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Management of prostate cancer patients with lymph node involvement: A rapidly evolving paradigm

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Abstract

Although widespread PSA screening has inevitably led to increased diagnosis of lower risk prostate cancer, the number of patients with nodal involvement at baseline remains high (nearly 40% of high risk patients initially staged cN0). These rates probably do not reflect the true incidence of prostate cancer with lymph node involvement among patients selected for external beam radiotherapy (EBRT), as patients selected for surgery often have more favorable prognostic features. At many institutions, radical treatment directed only at the prostate is considered standard and patients known to have regional disease are often managed palliatively with androgen deprivation therapy (ADT) for presumed systemic disease. New imaging tools such as MR lymphangiography, choline-based PET imaging or combined SPECT/CT now allow surgeons and radiation oncologists to identify and target nodal metastasis and/or lymph nodes with a high risk of occult involvement. Recent advances in the field of surgery including the advent of extended nodal dissection and sentinel node procedures have suggested that cancer-specific survival might be improved for lymph-node positive patients with a low burden of nodal involvement when managed with aggressive interventions. These new imaging tools can provide radiation oncologists with maps to guide delivery of high dose conformal radiation to a target volume while minimizing radiation toxicity to non-target normal tissue. This review highlights advances in imaging and reports how they may help to define a new paradigm to manage node-positive prostate cancer patients with a curative-intent.

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Keywords

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Introduction

At least 30% to 50% of patients with intermediate to high risk but clinically localized prostate cancer (PCa), (i.e. cN0), treated initially with a curative intent will manifest biochemical failure, suggesting a combination of persistent local, periprostatic, regional (pelvic lymph nodes) or distant (i.e. systemic) disease.[1–5] Despite higher doses of radiation and good surgical techniques, there is an increasing number of failures due to non-local treatment failure. If lymph-node metastases (LNM) are present in a patient with PCa, curative treatment using radical prostatectomy (RP) or radical radiotherapy directed only at the prostate will inevitably be doomed to failure.

For most other solid tumors, regional spread of the disease through lymphatic pathways is of great concern and impacts the therapeutic plan (e.g. breast cancer, head and neck cancers, rectal cancer, gynecological cancer, bladder cancer). For several decades, it has been suggested that PCa was different from other cancers as the presence of nodal metastasis indicated systemic disease. In addition, recent studies found that the incidence of LNM dropped to less than 10%. These numbers, however, do not reflect the true incidence because most series are based on patients managed without the benefit of the information gleaned from extended nodal dissection.[6–9] Although the percentage of patients with LNM has dropped, it may very well be these LNM-positive patients (nearly 40% for high-risk patients) who are most likely to die of prostate cancer, and who may therefore benefit from effective treatment. One of the major challenges in the management of PCa is the identification of early physical (as opposed to biochemical) evidence of metastatic disease. Ultimately, the objective of locoregional therapy is to control disease with minimal collateral damage, thereby optimizing both cancer and toxicity outcomes. Because of the historical inability to accurately visualize the local extent of disease, all local therapeutic interventions simply targeted the prostate gland. This paradigm has invariably led to both the over-treatment of low-burden disease and the under-treatment of locally extensive disease.

Improvements in the predictive accuracy of imaging are of great interest in PCa. Conventional imaging has not been reliable in identifying LNM. Advances in imaging technology, such as the development of hybrid imaging systems (e.g., PET/CT and SPECT-CT), which provide both structural and metabolic information, and geographic mapping (e.g. nanoparticle based MRI lymphangiography) have contributed to more accurate imaging assessments.

Clinical staging options for lymph node involvement

Several user-friendly but sometimes sophisticated tools (nomograms, tables or formulae) based on initial clinical and pathological characteristics have been developed to predict the risk of nodal involvement in patients.[10–14] These tools are useful for predicting the probability of finding positive nodes in populations of patients, but they cannot determine if and where nodes are involved in an individual. As a result, the use of these tools has generated a lot of controversy not only because of significant differences in the observed vs. expected rates of pathological stage in the modern era of lymph-node dissection, but also because of concerns about their clinical relevance.

This lack of consistency between studies can be explained by differences in surgical approaches and patient selection. For example, Heidenreich et al. analyzed the predictive accuracy of Partin tables and Classification and Regression Tree (CART) analysis in patients undergoing RP and extensive pelvic lymph node dissection (ePLND; i.e. removal of obturator, external iliac, hypogastric with or without presacral and common iliac nodes). Overall, both nomograms predicted a significantly lower rate of positive nodes than were detected after extended pelvic lymph node dissection (ePLND).[15] The most probable explanation for the underestimated number of positive of lymph nodes (LN) as derived from nomograms stems from the failure to perform adequate LN dissection and a sub-optimal pathological evaluation (i.e. absence of serial sections and immunohistochemistry) at the time the nomograms were established. In addition, there is little consensus as to whether any patients and if so which patients should be selected for whole pelvic radiotherapy (WPRT) or ePLND. Clearly, more accurate imaging tools are needed to determine “what” should be treated in this selected “high-risk” population, and to minimize the place of elective nodal irradiation.

Benefits/risk of extended pelvic lymph node dissection

There is no doubt that adequate LN dissection improves staging and as a consequence allows a better assessment of the disease, prognosis and potential management. Nevertheless, its beneficial effect on disease progression and survival has been questioned. Recent data suggest that nodal involvement from PCa is not always a systemic disease, but might rather be considered a locoregional disease. Patients with high-risk disease, especially those with micrometastatic disease, are more likely to benefit from ePLND, than are those with a low risk of involvement. Knowledge of lymph-node status allows the appropriate selection of patients for pelvic radiotherapy and adjuvant androgen deprivation while sparing those who do not need it.[16,17] The impact of any adjuvant therapy combined with RP + PLND on long-term cancer specific survival in patients with LNM remains to be clarified (Table 1). The importance of ePLND in determining the prognosis is supported by a host of recent studies. For example, Schumacher et al. showed that following ePLND and RP in patients with a PSA < 10 ng/mL, 25% of patients with a Gleason score ≥7 had LNM, while only 3% of patients with a Gleason score ≤6 were node positive.[18] A solitary LNM increased the risk of cancer-specific death almost fourfold. In patients with two or more LNM, the risk was increased two fold compared to that in patients with one positive LN.[19] The major drawback of this approach lies in the higher rate of complications in ePLND than in standard dissection: 2–10% vs. 20–75%, respectively.[20–22] However, the exact impact of ePLND on cancer-specific survival and patient outcomes has not yet been clearly proven, perhaps because of the lack of prospective randomized trials (Table 1). Results from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program showed that patients with at least 10 negative nodes removed had a lower risk of prostate cancer death at 10 years. Regarding staging accuracy, the greater the number of nodes removed, the greater the likelihood of discovering positive nodes.[23]

Imaging modalities for the evaluation of occult nodal disease

Conventional imaging

CT-scan, MR Imaging, MR Spectroscopy—Owing to their low sensitivity (0–30%) in detecting LNM, CT and MRI, are not recommended for the routine evaluation of PCa.[24,25] Even with sensitivity rates ranging between 30% and 60%, only round LNs with a short axis larger than 8 mm and oval nodes with a short axis larger than 10 mm could be considered metastatic.[26–28] Conventional morphologic imaging modalities, which rely predominantly on the size of the nodes, suffer from inadequate specificity, particularly in the detection of LNM.[25,29,30]

At 1.5T, MRS has no merit in the evaluation of pelvic LNs. Voxel sizes of 8–10 mm^3 are needed to produce an adequate signal-to-noise ratio, the majority of which should be taken up by the abnormal tissue to appreciate a change in signal. Thus small infiltrating lesions are likely to go unnoticed. In the future, 1H-MRS at higher fields might reveal macroscopically invaded nodes. Additional studies will be required to assess the minimal volume necessary for 1H-MRS to detect sufficiently high choline signals within a LN. Performing 1H-MRS at field strengths of 4 T or higher might make it possible to reduce the volume necessary to perform single voxel measurements and use 1H-MRS in smaller LNs. This technique remains experimental.

PSMA based SPECT imaging—The [111In] capromab pendetide scan (ProstaScint™ Scan, EUSA Pharma, Langhorne, PA, USA) SPECT uses a murine monoclonal antibody that reacts against prostate specific membrane antigen (PSMA), which is overexpressed in PCa compared with normal tissues. ProstaScint SPECT has been used to detect LNM and recurrent PCa after radical prostatectomy or radiation therapy. There is an extensive but controversial body of literature that evaluates the role of the use of this agent in the determination of LN status of patients being considered for definitive therapy. Several reviews suggest this imaging modality may be of value in identifying pelvic LNM and treatment planning for radiotherapy.[31–34] However, its sensitivity and specificity in detecting recurrent disease have been been reported to be suboptimal in a number of recent studies.[35,36] Some claimed that it provided no added benefit over other imaging modalities due to its low sensitivity for detecting local recurrences and bone metastases.[37,38] Several key issues concerning its structure explain these disappointing results. Firstly, because it is an antibody, its clearance remains slow, and secondly, it mainly targets the endodomain of PSMA, which renders imaging of intact living cells difficult. Given these drawbacks, the National Comprehensive Cancer Network (NCCN) recently decided to restrict its indications by removing Prostatscint as a recommendation in the work-up of patients with a recurrence after either radical prostatectomy or radiotherapy. Data from promising new investigational agents is discussed below.

Investigational imaging

A number of new promising functional and morphological imaging tools will soon be available. These tools have been evaluated and compared with combined standard imaging modalities, PLNDs and extended PLNDs. Developing these new approaches should allow improved LNM mapping, which could be used to design radiation treatment resulting in a decrease in the size of the field required to be effective, potentially leading to more selective irradiation and a reduction in the morbidity of treatment. Patients with very high-risk disease may in fact not always be amenable to ePLND (due to the morbidity of this surgery) and may be particularly likely to benefit from pelvic and paraaortic irradiation to areas that cannot be encompassed surgically.

MR imaging and iron oxide nanoparticles—Novel techniques such as high resolution MRI with the intravenous injection of lymphotrophic superpara-magnetic Ultra Small Particles of Iron Oxide (USPIO) (ferumoxtran-10) might improve the detection of LNM. Lymph node metastases as small as 1–2 mm in diameter were detected using this technique.[39] USPIO consist of densely packed dextran-coated iron oxide cores. These lymphotropic superparamagnetic particles are absorbed by the macrophages in the LNs and cause changes in the magnetic properties, which are detectable by MRI performed the day following the injection. After injection, the particles accumulate in normal LNs and produce a decrease in signal intensity, whereas in LNM the signal intensity does not change. On a node-to-node basis, Harisinghani et al. assessed 334 LNs and found that 71.4% of LNM in patients with PCa were within the normal size range.[40] Some authors reported that the

sensitivity and specificity of MR lymphangiography with USPIO were greater than those for conventional MRI (90.5% vs. 35.4%, $p < 0.001$ and 97.8% vs. 90.4% for sensitivity and specificity, respectively) for MR lymphangiography with USPIO.[40,41] These results have been confirmed by a large multicenter prospective study involving 375 patients with intermediate to high risk PCa.[39] Of the 61 patients with LNM, 50 were detected by MR Lymphangiography, of whom 40 (80%) had metastases in normal-sized LNs (i.e. <8 mm). The higher sensitivity (82% vs. 34%) and better negative predictive value (96% vs. 88%) of MR Lymphangiography suggests that in patients with a negative MRL, the chance of LNM was less than 4%. In another recent multi-center study from the same group, involving 296 patients with an intermediate to high risk of LNM, Heesakkers et al. evaluated the use of MR Lymphangiography with USPIO to detect and identify LNM occurring outside the normal area of a PLND. Among the 296 patients included, 19.6% had LNM on MRI with USPIO. Positive LNM were shown to be outside the routine area of LN dissection in 82% of the cases. Preliminary results from a study which tested USPIO at 3.0T revealed significantly better muscle-fat contrast, vessel-fat contrast, LN border delineation, and total image quality.[42] This technology has already demonstrated its usefulness for the design of radiation fields that ensure adequate coverage of LN areas at risk (Fig. 1).[43,44]

Shih et al. showed by lymphotropic nanoparticle-enhanced magnetic resonance imaging (LNMRI) that the “at-risk” pelvic nodes follow the vascular rather than skeletal anatomy of an individual.[44] A Clinical Target Volume (CTV) that included a 2-cm radial margin was found to encompass almost 95% of the nodes at risk. MR imaging with USPIO has been approved for use in some European countries. Preliminary work at UCSF suggests that this imaging modality had a profound impact on the design of radiotherapy treatment plans, particularly for patients failing prior therapy. Unfortunately, the Food & Drugs Administration (FDA) have not yet approved this technique for standard use in the United States. For this reason a new promising USPIO (carboxymethyl dextran-based magnetic nanoparticle (Ferumoxytol) is under clinical investigations and could become of great value if found to be comparable to ferumoxtran-10.[45] This new compound has already been approved by the FDA cleared for the treatment of iron deficiency.

Choline-based tracers and other radiotracers for combined PET/CT—Although [18F]-Fluorodeoxyglucose PET proved to be of limited value in the staging of early disease, it seems to be more valuable in advanced disease.[46,47] [11C]-Choline and [18F]-labeled choline analogs such as Fluoro-Choline PET (FCH-PET) have been studied for their ability to localize the disease within the gland and nodal tissue.[48–58] Concerning the short half-life of ^{11}C, the synthesis of [11C] compounds require an on-site cyclotron which means that it cannot be used as widely as [18F]. This strategy has changed the therapeutic care of 20% of high-risk patients, which suggests that PCa is an appropriate clinical indication for Choline-based PET procedures. Although FCH PET/CT is of limited value for T staging of PCa because it is unable to differentiate between benign prostate hyperplasia or prostatitis and cancerous lesions, it seems to be more helpful in the context of a biochemical recurrence for either localizing intra-prostatic areas of recurrence (for patients with repeated negative biopsies) in 25% of patients[59], or for regional LN involvement after prostatectomy or radiation therapy.[54,60–64]

In prior studies, the value of PET imaging with radiolabeled choline in the primary assessment of LNM ranged from promising[65] to limited usefulness.[56,66,67]

Controversial results on the sensitivity of FCH-PET in detecting LNM could hamper the development and widespread use of the technique. To date, some results suggest that FCH-PET may not be as sensitive as ePLND or radioisotope-guided SN dissection.[66] Due to the low spatial resolution of the cameras, micrometastases or involved nodes less than 5 mm

seem to remain undetectable with this technique. The technique could also be regarded as insufficiently sensitive for the accurate detection of nodes of 5 mm diameter or greater. In this regards, a single-centre prospective study evaluated the impact of 18F-Choline PET in improving the preoperative staging of 130 patients with intermediate to high risk PCa.[68] Extended PLND was performed, which led to the removal of 912 LNs (median: 9 nodes per patient). A per-patient analysis revealed that the sensitivity, specificity, and positive and negative predictive values of FCH PET/CT in the detection of LNM were 45%, 96%, 82%, and 83%, respectively. In contrast for LNM equal to or greater than 5 mm in diameter, the sensitivity, specificity, and positive and negative predictive values were 66%, 96%, 82%, and 92%, respectively. In other clinically relevant situations, such as a rising PSA, PET/CT could help identify the site of failure after surgery or radiotherapy. Although, the detection rate of recurrent disease with FCH-PET seems to increase in parallel with the rising PSA values (36% if PSA < 1 ng/ml; 43% if PSA between 1–<2 ng/mL; 62% if PSA between 2–<3 ng/mL and 73% if PSA value ≥3 ng/mL), postoperative recurrences could be localized even with low but rising PSA values <1.5 ng/mL.[69,70]

Serum PSA kinetics may be of use when assessing the potential value of PET scanning. For example, in a study involving 190 patients with a rising PSA after radical prostatectomy, it was revealed that PSA velocity and PSA doubling time could help in predict positive FCH-PET results.[71] In another study involving 100 patients with a rising PSA after primary surgery or radiotherapy (PSA > 0.1 ng/mL), 54 showed one or more areas of high FCH uptake on PET/CT scanning, and 53 of these (98%) had local and/or distant recurrences.[61] In another report, Breeuwsma et al. showed that out of 70 patients with a rising PSA after external beam radiotherapy only (median PSA value = 9.1 ng/mL), 57 had positive findings with 46 prostate-only recurrences and 11 LNM or bone metastases.[48] In this study, sensitivity was high (81%) even with a rising PSA < 4 ng/ml. Thus, FCH-PET in biochemically recurrent PCa could help physicians select patients for local and/or regional salvage therapy (Fig. 2).

In a German study, 20 patients with PCa were selected for FCH-PET followed by laparoscopic SLN detection and then ePLND. Although the sample size was small and these results need a wider confirmatory study, it suggested that the accuracy in the detection of occult LNM was enhanced with radio-immune guided intra-operative SLN detection rather than with FCH-PET.[66] However, these results could be misinterpreted as this finding may only be valid for proximal first-invaded nodes (e.g. sentinel node) whereas FCH-PET may be more likely to detect distant nodes and/or bone metastases.

Promising new radiotracers that target prostate cancer cells are also emerging. N-[N-[(S)-1,3-Dicarboxypropyl]-4-[18F] fluorobenzyl-L-cysteine ([18F]-DCFBC) localizes to PSMA.[72] [18F]-16β-fluoro-5-dihydrotestosterone (FDHT) is an analog of the primary ligand of the androgen receptors, dihydrostestosterone (DHT), and is thus a good candidate for imaging the androgen-receptor signaling axis.[46,73] Finally, the synthetic amino acid analog radiotracer anti-1-amino-3-fluorine 18-fluorocyclobutane-1-carboxylic acid (anti-3-[18F]-FACBC was evaluated in a prospective trial, and showed sensitivity of 100% and specificity of 100% for detecting extraprostatic relapse.[74]

SN detection by lymphoscintigraphy and combined SPECT/CT—The sentinel LN concept as applied to prostate cancer has been studied for many years but has seen a resurgence in popularity over the past few years.[75–79] SN imaging is performed following transrectal ultra-sound guided injection of a radioisotope (^{99m}Technetium nanocolloid, total dose of 225 MBq with each deposit of around 0.1 mL in both lobes of the prostate). After this injection, patients undergo preoperative planar lymphoscintigraphy using Single-Photon Emission Computed Tomography (SPECT). Then, an intraoperative gamma probe detector

allows the surgeon to detect the path of the lymph that spreads out in the first nodal station (i.e. the sentinel node) during the laparoscopic sentinel lymphadenectomy. In-line hybrid SPECT/CT is a more recent addition to the imaging armamentarium which allows the generation of coregistered SPECT and CT images acquired using a single apparatus during a single imaging session. This is further discussed in a dedicated paragraph. The use of this technique assumes that the lymphogenic spread of cancer follows the lymphatic channels that drain specific areas of the prostate gland is an orderly fashion such that if the initial major drainage site(s) identified by imaging is (are) spared subsequent drainage areas are also spared. In PCa the apparent sensitivity was 96% for identifying the location of lymphatic spread in node positive patients.[22]

As shown from radio-guided surgical LN, the identification and dissection of the lymphatic drainage system of the prostate is highly variable. Wawroschek et al.[80,81] and Weckerman et al.[82] tested the identification of the SLN with prostate lymphoscintigraphy and surgery in a large cohort with the aim to optimize lymphadenectomy techniques. They showed that SLN identification in PCa is feasible with a sensitivity of 93%. In addition, the detection rates of micrometastases were improved. Although these patients were unlikely to have high-risk disease (mean PSA 12.7 ng/mL), nearly 25% of them were found to have LN involvement after pathological examination.[80] Interestingly, the study found only 44.2% of cases with positive nodes in the obturator fossa, which is the most common area for limited lymphadenectomy. The most common areas of LN metastases were the external and internal iliac, followed by the obturator, common iliac, and presacral regions. These findings correspond to data obtained after ePLND in 103 patients.[15] Applying information from sentinel node imaging can help guide adequate coverage of nodal basins involved in sentinel lymphatic drainage (Fig. 3).

However, this technique has its limitations. First, only nodes in close contact with the gamma probe detector are detected. If these are not directly accessible there is a considerable likelihood that they will be missed. Bulky nodes may also impede lymph drainage upward. In addition, it is unclear whether this technique can be accurately applied to men who have undergone radical prostatectomy, not only because their drainage may be very aberrant, since nodal involvement may have been changed due to the surgical intervention, but also because the sites for injection are unclear. After treatment, the preliminary results suggest that it is feasible to perform SPECT/CT based sentinel node imaging. However, there also appears to be a significantly higher rate of aberrant locations (i.e. paraaortic, presacral or inguinal nodes) in treated than in untreated patients (80% vs. 34%, $p = 0.01$).[83]

At UCSF we have had limited but promising experience with sentinel lymph node (SLN) imaging. The concept of SLN involves using imaging to facilitate selective LN dissection in order to decrease dissection-related morbidity and has led to a shift towards more conservative therapeutic approaches. For example, after applying preoperative fusion imaging of SPECT (single-photon emission computed tomography) and CT scans following the intra-prostatic injection of Technetium-99 m-nanocolloid, multiple primary landing sites were identified with 30–40% of these landing sites found outside the usual area of PLND.[21]

In the University of Tuebingen, Germany, 25 patients with high-risk disease selected for combined WPRT and 3-year HT had SN-SPECT mapping incorporated into the treatment planning. A total of 142 SN were detected with a median of 6 nodes detected per patient. The most common sites of the SLN were the external iliac (50 SLN: 35%), followed by the internal iliac (26 SLN: 18.3%), common iliac (16 SLN: 11.3%), perirectal (12 SLN: 8.4%), sacral, and left para-aortic (each with 9 SLN: 6.3%) area. SLN were identified much less frequently at the seminal vesicle lymphatic plexus (6 SLN: 4.2%), the right para-aortic (4

SLN: 2.8%), the inguinal deep (3 SLN: 2.1%), the internal pudendal and perivesical (each 2 SLN: 1.4%) and the inguinal superficial, inferior rectal, and superior rectal (each 1 SLN: 0.7%) regions. The LN areas most strongly associated with a propensity for a geographic miss were the external iliac (ventral parts), the para-aortic, perirectal, and sacral regions. Krengli et al. also reported the impact of SPECT/CT findings on target volumes before external radiotherapy. Moreover patients had LN dissection after radio-immune SLN detection. The SLN and other intrapelvic LNs identified by SPECT were not included in the pelvic target volume for 25% of the patients.[84] Fig. 4 shows lymph node drainage patterns for a high risk PCa patient, which can help practitioners decide on the upper limit of the nodal clinical target volume. SPECT-CT to map lymph node areas that need to be considered for dissection has also been studied in 34 lower-risk patients (cT1-T2, median PSA value 8 ng/mL) who underwent subsequent gamma counter-guided ePLND.[21] They conducted an elegant study with intraoperative Gamma camera probe detection followed by ePLND which showed that even though none of patients had LNM, nearly two thirds of the detected nodes were removed with ePLND, while only one third were removed with limited PLND. This observation once again supports the rationale for performing ePLND (or SLN imaging) and further questions about the adequacy and accuracy of the standard PLND procedure. On the other hand, the proportion of common iliac and para-aortic sentinel nodes found in this study for low-risk patients was not negligible (16% and 12%, respectively). This raises questions about the global value of surgery with a curative intent for patients at risk of occult LNM and the fields selected for patients undergoing salvage EBRT, as in most cases these nodes are neither removed with ePLND, nor included in radiotherapy fields. One limitation of the SLN imaging technique, however, is that in the presence of bulky nodes roughly one third of LNM may remain unrecognized due to the impaired uptake of Technetium.[85] Fortunately, markedly enlarged nodes may be identified with standard anatomic imaging techniques. The advantages and disadvantages of MR with USPIO, SN-based SPECT/CT and FCH-PET are summarized in Table 2.

Small molecule PSMA based SPECT imaging (Trofex™)—Prostascint is a large molecule with poor penetration which binds to the intracellular component of PSMA. Due to its low sensitivity and specificity for detecting metastases, a new small Iodine-123 labeled molecule is currently being investigated and has shown promising preclinical findings: [^{123}I]MIP-1072, (S)-2-(3-((S)-1-carboxy-5-(4-iodobenzylamino)pentyl)ureido)pentanedioic acid (Trofex™) targets the extracellular domain of PSMA in patients with metastatic prostate cancer and allows the detection of both soft tissue and bone metastases.[86,87] Another compound, very close to [^{123}I]MIP-1072, namely [^{123}I]MIP-1095, (S)-2-(3-((S)-1carboxy-5-(3-(4-iodophenyl)ureido)pentyl)ureido)pentanedioic acid, is also being investigated.

MIP-1072 and MIP-1095 potently inhibited the glutamate carboxypeptidase activity of PSMA (K(i) = 4.6 +/− 1.6 nmol/L and 0.24 +/− 0.14 nmol/L, respectively) and, when radiolabeled with ^{123}I, exhibited high affinity for PSMA on human prostate cancer LNCaP cells (K(d) = 3.8 +/− 1.3 nmol/L and 0.81 +/− 0.39 nmol/L, respectively).

In initial Phase 1 clinical trials in patients with histologically confirmed metastatic prostate cancer, [^{123}I]MIP-1072 and [^{123}I]MIP-1095 detected both bone and soft tissue prostate cancer metastases at 1–4 h post-injection (Fig. 5).

The respective role and the place of each conventional and investigational imaging modality with respect to different clinical indications in routine clinical practice are provided in Table 3.

Benefits/risks of lymph node irradiation for node positive patients

The case for cN1 patients

If LN involvement is considered a springboard, and not merely a surrogate for distant metastatic spread, a loco-regional approach could be useful. This would suggest the need to favor systemic therapies alone or in combination with locoregional approaches. The latter startegy has been verified for patients with locally advanced PCa in a randomized phase III trial conducted by the Scandinavian Prostate Cancer Group (SPCG). The SPCG-7 study showed that combining prostate radiotherapy with long-term hormone therapy was superior to long-term hormone therapy alone in terms of overall survival.[88] The Radiation Therapy Oncology Group initiated a similar randomized trial for PCa patients with positive nodes (RTOG No. 9608). This study was prematurely closed due to poor accrual, which could be explained by the increase in the use of PSA testing.

The RTOG 75-06 trial attempted to evaluate the impact of peri-aortic LN irradiation (2D technique) vs. pelvic LN irradiation (without hormones) for high-risk patients with or without nodal involvement. In multivariate analysis, patients with N+ disease initially fared no worse than those without nodal metastasis.[89] Of the 566 patients, a subset of 90 patients with biopsy-proven pelvic node involvement was analysed. At 5 and 10 years, 31% and 7%, respectively of patients were still alive with no clinical evidence of disease.[90] Although it could be argued that the prognosis in these patients was initially grim, these results could lead to innovative treatment programs for patients with 1 or 2 positive nodes from their PCa. When radiotherapy is combined with hormone therapy in node-positive patients, retrospective data suggest excellent biochemical control rates at 5 years (ranging from 62% to 83%), as well as at 10 years (63%).[91–93] Four randomized trials evaluated the impact of combining long term hormones with WPRT radiation for patients with either clinically N0 or N1 disease: RTOG trials No. 85-31 and 92-02 and EORTC trials No. 22863 and 22961. In the RTOG 85-31 trial, a subset analysis of the 173 cN1 patients who were randomized between WPRT and WPRT combined with hormone therapy was performed.[94] Although the results confirmed that some N+ patients with external radiation alone survived with no biological progression at 5 and 9 years (33% and 4%, respectively), these results were statistically improved when WPRT was combined with hormone therapy (54% and 10%, respectively). New technologies in the field of radiation oncology, such as IMRT and IGRT, should make it possible to escalate the dose to positive nodes without compromising the safety of WPRT.

The case for pN1 patients

No randomized controlled study has ever tested the role of adjuvant RT in node-positive patients after RP and ePLND. In a large retrospective study, the role of adjuvant pelvic RT in the case of LN involvement after PR and ePLND was investigated. One hundred and twenty-one patients treated with adjuvant standard hormone therapy were compared with 129 patients treated with WPRT combined with HT. With a median follow-up of 95.9 months, the rates of biochemical recurrence-free and cancer-specific survival at 10 years were 53% and 80%, respectively. In multivariate analysis, no adjuvant RT and the number of positive LN were strong predictors of failure.[95]

The case for rN1 patients

Lymph node recurrent PCa after the primary treatment is considered an unfavorable situation, and systemic hormone therapy (androgen deprivation) is the gold standard in this patient population.[96] However, there are very few data on irradiation of recurrent LN disease. Elective LN irradiation (using conventional fractionated external beam radiotherapy) combined with SRT boosts to the recurrent LN could reduce the risk of

regional LN progression. This hypothesis has recently been strengthened by the results from a surgical study.[58] In this study, only LNM detected by [11C] choline PET/CT were removed by the surgeon and no adjuvant therapy was delivered. All of the patients had a PSA response and 3 out of the 6 patients included had a lasting complete PSA remission after a median follow-up of 24 months. Preliminary results from a small study on stereotactic radiotherapy for isolated LN relapses diagnosed with 11C-choline PET-CT have also been published recently.[97] Total doses ranged from 20 to 45 Gy (mean 27 Gy) given in 2–5 fractions. Rates of toxicity were low. After 19 months of follow-up, 8 of the 14 patients had no evidence of disease. Patients with progression had no in-field relapse. These pioneering results need to be confirmed, but are extremely promising. However, until more data on radiotherapy or surgery for recurrent LN disease are available, aggressive regional approaches should be considered investigational.

Technical considerations in radiation oncology: The case for MAP-IMRT

When a prostate cancer patient harbors a positive lymph node, physicians must be aware of the importance of technical issues involved in delivering higher doses of radiation. Firstly, the commonly used “box technique” for treating pelvic nodes (i.e. four orthogonal fields with 2D or 3D conformal radiation planning) is inappropriate in the case of LNM. When 45 Gy are prescribed to the whole pelvis with this technique, the planned dose to cover the nodes may be too low to be curative (Mean dose: 43.7 Gy and the dose received by 95% of the pelvis: 27.4 Gy).[98,99] Secondly, the dose required to treat with a curative intent positive nodes should be higher (i.e. ≥60 Gy). For this reason, IMRT to selected lymph nodes could result in better coverage of lymph node stations while sparing more surrounding tissues such as the small bowel.[99,100] IMRT makes it possible to deliver higher prophylactic dose to the whole pelvis (Mean dose: 49.6 Gy and dose received by 95% of the pelvis: 46 Gy when 50 Gy are prescribed to the whole pelvis).[99] A phase I trial ($n = 73$) on dose escalation with IMRT for WPRT for patients with PCa at a high risk of LNM was performed in the UK.[100] Acute and late toxicity was acceptably low using a pelvic dose of up to 55 Gy over 7 weeks, if the constraints for the bowel were followed. Engels et al. showed that dose escalation to positive LNs up to 60–65 Gy with IMRT was feasible with low rates of toxicity.[101] The incidence of grade 2 and 3 acute gastrointestinal (GI) toxicity was 7% and 0% respectively. Grade 2 and 3 acute genito-urinary (GU) side effects were observed in 14% and 4% of the patients respectively. Recently, a Phase III trial showed that a hypofractionation scheme delivered to the prostate (i.e. 62 Gy at 3.1 Gy per fraction) resulted in improved 3-year freedom from biochemical failure with no significant differences in late toxicity.[102] Preliminary results from studies that combined a similar hypofractionation scheme to the prostate with a conventional fractionation scheme to the whole pelvis (1.8–2.0 Gy) showed it was feasible.[103–105] Finally, when a patient has LNM with untreated primary prostate cancer, high dose radiation therapy should be given to both the prostate and positive nodes. Nevertheless, in this situation, radiation oncologists have to cope with two target volumes (one moving and one immobile).

Theoretically, if daily repositioning is performed on the bony anatomy, wider margins should be considered around the prostate to take into account daily variations of prostate position (up to 1.5 cm). If daily repositioning is performed on the prostate or on implanted fiducial markers in an attempt to protect mostly the rectum, then margins around the pelvic and/or paraaortic nodes should be increased. Real-time re-planning of dose distribution based on daily CBCT, which would take into account the position of both volumes, would be ideal but remains time-consuming. To circumvent this obstacle, we have proposed an alternative strategy that can be used in routine practice. This is referred to as multiple adaptive plans (MAP) IMRT.[106] Without requiring any additional hardware or software, the MAP strategy is to choose a plan from the pool that most closely matches the “prostate

position of the day". This position can be determined by dual imaging registrations: one aligned to the implanted markers in the prostate and the other aligned to the pelvic bones. Because the number of possible prostate positions for each patient could be very large, we created a pool of five plans based on a planning CT to compensate for the most significant prostate movements. With this strategy, we showed that the daily dose received by 95% of the target volumes was >95% of the prescribed dose in 100% of the treatment days for the lymph node volume and 65% of the treatment days for prostate volume.[106]

MAP-IMRT provides one feasible solution for tracking two concomitant targets independently and could be improved further either by increasing the number of plans to compensate for prostate position or by a leaf shifting strategy which can follow the movement of the prostate while not significantly affecting dose distributions to the pelvic lymph nodes. This latter strategy, which could significantly improve the results of MAP-IMRT is under investigations at UCSF.[107]

Conclusions

The goal of current cancer care is to administer risk-adjusted patient-specific treatment planned to maximize cancer control while minimizing the risk of complications. The challenge in patients with a high-risk of biochemical failure lies in part in the ability to detect which patients have occult nodal disease and where the involved nodes are. Three randomized and controlled trials have shown that hormone therapy alone is inferior to combined radiation (with or without WPRT) and long-term hormone therapy for locally advanced PCa patients in terms of overall survival.[88,108,109] One of these studies showed that patients treated systematically with HT and WPRT had significantly lower local and regional relapses.[108] Thus, some selected patients initially at a high risk of occult nodal involvement, who had LNM revealed using modern imaging techniques could benefit from prolonged survival or be cured with an adequate and well-targeted dose of radiation.

New imaging tools can provide urologists and radiation oncologists with accurate maps to guide the extent of the surgical procedure or the delivery of high-dose conformal radiation to a precise target volume while minimizing radiation toxicity to non-targeted normal tissue. Moreover, the availability of IMRT and IGRT allows higher doses of radiation to be delivered without increasing the toxicity to normal tissues. However the radiation oncologist will also have to deal with the risk of missing the microscopic disease in nodes. These new imaging tools could take radiotherapy to places it has never been before. To date, no randomized and/or controlled trial has definitively answered questions concerning the place of radiotherapy with or without hormone therapy for patients with occult lymph node involvement from PCa. To this end, the RTOG (RTOG 0924) are planning to launch a larger Phase III Trial to confirm the initial observations from RTOG 9413 to define the impact of WPRT on overall survival.

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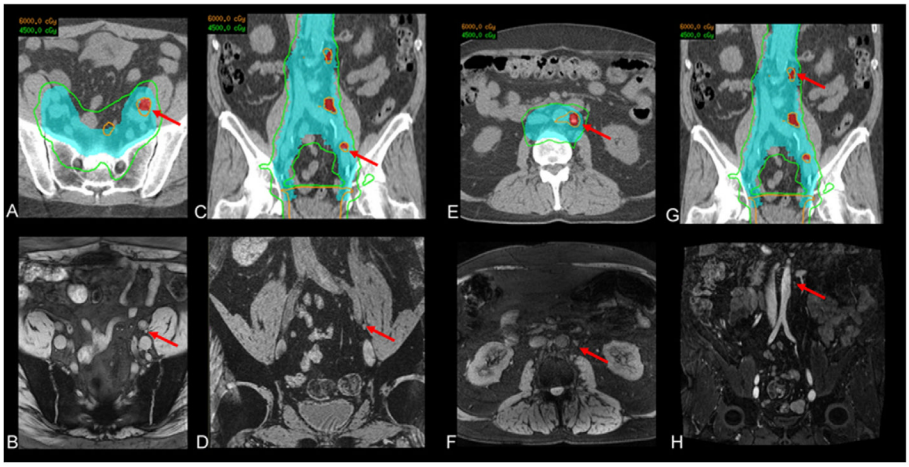

Fig. 1.

Magnetic Resonance Lymphangiography Guided Treatment for Prostate Cancer. Legend: This figure shows a treatment plan and associated magnetic resonance lymphangiography (MRL) for a patient with recurrent prostate cancer. For dose to nodes identified by MRL can be boosted to 6000 cGy. In the currently presented patient, multiple lymph nodes involving the left external iliac and para-aortic areas were identified. The clinical target volume was therefore extended from the standard whole pelvic nodal volume to include the para-aortic nodes. Doses to target volumes are depicted as 6000 cGy (orange) and 4500 cGy (green). (A) Planning CT (axial) with pelvic nodal volume depicted in cyan and an involved external iliac node, detected by MRL in red. (B) MRL (axial) with involved external iliac node identified with a red arrow. (C) Planning CT (coronal) showing the same involved external iliac node as seen in (A) and (B). (D) MRL (coronal) with the same involved external iliac node shown in (A) and (B) identified with a red arrow. (E) Planning CT (axial) with para-aortic nodal volume depicted in cyan and an involved para-aortic node, detected by MRL in red. (F) MRL (axial) with involved para-aortic node identified with a red arrow. G) Planning CT (coronal) showing the same involved para-aortic node as seen in (E) and (F). (H) MRL (coronal) with the same involved para-aortic node as shown in (E) and (F).

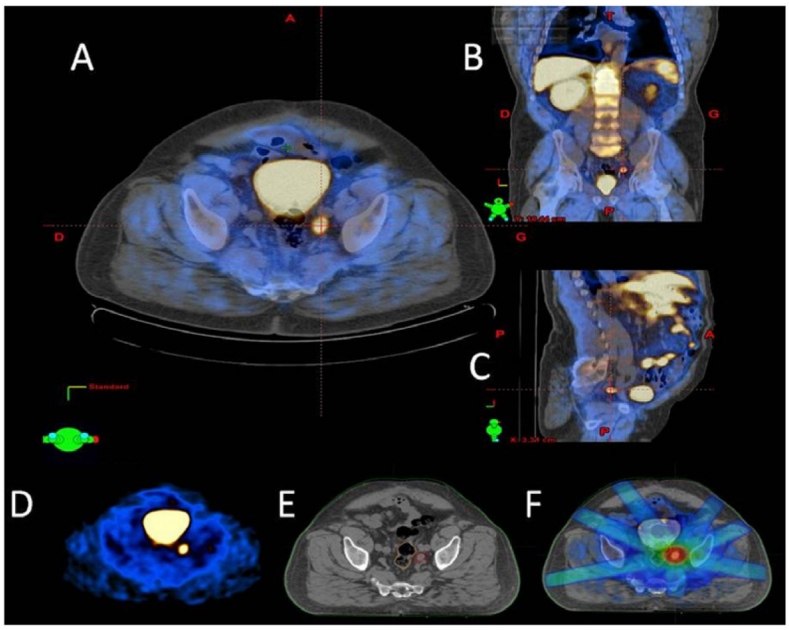

Fig. 2.

Fluorocholine (18F) Positron Emission Tomography (PET) combined with Computed Tomography (CT) guided treatment for isolated nodal relapses after prostatectomy. Legend: This figure shows a treatment plan and associated how (18F) PET/CT for a patient with recurrent prostate cancer in a single node. In the currently presented patient, a single left iliac node was identified. Treatment was delivered under stereotactic conditions. In the current presented patient, a biochemical failure occurred 61 months after radical prostatectomy. Initially, the pathologist has reported an adenocarcinoma, Gleason 7 (3 + 4), staged pT3 R0, pN0. After the PSA rose up, the patient underwent a salvage radiation to the prostatic fossa. FCH PET/CT demonstrated isolated pararectal uptake. A salvage PET-guided IMRT delivered 66 Gy (5 × 2 Gy/week). Two years after the treatment, the patient is still controlled without any androgen deprivation therapy. (A) (18F) PET/CT (axial) with the involved iliac node, as detected on Fluorocholine PET/CT in yellow. (B) (18F) PET/CT (coronal) with involved external iliac node identified with a red arrow. (C) (18F) PET/CT (sagittal) showing the same involved iliac node as seen in (A) and (B). (D) (18F) PET images used for fusion with planning CT (axial) with the same involved left iliac node shown in (A) and (B) identified with a red arrow. (E) Planning CT (axial) with left iliac nodal volume outlined in red. (F) Dose distribution after fusion between (18F) PET and planning CT. Doses to target volumes are depicted as 6600 cGy (red colorwash).

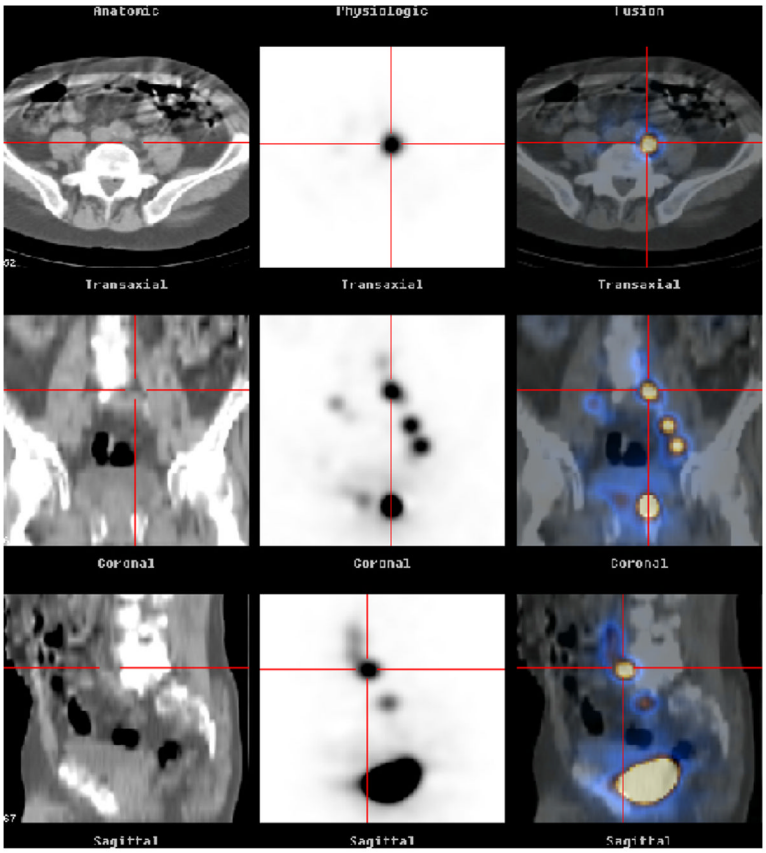

Fig. 3.

3D SPECT/CT imaging example with three sentinel lymph nodes (iliac left), radionuclide filled bladder (courtesy of Ute Ganswindt, with permission[110]). Legend: Transmission and emission scans were acquired 1.5 to 3 h after intraprostatic injection of 150 to 362 (median 295) MBq 99mTc-nanocolloid (Nanocoll, GE Healthcare Buchler GmbH, Braunschweig, Germany) depending on the individual prostate volume, followed by an anatomic-functional image fusion (SPECT/CT). The injection was performed in both lobes of the prostate.

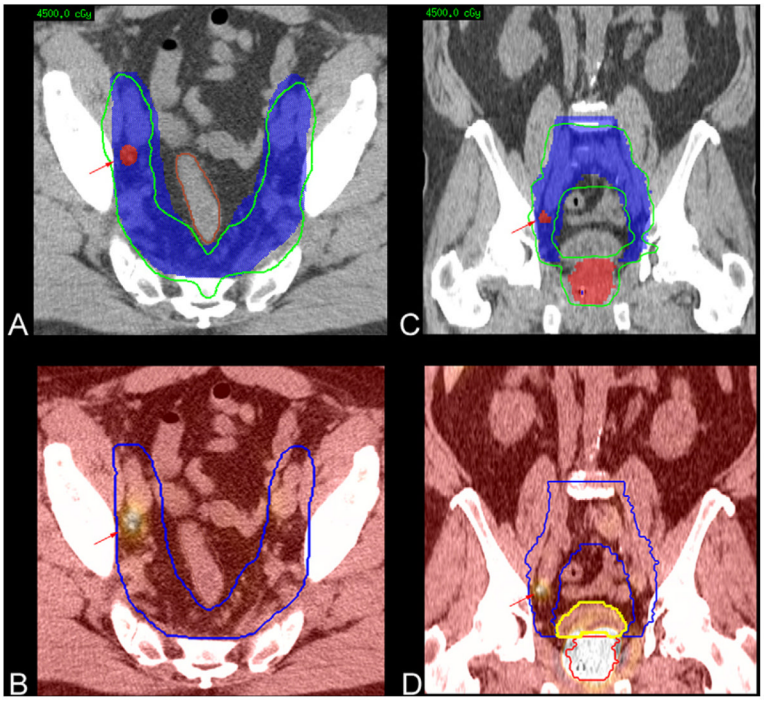

Fig. 4.

Sentinel Lymphangiography Guided Treatment for a high-risk Prostate Cancer. Legend: This figure shows a treatment plan and associated sentinel lymph node lymphangiography (SLNL) for a patient with locally advanced prostate cancer at a high risk of nodal involvement (Gleason 4 + 5). SLNL can identify sentinel lymph nodes and demonstrate lymph node drainage patterns, which can help practitioners decide on the extent of the nodal clinical target volume. Nodes identified by SLNL should be included in the clinical target volume. In the currently presented patient, a right external iliac sentinel lymph node was identified with no para-aortic sentinel lymph nodes. Hence, the clinical target volume was limited to a standard whole pelvic nodal volume. Doses to target volumes are depicted as 4500 cGy (green). (A) Planning CT (axial) with pelvic nodal volume depicted in blue and a potential right sentinel lymph node detected by SLNL in red. (B) SLNL (axial) with identified focus of uptake in the right pelvis side wall region identified with a red arrow. (C) Planning CT (coronal) showing the same involved external iliac node as seen in (A) and (B). (D) SLNL (coronal) with the same focus of uptake shown in (A) and (B) identified with a red arrow. The blue, yellow, and red contours are the clinical nodal volume, bladder, and prostate, respectively.

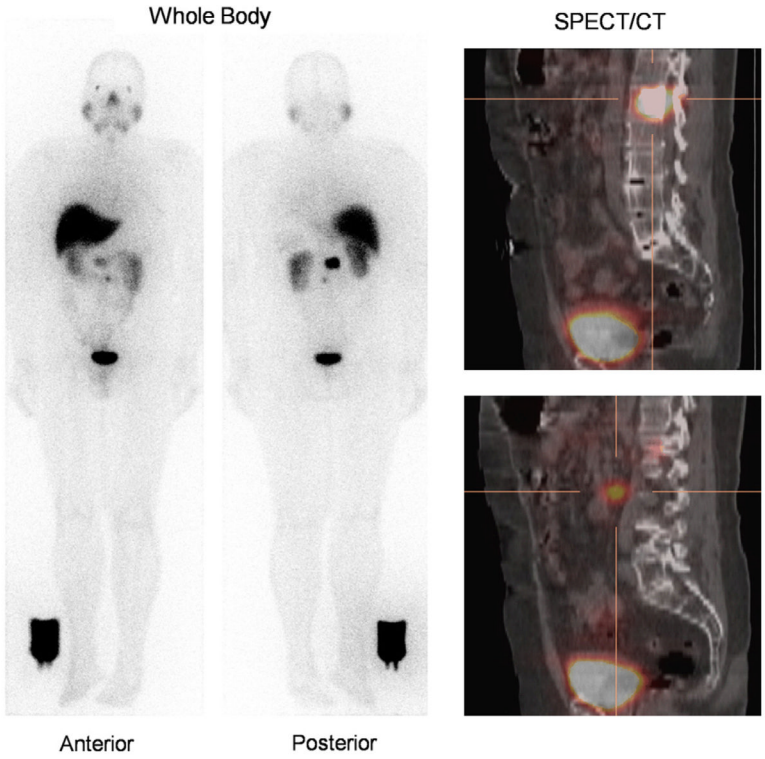

Fig. 5.
[^{123}I] MIP-1072 imaging in a patient with metastatic prostate cancer at 4 h post-injection.
Legend: This figure shows the case of a patient with a rising PSA after radical prostatectomy. Four hours after the injection of the radiotracer, a whole body Single Photon Emission Computed Tomography (SPECT) was performed (left side). On the right side, SPECT images and abdominal and pelvic CT-scan images were co-registered after a single acquisition on a hybrid machine which allowed the accurate location of the oligometastatic recurrence (i.e. a single common iliac node combined with a single bone metastasis in the first lumbar vertebra).

Table 1

Impact on long term cancer-specific survival of radical prostatectomy combined with lymph node dissection for prostate cancer patients with a nodal involvement.

Authors	*n*	Median FU (y)	E or L PLND	Median nb of nodes removed	% of patients with pN+	Adjuvant therapy (% of patients)	Cancer specific survival (%)	
							5-y	10-y
Bader et al.[88]	92	3.75	E	21	25	0	74	62
Cheng et al.[89]	322	6.3	L	12*	100	92	94	83
Boorjian et al.[14]	507	10.3	L	11	100	90	94	86
Briganti et al.[90]	703	9.4	E	13.9*	100	100	90	82
Zwergel et al.[91]	147	3.5	L	–	100	92	87	74
Spiess et al.[92]	100	5.2	L	11	100	30	94	75
Schumacher et al.[93]	122	5.6	E	22	100	0	85	60

FU: Follow-up; y: years; E: extensive; L: Limited; pN+: pathologically invaded lymph nodes.

*Mean.

Table 2

Summary of investigational imaging tools for patients with occult nodal involvement from prostate cancer in the context of radiation oncology.

	Requirements	Advantages	Disadvantages
MR Lymphangiography with USPIO	• Conventional MR scan • At least 1.5T IV injection of ferumoxtran-10 24–36 h before	• Non invasive • High sensitivity (82–90%) and specificity (96– 98%) • Reproducible results • Detection of LNM ≤2 mm • Better contrast with soft tissues and LN border delineation	• High false positive rate • Lack of FDA and EMA approval • Fusion CT/MR for treatment planning
Sentinel node SPECT/CT	• TRUS-guided injection of Technetium in each lobe 1–3 h before • SPECT camera combined with a CT scanner	• Visualization of lymph flow pathway • Fusion CT/CT for treatment planning	• Minimally invasive • It shows where are the SLN but not whether SLN are involved • Assumes that prostate cancer is not a systemic disease • Prostate must not be removed • Bulky N+(PSA > 20 ng/mL) may compromise Technetium uptake • May miss LNM or nodes distant from the camera
Choline-based PET/CT	• PET camera combined with a CT scan • Injection of the tracer 2 min. beforehand • Cyclotron needed for 11C-labeled choline tracers	• Non invasive • High specificity (96%) and NPV (92%) • Visualize distant nodes and extranodal metastatic disease (one-stop diagnostic procedure) • Fusion CT/CT for treatment planning	• Low sensitivity (vs. SN dissection or ePLND) • Low detection rate if PSA < 4 ng/mL • Distribution of tracers to institution depends on half life of each tracer • Low spatial resolution of cameras (LNM ≥5 mm only) • Lack of FDA approval

LNM: Lymph Node Metastasis; LN: Lymph Nodes; FDA: Food and Drug Administration; European Medical Agency; PSA: Prostate Specific Antigen; SLN: Sentinel Lymph Node; ePLND: extensive Pelvic Lymph Node Dissection; CT: computed tomography; MR: Magnetic Resonance imaging; T: Teslas; TRUS: Trans-Rectal Ultra-Sonography.

Table 3

The evolving place of conventional and investigational imaging modalities in the work-up of prostate cancer patients with respect to different situations.

	Imaging available for lymph node staging					
	CT	**MRI**	**PSMA-based SPECT**	**MRL (USPIO)**	**SPECT/CT**	**Choline PET**
High-risk prostate cancer requiring whole pelvic radiotherapy	+	+	+	+++	+++	+++
Postoperative radiotherapy (Undetectable PSA)	+	+	−	++	−	−
Postoperative radiotherapy (Detectable or rising PSA)	+	+	−	++	−	++
Rising PSA after external radiotherapy and/or brachytherapy	+	+	−	++	++	++

CT: Computed Tomography scan; MRI: Magnetic Resonance Imaging; MRL: Magnetic Resonance Lymphangiography with Ultra Superparamagnetic Particles of Iron Oxide; SPECT/CT: Single Photon Emission Computed Tomography/Computed Tomography; PET: Positron Emission Tomography; −: not recommended; +: not optimal; ++: recommended; +++: highly recommended.