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The Utility of PET/CT in External Radiation Therapy Planning of Prostate Cancer

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Abstract

Radiotherapy and radical prostatectomy are the definitive treatment options for patients with localized prostate cancer. A rising PSA after radical prostatectomy indicates prostate cancer recurrence, and these patients may still be cured with salvage radiotherapy. To maximize chance for cure, irradiated volumes should completely encompass the extent of disease. Therefore, accurate estimation of the location of disease is critical for radiotherapy planning in both the definitive and salvage settings. Current first-line imaging for prostate cancer has limited sensitivity for detection of disease both at initial staging and at biochemical recurrence. Integration of Positron Emission Tomography (PET) into routine evaluation of prostate cancer patients may improve both staging accuracy and radiotherapy planning. ^{18}F-fluorodeoxyglucose (FDG) PET/CT is now routinely used in radiation planning for several cancer types. However, FDG-PET/CT has low sensitivity for prostate cancer. Additional PET probes evaluated in prostate cancer include ^{18}F-sodium fluoride (Na-F), ^{11}C-acetate, ^{11}C- or ^{18}F-choline, ^{18}F-FACBC (fluciclovine, [Axumin™]), and ^{68}Ga- or ^{18}F- labeled ligands that bind prostate specific membrane antigen (PSMA). PSMA ligands appear to be the most sensitive and specific, but have not yet Food and Drug Administration (FDA) New Drug Application (NDA) approval for use in the United States. Retrospective and prospective investigations suggest a potential major impact of PET/CT on prostate radiation treatment planning. Prospective trials randomizing patients to routine radiotherapy planning versus PET/CT aided planning may show meaningful clinical outcomes. Prospective clinical trials evaluating the addition of fluciclovine-PET/CT for planning of

salvage radiotherapy with clinical endpoints are underway. Prospective trials evaluating the clinical impact of PSMA PET/CT on prostate radiation planning are indicated.

Introduction

Prostate cancer is expected to have an incidence of 161,000 and mortality of 27,000 in the Untied States during 2017 (*1*). Curative treatments for localized prostate cancer include radical prostatectomy or radiotherapy (*2*). Locally recurrent disease after radical prostatectomy may be cured by salvage radiotherapy (*3*). The effectiveness of any local therapy depends on accurate imaging to rule out areas of disease that would remain untreated. Technetium-99m (^{99m}Tc) bone scans and CT or MRI of the abdomen and pelvis are used to evaluate osseous metastases and evaluate soft tissue and nodal metastases, respectively, for prostate cancer staging. For initial staging, ^{99m}Tc bone scans have sensitivities and specificities for osseous metastases between 46-89% and 32-57%, respectively (*4*,*5*). CT or MRI both have sensitivities and specificities for nodal metastases of 39-42% and 82% (*6*). The accuracy of these scans is low, commonly resulting in underestimation of disease burden. After failure of local therapy, recurrence is detected by a rising PSA. However, the sensitivity of current first-line imaging is too low to visualize recurrence in time to guide salvage treatment (*7*–*9*).

Intuitively, irradiated volumes should completely encompass the extent of disease. Therefore, accurate estimation of the location of disease is critical during the process of radiotherapy planning. Radiation oncologists make a distinction in treatment volumes that include gross disease seen on imaging (GTV: gross target volume) and volumes that do not include radiographic visible disease but are at high risk of harboring disease (CTV: clinical target volume). Gross disease is prescribed a higher dose if feasible (taking into account risks to adjacent normal tissue) to increase the probability of tumor control and ultimately cure. Positron emission tomography computed

tomography (PET/CT) might improve staging accuracy and impact radiotherapy planning for prostate cancer.

Integration of PET/CT during radiotherapy planning is routine in many cancer types (*10*). ^{18}F-fluorodeoxyglucose (FDG), which detects increased glucose metabolism within malignant tumors (*11–13*), assists radiation planning for head and neck (*14*), lung (*15*,*16*), gastrointestinal (*10*), and cervix (*17*) cancers, and lymphoma (*18*,*19*). FDG-PET/CT, however, has a low sensitivity for detection of prostate cancer, severely limiting its use (*20*,*21*), with the possible exception of aggressive poorly differentiated and small cell prostate cancers (*20*,*22*), which constitute a small fraction of prostate cancers treated with radiotherapy.

Other PET probes have been evaluated in prostate cancer patients (*21*). These tracers can target either the metabolic changes characteristic of prostate cancer cells (phospholipids with ^{11}C- or ^{18}F-choline, fatty acids with ^{11}C-acetate, amino acids with ^{18}F-FACBC (fluciclovine)), bone remodeling from osteoblastic osseous metastases (Na-F), or overexpressed cell surface proteins (labeled ligands to prostate specific membrane antigen, PSMA) (*21*). ^{11}C-choline and Fluciclovine (Axumin™) have FDA NDA approval in the United States for imaging of recurrent prostate cancer after local therapy (*23*). The PSMA-ligands appear to be the most sensitive and specific for detection of local and metastatic disease (*24*,*25*), but are not yet approved for use.

We review the available scientific literature to i) describe how PET/CT imaging may impact prostate radiotherapy planning, ii) assess the potential impact of various PET/CT imaging strategies on the planning process, and iii) describe current investigations aimed to measure this impact.

PET probes, summary

Na-F PET/CT localizes preferentially to areas of active bone remodeling, which is characteristic of osteoblastic prostate cancer bone metastases. Advantages over planar ^{99m}Tc bone imaging include a higher signal-to-noise ratio and less time needed after injection to imaging (*26*). Some reports suggest improved sensitivity and specificity of Na-F PET/CT as compared to planar bone scan (*5*,*27*,*28*). Na-F PET/CT is approved but is not widely reimbursed, which has limited its clinical use. It does not image soft tissue or nodal disease.

^{11}C- and ^{18}F- choline probes offer selectivity to prostate cancer tissue due to increased choline transport, which might be due to changes in cell membrane synthesis and proliferation (*21*). Choline PET/CT can detect evidence of recurrent disease in 80% of patients with a biochemical recurrence after prostatectomy at a PSA of 2 ng/mL, greatly exceeding that of current first-line imaging. As a result, ^{11}C-choline was FDA approved in 2012 in the United States for imaging of recurrent prostate cancer after local failure (*29*).

Anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC, Fluciclovine, Axumin™), a synthetic amino acid analog, is taken up by cells through the amino acid transporters ASCT2 and LAT-1 (*30*,*31*). Like ^{11}C- and ^{18}F- choline tracers, the specificity of fluciclovine for prostate cancer relies on altered metabolic pathways. Fluciclovine PET/CT has been evaluated extensively in the setting of biochemical recurrence. A recent large multisite study reported a detection rate of 40% for patients with biochemical recurrence and a PSA of 0.79 ng/mL or less (*32*). Improved detection rates of recurrent prostate cancer using fluciclovine as compared to ^{11}C-choline led to

the approval of fluciclovine for imaging of recurrent prostate cancer in 2016 (*23*,*33*). Evaluations of fluciclovine in the initial staging of prostate cancer are ongoing (NCT03081884).

PSMA is a cell surface glycoprotein and folate hydrolase highly expressed on prostate cancer cells (*34*). Expression increases with gleason grade (*35*,*36*) and remains high during the castration resistant disease state (*37*). The most well-studied PSMA probes are small molecule ligands, such as ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL, that bind the enzymatic active site. A recent report of 120 intermediate and high-risk patients who underwent ^{68}Ga-PSMA PET/CT for initial staging followed by radical prostatectomy showed a sensitivity of 66% and specificity of 98.9% for lymph node metastases detected by ^{68}Ga-PSMA PET/CT (*38*). However, a smaller study (*39*) reported a lower sensitivity. Ongoing studies will be required for clarification. ^{68}Ga-PSMA PET/CT also outperformed planar bone scan for detection of osseous metastases in large retrospective analyses (*40*,*41*). ^{68}Ga-PSMA PET/CT, like ^{11}C-choline and fluciclovine, has been studied most in patients with recurrent prostate cancer after failure of local therapy. Large retrospective series reveal detection rates from 50% to 58% for patients with PSA <0.5 ng/mL, and more than 95% when PSA >2 ng/mL (*24*,*42*). The detection rate of ^{68}Ga-PSMA PET/CT for recurrent prostate cancer exceeds that of choline PET/CT (*43*,*44*), and may exceed fluciclovine PET/CT. No PSMA PET probes have FDA NDA approval for use in the United States, but numerous trials are underway (NCT02918357, NCT02919111, NCT02673151, NCT02940262). The high and largely specific expression of PSMA exclusive to prostate cancer cells led to development of PSMA targeted radio-ligand therapeutics (*45*). ^{177}Lu-PSMA has demonstrated efficacy in

patients with treatment refractory metastatic castration resistant prostate cancer (*45*,*46*). Larger trials are underway (NCT03042312).

The remainder of this review will focus on the use of choline, fluciclovine, and PSMA PET/CT imaging for definitive and salvage prostate radiotherapy planning.

Prostate Radiotherapy Planning

Prior to planning, the radiation oncologist first delineates areas of gross tumor (GTV) and areas with suspicion for occult tumor (CTV). A final volume (the planning tumor volume, or PTV) takes into account daily patient set-up errors and is typically an isometric expansion of the CTV. Organs at risk (OAR, e.g. bladder, rectum) are also delineated. The aim of the radiation oncologist is to deliver the highest possible dose to the tumor without impairing function of surrounding organs. Modern treatment planning leverages advances in patient positioning and immobilization systems, dynamic multi-leaf collimators, inverse planning techniques, and computerized delivery. The end result is highly conformal, reproducible delivery of dose to target volumes (CTVs and PTVs) with adequate sparing of adjacent normal tissues and organs (specifically, OARs). Therefore, the accurate delineation of the malignant tissue itself is a critical limiting factor for improving efficacy of modern radiotherapy. Treatment planning is most often based on CT because electron densities, which are required for accurate dose calculations, can be inferred from hounsfield units (HU). To aid target delineation, other imaging modalities such as MRI and PET/CT can be fused to the dedicated planning CT scan through mutual information based image registration. Planning target can be defined

based on these images and resultant target contours can be transferred back to the dedicated planning CT for treatment planning (See Figures 1 and 2).

Radiotherapy is a potentially curative therapy for localized prostate cancer alone or in combination with hormonal therapy, and a potentially curative salvage therapy for recurrent prostate cancer after radical prostatectomy. Notably, gross prostate tumor is often not visible on CT. MRI can reveal intraprostatic tumor foci with good sensitivity (*47*), but most prostate tumors are multifocal, with some occult lesions unseen on MRI (*48*). Therefore, in the definitive setting, the CTV includes the entirety of the prostate, with or without inclusion of the seminal vesicles and pelvic lymph nodes, depending on clinico-pathologic features. Figure 1A shows the CTV and organs at risk delineated for a typical low to favorable intermediate risk prostate cancer patient. The prostate is prescribed a higher dose than the nodes (if included). In the salvage setting, the CTV is the prostate fossa and seminal vesicle remnants, with or without inclusion of the pelvic lymph nodes. Figure 1B shows the CTVs, and organs at risk for a patient with recurrent prostate cancer to undergo SRT, with elective pelvic nodal coverage included. Salvage prostate radiotherapy (SRT) target volumes are usually drawn in the absence of radiographic evidence of recurrent disease. In practice, most physicians base their CTVs on published consensus guidelines. The RTOG has published guidelines for pelvic nodes (*49*). The RTOG (*50*), EORTC (*51*), and the Australian and New Zealand Radiation Oncology Genito-Urinary Group (*52*) have published guidelines for contouring of the prostate bed. These consensus CTVs are used in current clinical trials and guide routine care.

In both the definitive and salvage setting, the value of including radiographically negative pelvic nodes is unclear and the subject of current randomized trials (RTOG 0924, RTOG 0534, NCT00567580). In practice, many radiation oncologists include pelvic nodes for high-risk patients (typically, patients with any of the following: initial PSA >20, clinical or radiographic T stage 3 or higher, Gleason Grade 8 or higher, rapid PSA doubling time) in both the definitive and salvage settings. In patients with radiographic evidence of gross tumor within the nodes, the prostate bed, or within the prostate itself, a higher dose can be prescribed to cover the gross tumor. This can be accomplished either by the techniques of simultaneous integrated boost (SIB) (delivering a higher dose to the gross tumor in each fraction) or sequential boost (delivering extra fractions of dose to the gross tumor), or a boost delivered by brachytherapy (temporary or permanent implantation of radioactive seeds).

Incorporation of PET/CT may impact RT planning in numerous ways. First, PET/CT defined gross disease within a target volume can be prescribed a higher dose. Figure 2A shows a typical SRT plan for a patient with recurrent prostate cancer. The dose is displayed as a heat map. The dose-volume histogram (right) shows the dose (horizontal axis) that covers a given volume percent (vertical axis) of each delineated volume. Figure 2B shows an SRT plan in which a PSMA positive left sided internal iliac node receives a higher dose than the surrounding pelvic nodal volume. Note that 100% of the PSMA positive node (plus a margin) receives more than 65 Gy (dotted line) whereas 100% of the total pelvic nodal volume receives 45 Gy (solid purple line).

Second, CTVs can be expanded to encompass areas of disease not seen by current first-line imaging and not normally targeted by consensus CTVs (Figure 3). Third,

evidence of metastatic disease indicates that local therapy alone would not offer cure. In the setting of oligometastatic disease (limited metastatic disease burden, variously interpreted to mean up to 3 or 5 distinct sites), many physicians offer metastasis directed therapy aimed at local ablation of the metastases (Figures 4 - 6). Metastasis directed therapy is the subject of numerous current clinical trials (*53*). Finally, in some cases where PET/CT shows unexpected diffuse metastatic disease, RT may be considered futile and abandoned.

Potential Impact of PET/CT on Definitive Prostate Radiotherapy.

Several studies assessed the impact of molecular PET/CT imaging on Definitive Prostate Radiotherapy planning (Table 1). Lopez et al conducted a retrospective analysis on the impact of ^{11}C-choline PET/CT on definitive prostate radiotherapy in 9 patients (*53*). Four of the 9 patients had a change in contouring and prescription dose. Two had extension of volumes to include additional nodal regions that were not initially targeted. One received metastasis directed therapy to a solitary bone metastasis in addition to treatment of the prostate and nodes. One patient was down-staged due to lack of ^{11}C-choline uptake in a suspected metastasis seen on current first-line imaging. Kuang et al (2015) reported on the feasibility of focal dose escalation to PET defined intraprostatic lesions in 30 patients who underwent ^{18}F-choline PET/CT prior to radiation planning (*55*). They showed that focal escalations to 105 Gy within a prostate CTV receiving 79 Gy was dosimetrically feasible with adequate protection of normal tissue. Vees et al evaluated 19 high-risk prostate cancer patients who underwent both ^{18}F-choline PET/CT and sentinel node single photon emission computed tomography

(SPECT/CT) (*56*). ^{18}F-choline PET/CT identified two nodes that were within standard CTVs. These positive nodes were treated with an escalated dose. Notably, sentinel node SPECT/CT identified 104 nodes, 27 of which would not have been included in consensus CTVs.

Zamboglou et al reported on the feasibility of boosting PSMA-defined intraprostatic lesions to 95 Gy within a prostate receiving 77 Gy in 10 patients (*57*). The same group also reported a concordance in intraprostatic disease between ^{68}Ga-PSMA PET/CT and multiparamtetric MRI (mpMRI) (*58*). Dewes et al reported on 15 patients who were treated with radiotherapy and underwent ^{68}Ga-PSMA PET/CT prior to planning (*59*). The ^{68}Ga-PSMA PET/CT changed the TNM stage in 8 of the 15 patients. Modifications of CTVs and changes in the prescription dose occurred in 5 and 12 patients, respectively. Two patients with suspected metastatic disease from a prior ^{11}C-choline scan were down-staged. Sterzing et al reported on 15 patients who underwent ^{68}Ga-PSMA PET/CT for radiotherapy planning (*60*) Four patients had a change in TMN staging resulting in a change in CTV or prescription.

Randomized, prospective investigations evaluating the impact of PET/CT on definitive prostate radiotherapy planning are lacking. The recent Phase III ASCENDE-RT trial showed of patients with mostly high-risk prostate cancer treated with the combination of radiotherapy and androgen deprivation had 9-year progression-free and metastasis free survivals of 73% and 87%, respectively (*61*). The long natural history of prostate cancer and the success rates of definitive radiotherapy in even high-risk patients (*61*) requires large patient numbers to power a trial to detect an improvement in

metastasis free survival. A biochemical progression free survival primary endpoint, often used in trials in the localized setting, would require fewer patients.

Potential Impact of PET/CT on Salvage Prostate Radiotherapy.

Several studies assessed the impact of molecular PET/CT imaging on salvage Prostate Radiotherapy planning (Table 2).

Souvatzoglou et al conducted a retrospective study on 37 patients with biochemical recurrence (median PSA 0.5) after radical prostatectomy who underwent ^{11}C-choline PET/CT. ^{11}C-choline PET/CT was positive in 30% of patients, with 5 patients having recurrence in the pelvic nodes and 6 within the prostate bed (*62*). All patients were initially planned for SRT to the prostate bed alone; the ^{11}C-choline PET indicated inclusion of the pelvic nodes in 13.5% of patients. Würschmidt et al similarly reported on 18 patients with biochemical recurrence (median PSA 1.9) that underwent ^{18}F-choline PET/CT (*63*). All patients were initially planned to undergo SRT directed to the prostate bed alone. ^{18}F-choline PET/CT was positive in 87.5% of patients and impacted SRT through dose escalation or inclusion of pelvic nodes in all but one patient. Ceci et al reported that 62% of 95 patients with biochemical recurrence after prostatectomy (median PSA 1.6) had a positive ^{11}C-choline PET/CT, with 31.5% of patients having a change in target volumes and 15.8% having the planned SRT not delivered (due to distant metastases), consequent to the PET findings (*64*). Castelluci et al reported on 605 patients with biochemical recurrence after radical prostatectomy (19 of whom also received adjuvant prostate bed RT, median PSA 1.07, range 0.2 to 2) that underwent

^{11}C-choline PET/CT prior to planning of SRT (*65*). ^{11}C-choline PET/CT was positive in 28.5% of patients, with 14.5% of patients showing evidence of distant metastases. ^{11}C-choline PET/CT changed the planned SRT in 23% of patients, of which 14.7% of patients did not undergo the initially planned treatment due to the presence of distant disease. Jereczek-Fossa et al reported on 60 patients with biochemical failure after radical prostatectomy (5 of which were on long term ADT with evidence of castration resistance) that underwent ^{11}C-choline PET/CT for SRT planning (median PSA 1.1) (*66*). ^{11}C-choline PET/CT was positive in 51%, and all patients with a positive scan and recurrent disease in the pelvis had the recurrent disease focus boosted to 80 Gy in addition to irradiation of the prostate bed and pelvic nodes. Toxicity was deemed acceptable (acute grade 3 GI toxicity was 5%). Taken as a group, these studies found that addition of choline PET to SRT planning changed the initial plan in 357 of 1083 patients (33%) (*62–69*). The main limitation of these studies is that the median PSA at the time of choline PET was significantly higher then the PSA threshold when SRT is commonly initiated. The success rate of salvage radiotherapy decreases with increasing PSA at the time of salvage, most physicians initiate salvage radiotherapy at PSA <1ng/mL, and preferably, at or below 0.2 ng/mL (*70*). Therefore, imaging that detects disease at or below these thresholds has the best chance to impact salvage prostate radiotherapy.

For PSMA PET/CT, detection rates of about 50% are reported even at PSA levels of <0.5 ng/ml (*71*), which is low enough to impact target volume delineations for routine SRT. The potential impact of ^{68}Ga-PSMA PET/CT on RT planning has been assessed in 7 studies. Shakespeare et al. reported that ^{68}Ga-PSMA PET/CT changed radiotherapy

management in 46% of their patient series (which included primary RT, post-prostatectomy SRT, post-primary RT salvaged with additional RT) (*72*). Sterzing et al reported on 42 patients with biochemical recurrence after prostatectomy (median PSA 2.8) that underwent ^{68}Ga-PSMA PET/CT. The PET had an impact of 51 % on radiotherapy management (*60*). Albisinni et al. reported an impact on subsequent management in 99/131 patients (76%) with rising PSA after various treatment with curative intent (surgery, radiotherapy, HIFU) (*73*). Blumel et al reported on 45 patients with biochemical recurrence after prostatectomy who underwent ^{68}Ga-PSMA PET/CT (*43*). The scan was positive in 53.3% of patients, resulting in a change in SRT for 42.2% of all patients. These changes included expansion of the target volumes, dose escalations, or elimination of SRT entirely in 47%, 32%, and 10% of patients, respectively. Habl et al reported on 83 patients with biochemical recurrence after prostatectomy that underwent ^{68}Ga-PSMA PET/CT prior to SRT (median PSA 0.69) (*71*). The PET was positive for 71% of patients, impacting the SRT plan in 56.5%. Schiller et al. reported 31 patients with PSMA positive LNs discovered prior to initiating SRT, and found that 40% of the PSMA positive pelvic LN were not covered by the standard RTOG CTVs. Consequently, the ^{68}Ga-PSMA PET/CT resulted in SRT planning changes in 87% (dose escalation, expansion of target volumes, and addition of metastasis directed SBRT in 51.5%, 40%, and 3% of patients, respectively) (*71*). Taken as a group, the pooled median rate of impact of ^{68}Ga-PSMA PET/CT on SRT planning is 46% (range 34.5-87%). The primary limitations of these reports are the inhomogeneity of the patients, inconsistent description of anatomic patterns of relapse, and the wide range of PSA values at the time of the PET/CT (*43*,*60*,*71–75*). Evaluations of a more homogenous patient cohort with biochemical failure after radical prostatectomy at low

PSA values (ideally <1) would offer the most insight into the potential impact of PSMA PET/CT on SRT.

Potential Impact of PET/CT on systemic staging and metastasis directed therapies.

Current first-line imaging was used in the many clinical trials that guide current prostate treatment paradigms. As PET/CT becomes incorporated into routine care, it is likely that many patients staged N0 or M0 by current first-line imaging will be more accurately staged as N1 or M1. Roach et al recently reported on the results of ^{68}Ga-PSMA PET/CT in 431 patients with primary and recurrent prostate cancer with negative or equivocal current first-line imaging (*76*). The PET scans revealed previously unknown nodal disease and distant metastatic disease in 39% and 16% of patients, respectively (*76*).

It is likely that many of patients upstaged by PET/CT will have limited metastatic disease burden. For patients with radiographic evidence of N1 disease at initial staging, current guidelines include radiotherapy of the prostate and pelvic nodes with long-term ADT (*77*). Treatment of patients with radiographic evidence of N1 disease after local failure is less clear. The primary therapy for prostate cancer patients with M1 disease is ADT. However, to many clinicians, it seems reasonable to approach a patient with limited metastatic disease (oligometastatic) differently than a patient with diffuse metastatic disease. (Investigators have variously defined oligometastatic prostate cancer as having at most 3 or 5 distinct distant metastases.) Metastasis directed therapy, via

SBRT or metastatectomy, with or without systemic therapy is a strategy under evaluation in a number of ongoing and planned prospective trials (*78*). Whether or not prostate cancer patients with oligometastatic disease ultimately benefit from a different therapeutic strategy than patients with diffuse metastatic disease remains unknown. In any case, identification of these patients is likely to increase substantially as clinicians adopt PET/CT for initial and recurrent staging.

Prospective trials evaluating the impact of PET/CT on prostate radiotherapy planning

A number of ongoing prospective trials are evaluating the impact of PET/CT on prostate cancer treatment in a variety of clinical settings (Table 3). In the setting of biochemical recurrence, the FALCON trial (NCT02578940) is evaluating the impact of ^{18}F-fluciclovine PET/CT on salvage therapy management. The Lawson Health Research Institute in Ontario is conducting three trials evaluating the impact of ^{18}F-choline PET/CT on salvage therapy management in patients with negative current first-line imaging (NCT01804231, NCT02131649, NCT01804231). The University of Toronto is also conducting a single arm trial of ^{18}F-DCFPyL PET/CT in patients with biochemical failure after surgery and negative current first-line imaging (NCT03160794). The endpoints are detection of oligorecurrent disease and boichemical response to oligometastatic SBRT offered to patients with detectable disease amenable to this treatment.

Two single arm prospective trials are evaluating the impact of PET/CT on SRT. The University of Wisconsin is prospectively evaluating ^{18}F-DCFPyL PET/CT in 36

patients planned for surgery or SRT (NCT03232164). The Champalimaud Foundation in Portugal is conducting a feasibility trial of SRT delivered by SBRT technique in patients planned with either PSMA or ^{11}C-choline PET/CT (NCT02976402). A phase II trial of ^{11}C-choline PET/CT guided definitive radiotherapy trial in 63 patients, including focal dose escalation to intraprostatic foci, is being conducted by the Alberta Health Services, CancerControl Alberta (NCT02004418). The NCI is conducting a prospective phase I trial of ^{18}F-DCFPyL PET/CT guided SBRT for locally recurrent prostate cancer after definitive radiotherapy (NCT03253744).

In the oligorecurrent metastatic setting, the STOMP trial (NCT01558427) at the University Hospital, Ghent, is randomizing patients re-staged with ^{11}C-Choline PET to metastasis directed therapy versus observation. The primary endpoint is time to initiation of androgen deprivation therapy.

Jani et al at Emory University are conducting a prospective phase III trial evaluating the use of ^{18}F-fluciclovine PET/CT to guide and improve outcomes in patients planned for SRT (NCT01666808). In this ongoing trial, 162 patients with rising PSA after radical prostatectomy and current first-line imaging negative for distant metastases are being randomized to routine SRT guided by current first-line imaging versus SRT guided by abdominal-pelvic ^{18}F-fluciclovine PET/CT. The primary endpoint is biochemical control. Although no cancer control outcome data are yet available, the investigators have reported on the impact of the ^{18}F-fluciclovine PET/CT on the planning for patients randomized to the experimental arm and the acute toxicity of SRT guided by the PET/CT compared to SRT guided by current first-line imaging (*79*). Patients randomized to the PET/CT arm were planned first with and then without information from the PET. Target

volumes were modified in 31 of the first 41 patients (73%) in the PET arm (median PSA 0.43). Doses to critical organs at risk (rectum, bowel, bladder) were not significantly different for the PET-assisted treatment volumes, despite the volumes being larger. Acute toxicity was also no different between the treatment arms, suggesting that the additional treatment volumes guided by PET may not increase long-term toxicity. Additional follow-up is required to assess the impact of the fluciclovine PET/CT on biochemical control and late toxicity.

Conclusion

Conventional systemic imaging of prostate cancer suffers from poor sensitivity and underestimates the extent of disease in many patients. PET/CT using ^{11}C- or ^{18}F-choline, ^{11}C-acetate, ^{18}F-FACBC (fluciclovine), or ^{68}Ga- or ^{18}F-ligands that bind PSMA improve imaging accuracy. Of these probes, the PSMA ligands are the most sensitivity and specific. Incorporation of PET/CT into current practice is expected to upstage a substantial proportion of patients, with clear implications for current treatment paradigms. Modern radiotherapy planning is immediately amenable to integration of these PET scans Retrospective assessments support the hypothesis that integration of PET/CT into radiotherapy planning could have a meaningful clinical benefit to patients. Results from prospective trials are required to assess this impact.

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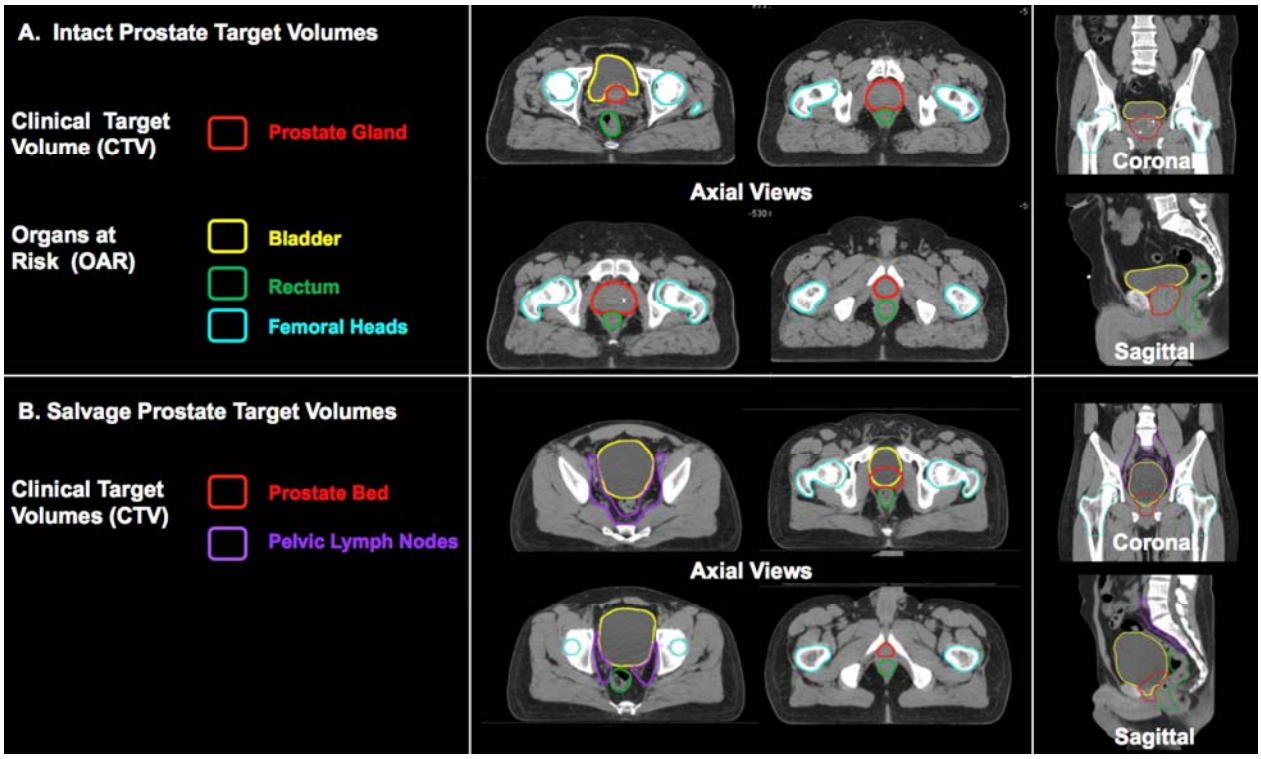
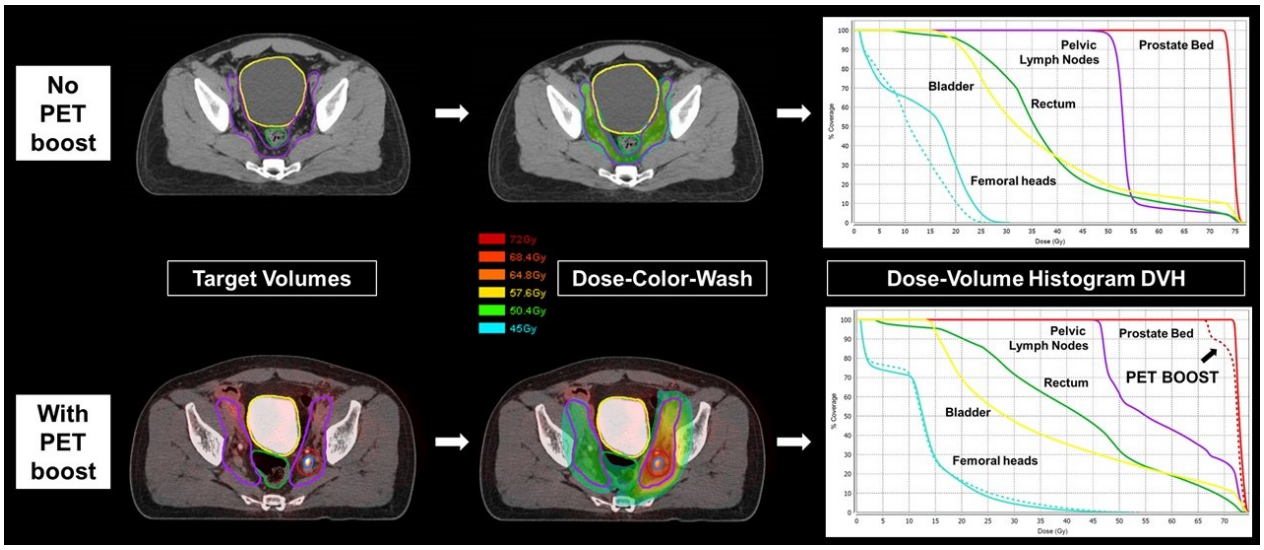
Figure 1



Clinical target volume (CTV) contours and organs at risk are contoured by a radiation oncologists on a dedicated planning CT (CT simulation). The CTV for an intact (definitive) prostate is the prostate gland itself (A) with or without pelvic nodes and seminal vesicles. The CTV for salvage radiation therapy (B) includes the prostate bed with or without pelvic nodes. The CTV is drawn usually in the absence of radiographic evidence of recurrent disease. Instead, CTVs are based on consensus guidelines to encompass the prostate bed with or without the pelvic lymph nodes. The most commonly used external beam dose-fractionation schedules for definitive prostate RT deliver 75.6 to 79.2 Gy in fractions of 1.8 to 2 Gy, while those for salvage radiation therapy deliver 66 to 72 Gy. When included, pelvic nodal volumes are prescribed 45 to 50.4 Gy.

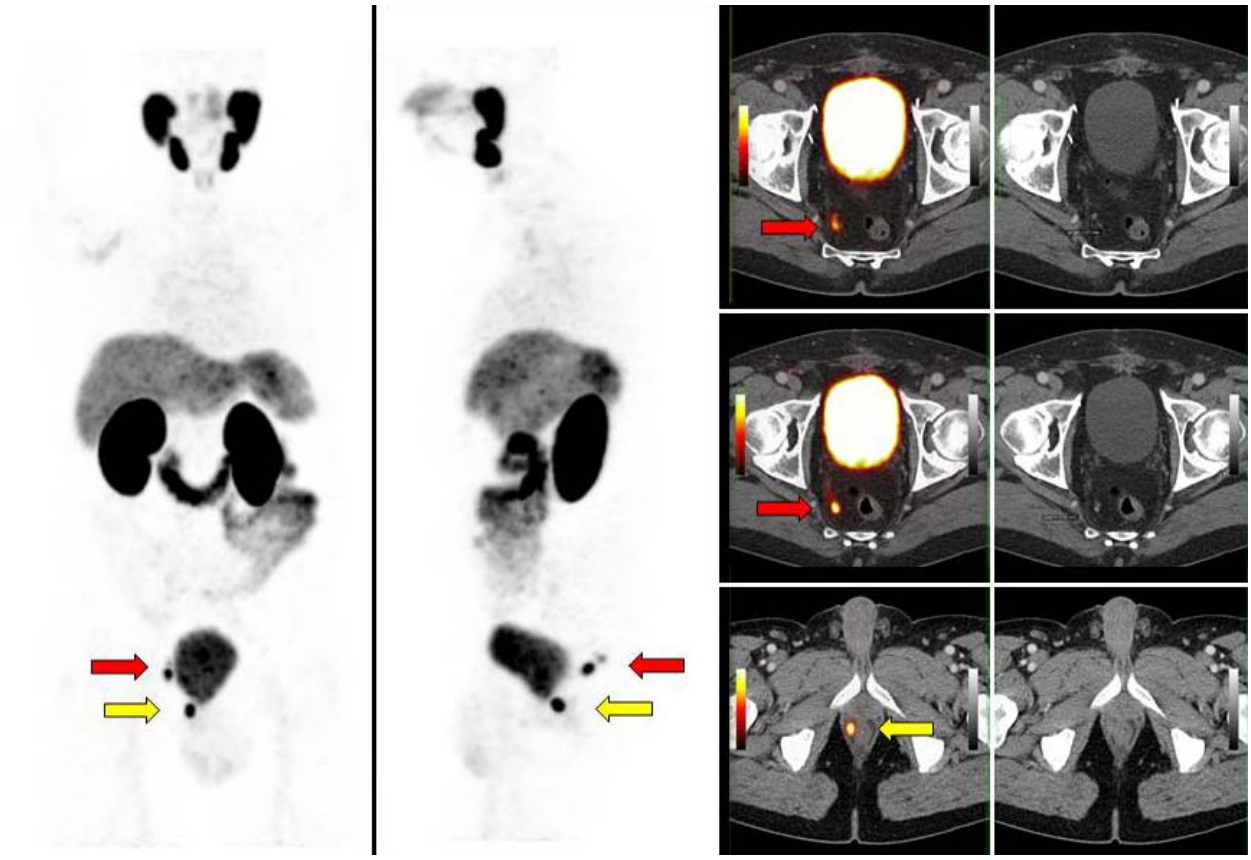
Red: Prostate and Prostate bed CTV; Purple: Pelvic Lymph Nodes CTV; Yellow: Bladder; Green: Rectum; Turquoise: Femoral Heads.

Figure 2



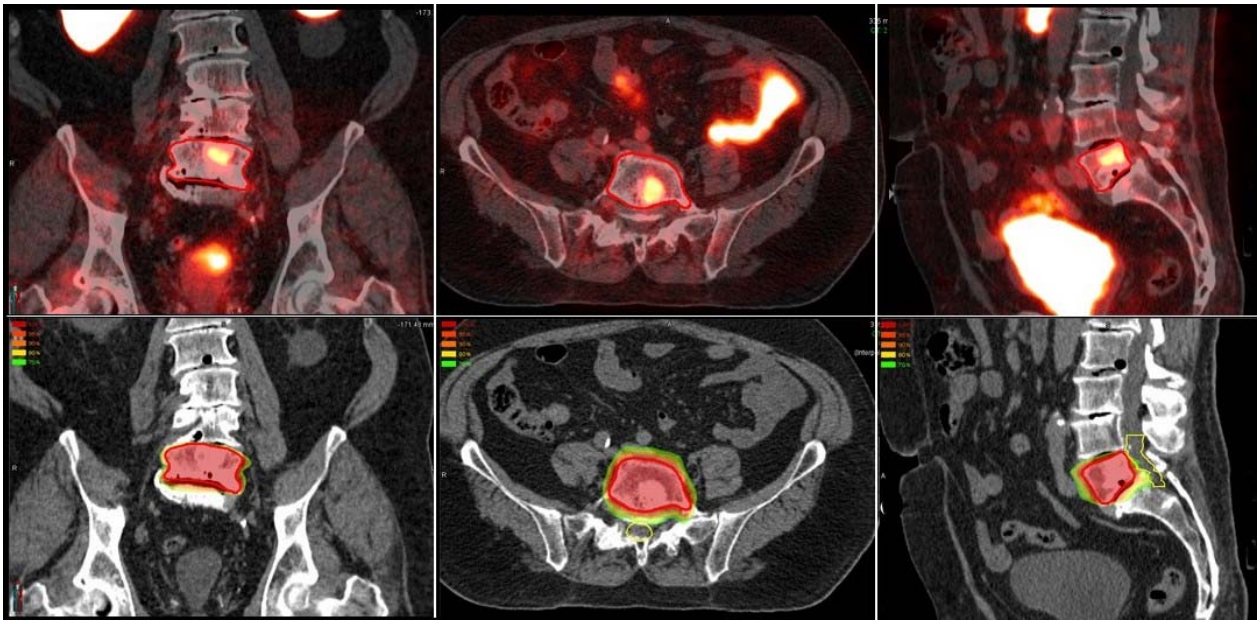
PSMA PET enables identification of areas of gross disease that are missed on CT. Intensity modulated radiotherapy (IMRT) can be used to deliver a higher dose to areas with gross disease. (Top). Example of a salvage prostate RT plan and dose-volume histogram (DVH) of a patient with rising PSA after radical prostatectomy planned without radiographic evidence of visible gross disease. The pelvic nodal and prostate bed volumes are prescribed doses of 45 and 72 Gy, respectively. (Bottom). Example of a salvage prostate RT plan and dose-volume histogram (DVH) of a patient who underwent a ^{68}Ga-PSMA PET prior to planning. PSMA PET enables identification of a PSMA-positive left internal iliac pelvic node. IMRT was used to focally increase dose to the gross disease to beyond 65 Gy while adequately sparing normal organs at risks. Dose-color-wash displays the simulated dose on the CT simulation scan with a color scale (blue 45 Gy to red 72 Gy). DVH is plotted with bin doses along the horizontal axis and percentage of the structure that receives dose greater than or equal to that dose on the vertical axis (right panel). Each line on the DVH plot represents a particular volume (e.g. CTV, and relevant organs at risk).

Figure 3



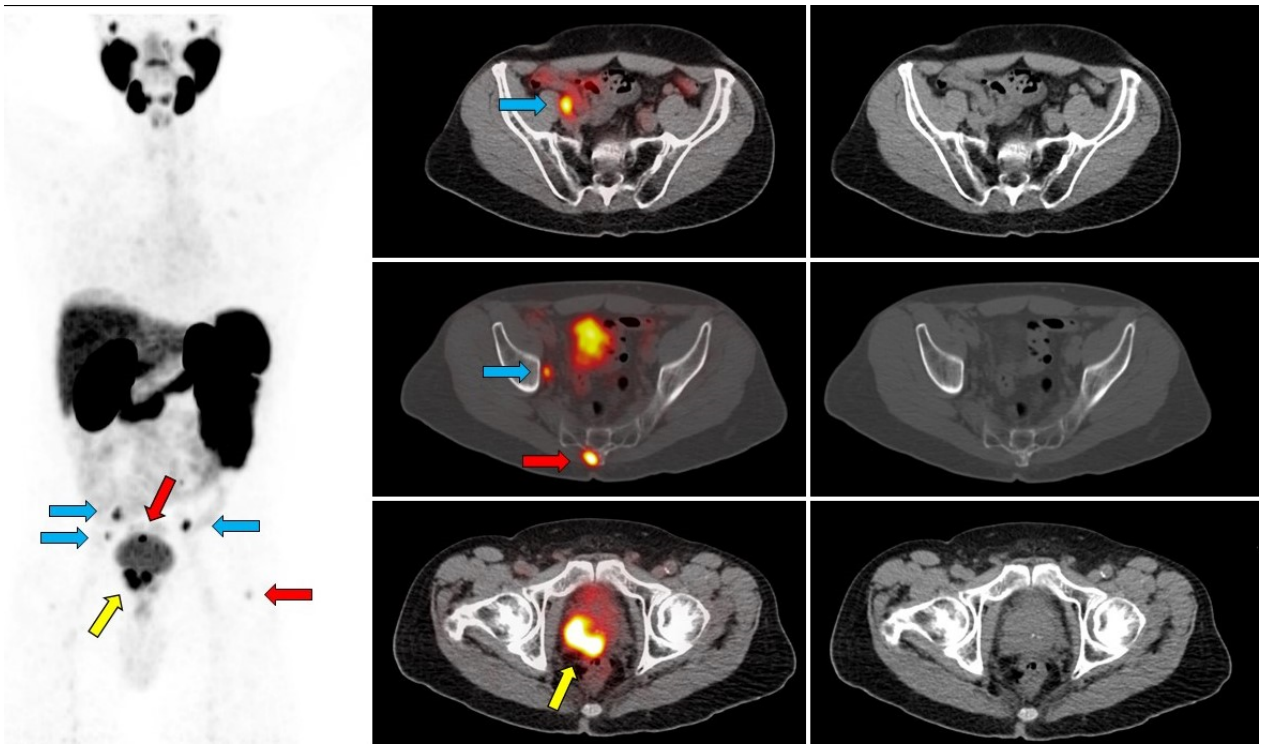
Impact of ^{68}Ga-PSMA PET/CT on target volumes. A patient with biochemical recurrence (PSA 0.81 ng/ml) one year after radical prostatectomy (Gleason 9) was referred for salvage radiation therapy. ^{68}Ga-PSMA PET showed a focal ^{68}Ga-PSMA uptake in the right side of the prostate bed (yellow arrows) with nodular tissue thickening on CT. In addition, ^{68}Ga-PSMA PET also revealed focal ^{68}Ga-PSMA uptake in two right peri-rectal subcentimeter lymph nodes (short axis 4 mm, red arrows). Peri-rectal nodes are not covered by standard salvage RT, and would not have been suspected to harbor recurrent disease based on the CT. The salvage RT volumes were expanded to encompass the peri-rectal nodal region.

Figure 4



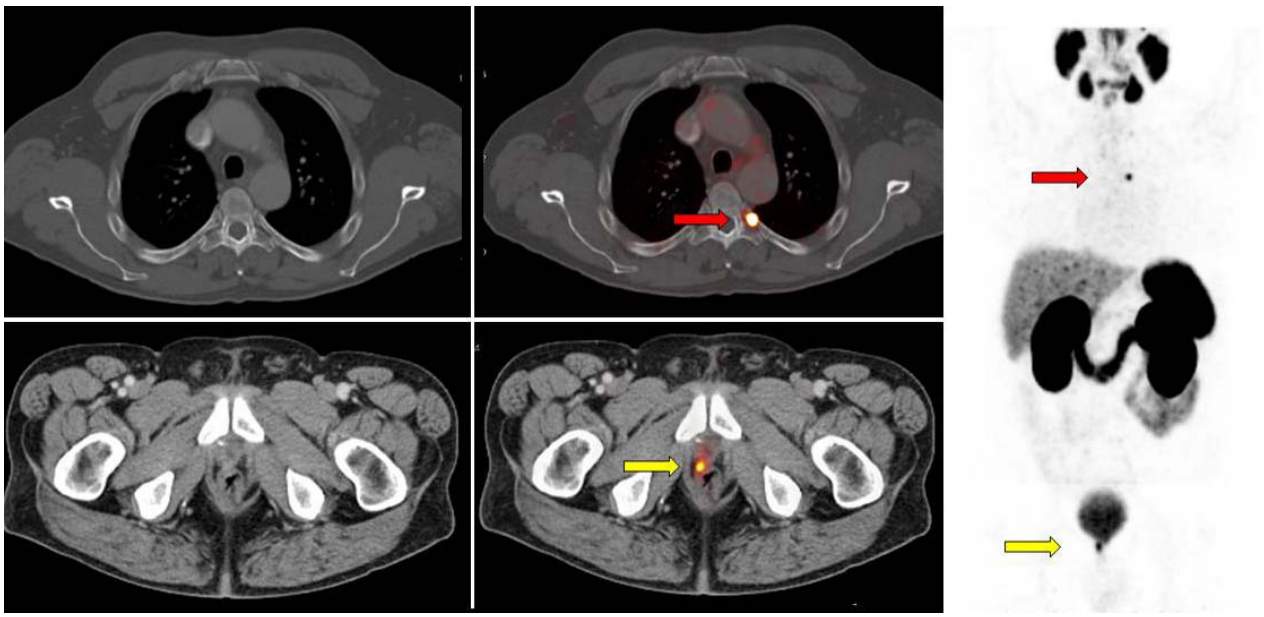
^{68}Ga-PSMA PET/CT identified a solitary L5 metastasis in a patient with recurrent prostate cancer after prostatectomy and a PSA of 1. Stereotactic Body Radiotherapy (SBRT) was used to deliver 18 Gy in a single fraction to the solitary metastasis. Dose-color-wash shows 100% of the prescribed dose covers the target volume while sparing the cauda equine (yellow contours).

Figure 5



Impact of ^{68}Ga-PSMA PET/CT on initial management of high-risk prostate cancer. A 77 year old man with newly diagnosed prostate cancer (initial PSA 7.1, GS 4+5=9) underwent MRI showing a right posterolateral prostate lesion with gross extra-capsular extension and right seminal vesicle invasion. Bone scan was negative. ^{68}Ga-PSMA PET/CT showed intense PSMA uptake in the prostate with seminal vesicle invasion (yellow arrow), PSMA-positive sub centimeter external iliac lymph nodes (blue arrows), and focal PSMA uptakes in 2 bone lesions (red arrows). The patient was staged as hormone sensitive oligometastatic M1b and offered SBRT to the two bone metastases in addition to radiotherapy to the prostate and pelvic nodes with concurrent ADT.

Figure 6



A patient with biochemical recurrence (PSA 1.85 ng/ml) seven years after radical prostatectomy (Gleason 7, pT2c) underwent ^{68}Ga-PSMA PET/CT that showed focal PSMA uptake in the right side of the prostate bed (yellow arrows) and intense focal PSMA uptake in the proximal portion of left 5th rib (red arrows). The patient was offered metastasis directed SBRT in addition to salvage RT to the prostate bed and nodes.

Table 1.

Author	Year	PET/CT Probe	Median PSA (range)	*n*	PET +	% PET +	Change in RT Plan (%)
Würschmidt	2011	^{18}F-Choline	10.4 (2.5-731)	7	7	100%	28.50%
Vees	2012	^{18}F-Choline	30.5 (6.4-66.5)	19	NA	NA	22%
Jereczek-Fossa	2014	^{11}C-Choline	NA	16	NA	NA	12.50%
Garcia	2015	^{11}C-Choline	(6.3-30.4)	61	61	100%	24.50%
Lopez	2015	^{11}C-Choline	18.18 (4.90–55.40)	9	NA	NA	44%
Alongi	2015	^{18}F-Choline	6.5 (4.1-143)	60	57	95%	21.60%
Sterzing	2016	^{68}Ga-PSMA	7.04 (0.28–45)	15	9	60%	26.50%
Dewes	2016	^{68}Ga-PSMA	13.5 (8.2-63.9)	15	15	100%	33.30%
Schreibmann	2016	^{18}F-FACBC	0.43 (0.02-11.15)	41	32	78%	73%

Table 2.

Author	Year	PET/CT Probe	Median PSA	*n*	PET+	Extrapelvic PET+	Any SRT Planning Change	RT Considered Futile
Souvatzoglou	2011	^{11}C-Choline	0.5 (0.25–12.3)	37	0.3	0	0.135	0
Würschmidt	2011	^{18}F-Choline	1.9 (0.42-4.8)	16	0.875	0.065	0.815	0.065
Ceci	2014	^{11}C-Choline	1.6 (0.2–7.1)	95	0.62	20	0.475	0.158
Castelluci	2014	^{11}C-Choline	1.1 (0.2–2)	605	0.285	0.145	0.23	0.147
Goldstein	2017	^{11}C-Choline	2 (0.16-79)	6		NA	0.335	0
Jereczek-Fossa	2014	^{11}C-Choline	1.1 (0.2-16.2)	55	0.51	NA	0.31	NA
Shakespeare	2015	^{68}Ga-PSMA	1.1 (0.017–20.4)	18		NA	0.46	NA
van Leeuwen	2015	^{68}Ga-PSMA	0.2 (0.05-0.99)	70	0.545	0.055	0.345	0.071
Sobol	2016	^{11}C-Choline + mpMRI	2.3 (1.4-5.5)	260	0.775	0.265	0.515	0.265
Sterzing	2016	^{68}Ga-PSMA	2.8 (0.16–113)	42	0.595	NA	0.605	NA
Albisinni	2016	^{68}Ga-PSMA	2.2 (0.72–6.7)	48		NA	0.76	NA
Bluemel	2016	^{68}Ga-PSMA	0.67 (0.10–11.2)	45	0.535	0.09	0.42	0.044
Lamanna	2017	^{18}F-Choline/ ^{11}C-Acetate	1.9 (0.3-3)	9	NA	0	0.22	0
Akin-Akintayo	2017	^{18}FACBC	0.55 (0.07–11.2)	42	0.81	0.05	0.405	0.048
Habl	2017	^{68}Ga-PSMA	0.69 (0.09-14.7)	83	0.71	0.095	0.565	0
Schiller	2017	^{68}Ga-PSMA	0.71 (0.12-14.7)	31	1	0.03	0.87	0

Table 3.

Trial Number	PET Probe	Cohort	Phase	Arms	Total N	Primary Endpoint	Sponsor
NCT02578940	Fluciclovine	biochemical failure after local therapy	3	Single arm: fluciclovine PET	180	Impact on salvage therapy	Blue Earth Diagnostics
NCT01804231	18-F Fluorocholine	biochemical failure after local therapy and negative conventional imaging	2	Single arm: 18F-FCH PET-MRI	22	Impact on salvage therapy	Lawson Health Research Institute
NCT02131649	18-F Fluorocholine	biochemical failure after surgery and negative conventional imaging	2	Single arm: 18F-FCH PET-CT, planned for SRT	140	Impact on salvage therapy	Lawson Health Research Institute
NCT01804231	18-F Fluorocholine	biochemical failure after local therapy and negative conventional imaging	2	Single arm: 18F-FCH PET-MRI	22	Impact on salvage therapy	Lawson Health Research Institute
NCT03160794	[18F]DCFPyL	biochemical failure after surgery and negative conventional imaging	2	Single arm: [18F]DCFPyL-MRI	75	Detection of oligorecurrent disease, boichemical response to oligometastatic SBRT	University of Toronto
NCT02131649	18-F Fluorocholine	biochemical failure after surgery and negative conventional imaging	2	Single arm: 18F-FCH PET-MRI	140	Evidence of extraprostatic disease on PET	Lawson Health Research Institute
NCT03232164	[18F]DCFPyL	pre-surgery, pre-SRT, or metastatic	1	Single arm: [18F]DCFPyL PET-MRI	36	Biochemical response for pre-SRT patients	University of Wisconsin
NCT02976402	Any PSMA or choline	biochemical failure after surgery and no distant metastases by PSMA or choline PET	1	Single arm: Any PSMA or choline PET-CT	30	Feasibility of delivering SRT by SBRT technique	Fundacao Champalimaud
NCT02004418	11C-Choline	intermediate risk localized prostate cancer	2	Single arm: 11C-Choline PET guided prostate RT with SIB	63	3- and 5- year FFS, toxicity	AHS Cancer Control Alberta
NCT01558427	11C-Choline	oliogmetastatic recurrence after local therapy	2	A: observation, B: 11C-Choline PET guided metastasis directed therapy (including SBRT)	54	Time to initiation of androgen deprivation	University Hospital, Ghent

NCT01666808	Fluciclovine	biochemical failure after surgery and negative conventional imaging	3	A: fluciclovine PET guided SRT, B: routine SRT	162	3-year FFS	Emory University
NCT03253744	18F-DCFPyL	biochemical failure after defintiive radiation	1	Single arm: Salvage SBRT guided by PET-CT	52	Safety/MTD	National Cancer Institute