the benefits of the radio- and fluorescence guided surgery concept, bimodal or rather hybrid tracers have been introduced in the clinic e.g. for sentinel node imaging in PC patients (48). The clinical impact of this work has also sparked the development of hybrid tracers for PSMA-targeted applications (Figure 5c). Examples of small-molecule hybrid PSMA-tracers under investigation in the preclinical arena are: $^{111}$In-LICOR-
800CW-Lys-DOTA-EuK (49), $^{68}$Ga-NIR 800CW-PSMA-11 (50), $^{68}$Ga-PSMA I&F (51), $^{99m}$Tc-EuK-(SO$_3$)Cy5-mas3 (52). These promising hybrid initiatives are further extended with ongoing efforts that explore Cerenkov imaging of $^{68}$Ga-PSMA-11 (Figure 5d) (53).

**COMPARISON OF PSMA GUIDED SALVAGE LYMPH NODE DISSECTION TO STANDARD APPROACHES**

Currently, PSMA guided surgery has been mostly used in recurrent PC. The main goal of metastasis-directed therapy in recurrent PC is to delay cancer progression and limit the associated toxicity of systemic palliative therapy (e.g. androgen deprivation) (31). While still considered experimental by guidelines, with the advancements of molecular imaging and especially since the introduction of PSMA-ligand PET, targeted salvage therapies like sLND or salvage radiotherapy are increasingly sought after in patients with minimal recurrent disease (54). However, diverging short-term outcomes after standard sLND based on PSMA-ligand PET are reported with rates of complete biochemical response (postoperative PSA < 0.2ng/ml) ranging between 19 and 59% (21,25,29,55,56). Some authors even conclude that sLND is neither appropriate to cure nor even to delay further systemic treatment (55). On one hand, these seemingly contradictory results might be due to patient characteristics with different likelihood of harboring systemic disease (23). To estimate the risk and to counsel patients about sLND or salvage radiotherapy, several clinical variables can be taken into consideration in addition to findings of PSMA-ligand PET imaging.

A recent large multi-institutional analysis evaluated significant predictors of early clinical recurrence (<12months) after sLND (25). Multivariate analysis suggests that higher Gleason grade group, shorter time from radical prostatectomy to rising PSA values, concurrent antiandrogen deprivation therapy, higher absolute PSA values besides higher number of lesions on PET as well as retroperitoneal localization are significant predictors of early clinical recurrence after sLND (25). On the other hand, poor outcomes could also be caused by incomplete removal of metastatic lesions (55). After previous ePLND and/or salvage radiotherapy the surgical field might be complicated by fibrotic changes. Small-sized metastatic lymph nodes could also be located in the deep pelvis and outside the usual field of dissection. Thus, especially in sLND, guidance using molecular targeted approaches like PSMA radioguided surgery has created much interest in the urological and nuclear medicine community (32,37,43,57,58).

In the largest series of 121 patients undergoing PSMA radioguided surgery, metastatic lesions could be removed in almost all patients (99%), leading to a complete biochemical response in 66% of patients. Low PSA and single lesion on PSMA-ligand PET were associated with higher likelihood of complete biochemical response (84%) and longer biochemical recurrence-free survival (14 months). However, it has to be noted that microscopic spread to neighboring lymph nodes cannot be detected using either PSMA-ligand PET or PSMA radioguided surgery. Although the extent of sLND using PSMA radioguided surgery (or sLND in general) is currently under intensive discussion,
treating only the suspicious lymph node on PSMA-ligand PET is not advisable. Conversely, sLND procedures should be accompanied by at least a clean dissection of the respective side. Still, emerging data seem to hint at the superiority of PSMA radioguided salvage surgery procedures compared to standard sLND (59). Main drawbacks for analysis and comparisons of sLND series are not only the differences in study populations and lack of long-term follow-up in most studies, but also the difference concerning evaluated endpoints or definitions of progression (23).

External beam radiotherapy is another treatment option for treating locoregional recurrence or oligometastatic disease. However, the comparison of sLND series to salvage radiotherapy is impeded even more by the different characteristics of treated patient cohorts. While a major portion of patients subjected to sLND do not harbor metastatic disease (M1) per definition, but instead present with molecular imaging-classified locoregional lymph node metastases, patients undergoing metastasis-directed therapy by radiation therapy often show oligometastatic bone lesions and thus represent truly M1 patients and consequently a more advanced disease state (31,60). Nevertheless, although oncological outcome data are still awaited, it is tempting to believe that sLND might provide benefits for locoregional lymph node metastases in fit patients as it shows a good safety profile, yields histological proof and allows radiotherapy as an additional treatment option.

In summary, PSMA-ligand PET enables early detection of metastatic lesions in recurrent PC and is currently recommended in this indication by the guidelines of the European Association of Urology (20). In selected and well-informed patients sLND can be discussed as an experimental approach on the basis of clinical characteristics as well as PSMA-ligand PET imaging, but should ideally be undertaken only in the context of well-conducted clinical trials. In addition, PSMA guided procedures might further enable precise intra-operative identification and removal of metastatic lesions, and thus might be a useful adjunct to sLND. Clinical trials to investigate oncological benefits of sLND as well as the benefit of management change on the basis of PSMA-ligand PET are now warranted.

**COMPARISON OF PSMA GUIDED PRIMARY LYMPH NODE DISSECTION TO STANDARD APPROACHES**

In primary PC, the goal of primary LND is twofold: 1. To stage disease status accurately; and 2. To achieve potential cure in a selected group of men with node-positive disease. However, there is no prospective evidence supporting the benefit of ePLND on oncological outcomes (61-66). This, combined with the perceived increased morbidity of the added procedure, is driving a decline in the practice of lymphadenectomy, except in the presence of high-grade/high volume disease. Current guidelines recommend treatment of the lymphatic drainage at time of radiotherapy or radical prostatectomy if the risk of nodal metastasis exceeds 5% by commonly used nomograms e.g. the Briganti, Partin and Memorial Sloan Kettering Cancer Center (MSKCC) nomograms (usually representing intermediate and high-risk PC) (67-69). It is also guideline recommendation that primary
PC patients with higher risk profile should not be spared ePLND irrespective of negative findings on imaging (20). As lymphatic drainage of primary PC is diverse, an ePLND is recommended at the time of surgery since the majority of involved lymph nodes are located in the internal, external and common iliac as well as the obturator fossa lymph node template fields (20,70). Thus, although ePLND has not shown improvement of oncological outcome yet, it currently represents the method of choice for correct staging and prognosis (26).

On the downside, ePLND might be associated with potential complications. This further reinforces the importance of precision surgery strategies that aide nodal dissections. These approaches need to accommodate for both, micro- and macrometastases. As the first draining lymph nodes in some patients might be located outside the usual proposed ePLND template, sentinel approaches targeting the lymph node have been proposed and have already shown additional value for correct lymph node staging as well as reduction of morbidity (71,72). In a recent systematic review, different lymphatic mapping techniques have shown a high sensitivity of 95.2% as well as a high negative predictive value of 98.0% compared to ePLND and seem to improve the nodal yield when combined with ePLND (20,73).

When trying to identify macrometastases, PSMA-ligand PET seems to be the method of choice and could influence the clinical management like e.g. extending the dissection of regular ePLND in case of out-of-template lymph node metastases. Although PSMA-ligand PET shows higher sensitivity as compared to conventional imaging it still falls short for detection of small-sized metastatic lesions hindering its use to preclude patients without evidence of nodal disease from ePLND. Thus, for the identification of micrometastases in the lymphatics it seems one still needs to revert to traditional lymphatic mapping approaches mentioned above (72).

Will PSMA guided surgery impact clinical care in the primary treatment of PC? In theory, it could be used in primary high-risk, high volume PC patients with evidence of lymph node positive disease on PSMA-ligand PET (32). However, the likelihood that additional small lymph node metastases are present in primary PC that are not detected by PSMA-ligand PET is likely and clinical parameters (e.g. PSA value) are not as helpful as in recurrent PC. Thus, in patients with PSMA-ligand PET positive lymph nodes (if considered for surgery) ePLND is still advisable and the additional value of PSMA radioguided surgery might only be evident in atypical located lesions that are not readily accessible.

**FUTURE PERSPECTIVES**

The concept of molecular targeted PSMA guided surgery has been first developed and is increasingly employed to detect metastatic lymph nodes in the salvage setting. It can be expected, as more data on oncological short- and long-term follow-up emerges, that this technology will spread and be offered in an increasing number of specialized centers during sLND procedures. Here, careful selection of patients with loco-regional recurrence on the basis of PSMA-ligand PET and suitable clinical
characteristics is mandatory (57). With the development of drop-in gamma probes for robot-assisted minimal-invasive surgery, patient discomfort and morbidity are likely to decrease, fueling further demand for such molecular targeted approaches to achieve effective precision surgery with improved outcomes (41,42). Modifications and further developments of PSMA-directed tracers and especially in combination with fluorescence will enable visual or even bimodal tracking by fluorescence cameras and gamma probes (46,47,49,50). Tools for advanced intraoperative navigation via augmented- and virtual reality displays may further help to increase the surgical targeting accuracy while reducing morbidity (74).

Currently, there is also great interest in translating PSMA-targeted surgery approaches to the primary setting – in the context of LND or even during margin assessment of the prostate during radical prostatectomy. In patients with suspicious lymph nodes on PSMA-ligand PET, combining ePLND with intraoperative PSMA guidance could be helpful especially when those involved lymph nodes are located outside the standard template. However, the likelihood of underestimation of lymphatic spread by PSMA-ligand PET especially at primary diagnosis has to be considered. Furthermore, all current available tracers for PSMA radioguided surgery show urinary excretion and urinary spillage from the bladder during radical prostatectomy, which can contaminate the field for PSMA guided LND (75). Here, development of tracers with less or even without renal elimination are desirable. As for margin assessment, urinary excretion for current available tracers is even a greater challenge. Moreover, when evaluating the prostatic fossa after prostatectomy to detect the presence of residual cancer cells, physiological background from tracer accumulation within the rectum wall impedes a precise, compounded by weak signals from few and dispersed cancer cells. In these clinical scenarios, development of tracers without renal elimination and less unspecific accumulation in the rectum wall are desirable. When measuring the prostatectomy specimen for evaluation of positive surgical margins, the tissue penetration of gamma rays precludes current PSMA tracers for radioguided surgery from use as only tumor cells on the surface of the positive resection margin are of interest. Here, a clear unmet need is the development of tracers without penetration of healthy tissue layers and without urinary excretion. Optical surgical guidance methods could also help provide a possible solution to this problem.

Over the past decade, major advances have been achieved in image-guided surgery for PC. With advancing technologies, new tracers, and optical engineering, it is likely that this will impact on management of the disease in the near future. Further evaluations of these technologies are warranted through well-conducted clinical trials to provide robust evidence of effectiveness, cost-effectiveness and reproducibility of outcomes. Finally, experiences in the field of PSMA guided surgery may serve as an exemplar for the development and utilization of similar molecular guided approaches in other malignancies and diseases in the future (76).
References


57. Horn T, Kronke M, Rauscher I, et al. Single lesion on prostate-specific membrane antigen-ligand positron emission tomography and low prostate-specific antigen are prognostic factors for a


## Treatment options in prostate cancer for:

<table>
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<th>Locoregional metastasis</th>
<th>Oligometastatic disease</th>
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| **Primary prostate cancer**
  ePLND + RT
  RT + ADT
  *Neoadjuvant therapy*
  Sentinel LND (PSMA guided LND) | **RT + Doc/ADT**
  Combination therapies
  *Neoadjuvant therapy*
  ePLND + combination therapies |
| **Recurrent prostate cancer**
  Watchful waiting
  ADT
  Salvage RT
  Salvage LND
  PSMA guided LND | **ADT**
  Combination therapies
  Watchful waiting
  *MDT: Salvage RT* |

* in combination with local treatment

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**Figure 1:**

Treatment options for locoregional or oligometastatic primary and recurrent prostate cancer on advanced molecular imaging:

Standard options in black, experimental approaches in italic red.

(RP: radical prostatectomy; ePLND: extended lymph node dissection; RT: radiotherapy; ADT: androgen deprivation therapy; Doc: Docetaxel; LND: lymph node dissection)
Figure 2:
Conventional rigid wireless gamma probe (A) for open and Drop-in gamma probe (B) for minimal-invasive robotic PSMA radioguided surgery procedures.
Figure 3:
Preoperative PSMA-ligand PET/CT fusion images (A, C) and corresponding preoperative $^{99m}$Tc-PSMA-ligand SPECT/CT (B, D) of patients who underwent PSMA radioguided surgery with histological confirmation of lymph node metastasis: while larger lymph nodes on PSMA-ligand PET/CT (e.g. perirectal lymph node in A) can also be detected on preoperative $^{99m}$Tc-PSMA-ligand SPECT/CT (B), smaller lymph nodes on PSMA-ligand PET/CT (e.g. iliacal lymph node in C) might not be detectable by preoperative $^{99m}$Tc-PSMA-ligand SPECT/CT (D).
Figure 4:
Ex vivo measurements with gamma probe during PSMA radioguided surgery (A). Histology reveals lymph node metastasis in HE-staining (B) and PSMA immunohistochemistry (C)
Figure 5:
Examples of novel optical and hybrid PSMA applications:
Clinical application of fluorescent PSMA tracer guided dissection of lymph node metastasis during robotic surgery (A, B). Preclinical application of hybrid $^{99m}$Tc-EuK-(SO$_3$)Cy$_5$-mas$_3$ PSMA-ligand combining for radio- and fluorescence guided surgery (C) (52). Cerenkov imaging of radical prostatectomy specimen by the use of $^{68}$Ga-PSMA-11 (D) (53).