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Predictors of ^{18}F-DCFPyL-PET/CT Positivity in Patients with Biochemical Recurrence of Prostate Cancer After Local Therapy

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Brief-Title: ^{18}F-DCFPyL-PET/CT in BCR prostate cancer.

ABSTRACT

Purpose: To investigate the factors predicting scan positivity and disease location in patients with biochemical relapse (BCR) prostate cancer (PCa) after primary local therapy using prostate-specific membrane antigen (PSMA)-targeted ^{18}F-DCFPyL-PET/CT.

Methods: This is a two-institution study including 245 BCR PCa patients after primary local therapy and negative conventional imaging. Patients underwent ^{18}F-DCFPyL-PET/CT. Lesion detection rate and disease location were correlated with patient's tumor characteristics, time from the initial therapy, prostate-specific-antigen (PSA) and PSA doubling time (PSAdt). Multivariate logistic regression analyses were used to determine predictors of a positive scan. Regression-based coefficients were used to develop nomograms predicting scan positivity and extra-pelvic disease.

Results: Overall, 79.2% (194/245) of patients had a positive ^{18}F-DCFPyL-PET/CT, with detection rates of 48.2% (27/56), 74.3% (26/35), 84% (37/44), 96.7% (59/61) and 91.8% (45/49) for PSA <0.5, 0.5 to <1.0, 1.0 to <2.0, 2.0 to <5.0 and ≥5.0 ng/mL, respectively. Patients with lesions confined to the pelvis had lower PSAs than those with distant sites (1.6±3.5 vs. 3.0±6.3 ng/mL, p<0.001). In patients treated with prostatectomy (n=195), 24.1% (47/195) had a negative scan, 46.1% (90/195) showed intra-pelvic disease and 29.7% (58/195) extra-pelvic disease. In the post-radiation subgroup (n=50), ^{18}F-DCFPyL-PET/CTs were always negative at PSA lower than 1.0 ng/mL and extra-pelvic disease was seen only when PSA >2.0 ng/mL. At multivariate analysis, PSA, PSAdt were independent predictive factors of scan positivity and the presence of extra-pelvic disease in post-surgical patients, with area under the curve (AUC) of 78% and 76%, respectively. PSA and PSAdt were independent predictors of the presence of extra-pelvic disease in the post-radiation cohort, with AUC of 85%. Time from treatment to scan was significantly longer for

prostatectomy-bed-only recurrences than for those with bone or visceral disease (6.2±6.4 vs. 2.4±1.3 years, $p<0.001$).

Conclusion: ^{18}F-DCFPyL-PET/CT offers high detection rates in BCR PCa patients. PSA and PSAdt are able to predict scan positivity and disease location. Furthermore, the presence of bone/visceral lesions are associated with shorter intervals from treatment compared to prostate-bed-only recurrences. These tools might guide clinicians to select the most suitable candidates for ^{18}F-DCFPyL-PET/CT imaging.

Keywords: *prostate cancer;biochemical recurrence;PSMA;^{18}F-DCFPyL;PET.*

INTRODUCTION

Patients with localized prostate cancer (PCa) are usually treated with either radical prostatectomy, some variation of external beam radiation, brachytherapy or active surveillance (*1*,*2*). Despite definitive therapy with either surgery or radiation, approximately 20-40% of patients will recur within 10 years of the initial treatment (*3*). Biochemical recurrence (BCR) occurs when prostate-specific-antigen (PSA) increases during post-treatment monitoring, often without positive findings on conventional imaging, and can be seen months or years following the initial local therapy (*4*).

In the setting of BCR, understanding the specific site(s) of relapse and the patterns of recurrence improves understanding of the disease process. Local recurrence alone is usually associated with a better prognosis and slower disease kinetics, whereas nodal, bone or visceral metastases imply a more aggressive phenotype that carries a worse prognosis. Defining the extent of disease spread with imaging can be crucial for therapeutic decision-making and mapping potential treatment fields in PCa patients. The lack of sensitivity of conventional imaging (*5*) has limited the understanding of disease spread in BCR. With the advent of positron emitting (PET) probes targeting prostate-specific membrane antigen (PSMA), molecular imaging has yielded new insights into PCa recurrence (*6*), with improved sensitivity and specificity that far exceeds conventional imaging and earlier types of PET agents (*7*). ^{18}F-DCFPyL is a recent U.S Food and Drug Administration (FDA)-approved PSMA-PET agent with high affinity for PCa (*8*,*9*).

Men with recurrent disease are a highly heterogeneous population, carrying different profiles of disease aggressiveness; therefore, selecting the most suitable candidates for imaging with ^{18}F-DCFPyL-PET/CT might be critical to optimize its use and to spare lower-risk patients by potentially unnecessary staging procedures. We report the results of ^{18}F-DCFPyL-PET/CTs in a cohort of 245 BCR PCa patients from two institutions. We hypothesized that patient's clinical

features, including time from initial treatment, PSA and PSA-doubling time (PSAdt) might predict location and extent of disease. We also sought to develop clinical nomograms to assess the likelihood of each patient to have a positive scan and extra-pelvic disease, using Gleason score, PSA and PSAdt as predictive variables, in different settings based on primary initial therapy.

MATERIALS AND METHODS

Patient Population and Study Design

This study includes two institutional, Health Insurance Portability and Accountability Act compliant trials. Institutional review boards approved the studies, and all subjects signed a written informed consent. We included 245 patients who met eligibility criteria for protocols NCT03181867, NCT02825875 (ClinicalTrials.gov): 147 from the National Cancer Institute (NCI) and 98 from Johns Hopkins Hospital. A cohort of 90 of these patients was previously published (*10*). Patients had BCR, defined as PSA >0.2 ng/ml for those who underwent radical prostatectomy, or at least 2 ng/mL greater than nadir after radiation (ASTRO-Phoenix criteria) or considered clinical failure (*11*). Patients had negative conventional imaging (CT and bone scan). Exclusion criteria included current androgen deprivation therapy (ADT) at enrollment; inability to tolerate PET/CT and creatinine >2 times normal upper limit. Patients were classified by prior initial treatment (post-prostatectomy vs. post-radiation). Time from treatment to scan, Gleason score, PSA and PSAdt were recorded.

^{18}F-DCFPyL-PET/CT Protocol

^{18}F-DCFPyL-PET/CTs were performed at 2-h post-injection using a GE-Discovery MI DR time-of-flight (TOF) camera (NCI), and at 1-h using a GE-Discovery RX or Siemens Biograph

mCT TOF (Johns Hopkins Hospital). Scanners used low-dose CT (120 KV, 60 mAs). Images were reconstructed with manufacturer supplied MLEM or OSEM algorithms.

^{18}F-DCFPyL was synthesized under good manufacturing practice (GMP) conditions, as previously described (*8*). Patients received IV injection of ^{18}F-DCFPyL, mean injected activity 296±33.3 MBq [8.0±0.9 mCi] (range 207.2-325.6 MBq [5.6-8.8 mCi]), followed by a whole-body PET/CT at 1-2 hours post-injection (3min/bed). Furosemide wasn't given. Patients were monitored for adverse events during injection, after scan, and next day via telephone query.

Imaging Interpretation

Two board-certified nuclear medicine physicians in each institution independently review the images, resolving disagreements by consensus. ^{18}F-DCFPyL-PET/CTs were reviewed using MIM (version 6.9.2, MIM Software Inc., Cleveland, OH) or SyngoVia-20 (Siemens Healthineers, Erlangen, Germany). Maximum intensity projection (MIP), axial, coronal, and sagittal PET-CTs were reviewed. Only clear foci of abnormal uptake above the surrounding background (*12*), not associated with physiological uptake or known pitfalls (*13*) were considered positive. Foci with subtle or very mild uptake not definitive for disease were called indeterminate and considered negative to avoid confusing results. PET-positive lesions were classified as recurrence in the prostatectomy/prostate, pelvic/extra-pelvic nodes, or organ/bone.

Statistical Methods

^{18}F-DCFPyL-PET lesion detection rates were analyzed as a function of PSA. Scan positivity was evaluated stratifying PSA at ranges of <0.5; 0.5 to <1.0; 1.0 to <2.0; 2.0 to <5.0; ≥ 5.0 ng/ml. Sites of recurrence by ^{18}F-DCFPyL-PET were correlated with PSA, PSAdt, and time from local treatment, using Wilcoxon rank tests. Subgroup analysis was conducted by treatment

type (prostatectomy vs. radiation). Patients were categorized as having Gleason <7 vs. ≥7, and oligometastases (1-5 lesions) vs. multiple metastases (>5 lesions). Descriptive values were expressed as mean ± standard deviation.

Proportional odds model was used to associate clinical factors with scan result, classifying scans as negative, positive with intra-pelvic or extra-pelvic disease. Clinical factors included Gleason score, PSA, PSAdt, years since treatment, and treatment type (surgery vs. radiation). Analyses were exploratory, thus adjustment for multiple comparisons weren't implemented. Variable-selection procedure based on Akaike information criterion was used to determine the best fitted model. Model fit was examined by calibration plot of predicted vs. observed probability of positive scan and presence of extra-pelvic disease, calculating observations in each decile of predicted probability. Diagnostic accuracy of the predicted model was measured by area under the curve (AUC). Nomograms were generated using the R-package rms (*14*). All tests were two-sided and *P*-values<0.01 were considered significant. Statistical analyses were performed using R version 3.5.0.

RESULTS

Patient Population

Two hundred and forty-five patients (mean age: 66 years, range: 48-85 years) underwent ^{18}F-DCFPyL-PET/CT. Median PSA of 1.6 ng/mL (range: 0.2-35.5). Prior primary local therapy consisted of radical prostatectomy (n=195) or radiation +/- androgen deprivation therapy (ADT) (n=50). Patients weren't actively receiving ADT at imaging. Mean time from prostatectomy to scan was 6.1±5.1 years (range: 1.5 months-23.8 years), and from radiation was 4.9±3.6 years (9

months-14.9 years). No adverse events were seen following ^{18}F-DCFPyL-injection. Table 1 shows patient's characteristics.

^{18}F-DCFPyL-PET/CT versus PSA

Overall, patient-based lesion detection rate for ^{18}F-DCFPyL-PET/CT was 79.2% (194/245), which increased as PSA increased: 48.2% (27/56), 74.3% (26/35), 84% (37/44), 96.7% (59/61) and 91.8% (45/49) at PSA <0.5, 0.5 to <1.0, 1.0 to <2.0, 2.0 to <5.0 and ≥5.0 ng/mL, respectively (Figure 1). Detailed analysis by cohort and institution is reported at Supplemental-Tables 1-3. No differences were seen in lesion detection between institutions. Out of 51 cases with negative scan, 13 showed indeterminate findings, with 17 indeterminate foci.

Patients with positive pelvic findings had significantly lower PSA than those with positive extra-pelvic lesions (i.e. retroperitoneal, distant nodes and/or bone or visceral sites) (2.8±3.5 vs. 5.0±6.3 ng/mL, P<0.001), suggesting pelvic nodes may precede extra-pelvic adenopathy. At PSA <2.0 ng/mL, ^{18}F-DCFPyL-PET/CT detected higher proportion of patients with localized pelvic disease, whereas the proportion of patients with extra-pelvic lesions was higher than intra-pelvic lesions for PSA >5 ng/mL (Figure 2).

Impact of Time from Local Treatment

The time from prior therapy (prostatectomy vs. radiation) and disease location was evaluated. In the prostatectomy cohort (n=195), time from treatment to scan was longer for men with findings at the prostatectomy-bed-only than for those with only bone/visceral lesions or for those with nodal lesions (7.4±6.3 vs. 2.3±1.3 vs 3.1±4.1 years, P<0.001). When findings were confined to the prostatectomy bed, 53.8% of patients were treated less than 8 years prior to scan and 46.1% had prostatectomies performed more than 8 years. For patients with extra-prostatic

extension, 75.5% were treated less than 8 years prior to scan, and 24.5% more than 8 years prior. Thus, ^{18}F-DCFPyL-PET/CT positive nodal findings, bone + nodal disease, bone only disease or visceral lesions were mostly seen when initial treatment was less than 8 years prior: in 79.7%, 88.9%, 100.0%, and 100.0% of cases, respectively (Figure 3A). Same patterns of disease distribution vs. time from initial therapy were seen in a separate analysis by institution. Figure 4 and supplemental-Figure 1 show disease patterns vs. time from prostatectomy by PSA and PSAdt**.** There were no differences in the distribution of times from prostatectomy between patients with oligometastases vs. multiple disease (4.8±3.8 vs. 5.3±5.7 years, *P*=0.054).

In the post-radiation cohort (n=50), men with positive prostate involvement showed significantly longer times from radiation than subjects with bone or visceral lesions (6.7±4.1 vs. 2.6±2.8 years) (Figure 3B). Significant longer times from radiation were seen in men with pelvic findings only compared to those with extra-pelvic lesions, with median times of 6.4±3.7 vs. 2.9±2.8 years. When recurrence was exclusively within the prostate, 38.9% of patients were initially treated more than 8 years prior to scan and 61.1% had radiation less than 8 years prior. For positive extra-prostatic extension, most patients (93.3%) were treated less than 8 years prior. No differences were seen in times from radiation between patients with oligometastases vs. multiple lesions (3.6±3.1 vs. 2.9±2.6 years, *P*=0.66).

Impact of Clinical Features on Scan Positivity

In the cohort treated with radical prostatectomy (n=195), 75.9% (148/195) showed at least one positive lesion (Figure 5). Lesions confined to pelvis were seen in 46.2% (90/195) of patients, especially driven by local recurrence at the prostatectomy bed in 44.5% and pelvic nodes in 55.5%, whereas extra-pelvic lesions were seen in 29.7% (58/195) of cases, often at PSA >5.0 ng/mL.

PSAdt was significantly longer for patients with disease confined to pelvis than for those with distant extra-pelvic lesions (7.1±8.6 vs. 5.7±2.7 months, $P<0.001$).

In patients who received radiation (n=50), only 8% (4/50) had a negative scan, 48% had positive intra-pelvic disease (75% within the prostate and 25% in pelvic nodes), whereas 44% showed extra-pelvis findings (Figure 6), and only when PSA >2.0 ng/mL. Similarly, PSAdt was greater for patients with pelvic recurrences than with extra-pelvic lesions (17.2±17.1 vs. 6.2±5.7 months, $P<0.001$).

The multivariable regression analysis revealed that PSA, PSAdt and Gleason (≥7) were independent predictive factors of scan positivity and presence of extra-pelvic disease in post-surgical patients. In the post-radiation cohort, PSA and PSAdt were independent predictors for the presence of extra-pelvic disease. Multivariable derived coefficients were used to develop nomograms to predict probability of having a positive scan and having extra-pelvic disease. The nomogram-based on prior therapy were built using patient's Gleason score, PSA and PSAdt as predictors (Figure 7). In post-surgical patients, AUC was 78% (95%Confidence Interval (CI)=68-89%) for predicting scan positivity, and 76% (95%CI=67-85%) for predicting extra-pelvic disease. In post-radiation cohort, AUC was 85% (95%CI=71-98%) for predicting extra-pelvic disease. The number of patients having a negative scan was only 4, therefore the prediction model for scan positivity wasn't considered for this cohort.

DISCUSSION

This study demonstrates that ^{18}F-DCFPyL-PET/CT detects lesions in the majority of BCR patients. Prostatectomy-bed-only recurrence is associated with the longest duration (mean 7.4

years) from treatment indicating the least aggressive disease trajectory. Pelvic nodal involvement is associated with a shorter duration (3.1 years) from treatment implying a more aggressive trajectory, while bone and visceral involvement manifests at even earlier times (2.3 years) after prostatectomy. Post-radiation cohort showed a similar pattern, where bone/visceral involvement was seen after a shorter duration from therapy compared with prostate recurrences (2.6 vs. 6.7 years). We observed no differences in times from treatment between patients with oligometastases vs. multiple lesions in different clinical settings, suggesting that oligometastatic disease may be an early form of an aggressive phenotype.

The likelihood of having a scan with extra-pelvic lesions was determined in surgical and post-radiation patients using nomograms. The most relevant predictors for scan positivity were PSA and PSAdt, in line with other studies. For instance, Rauscher et al. (*15*) proposed a nomogram to predict positive ^{68}Ga-PSMA-11-PET/CT in BCR patients after prostatectomy with PSA ≤1 ng/ml. In their analysis, PSA and concurrent ADT were associated with scan positivity. Ceci et al. reported a nomogram with 82% accuracy, based on ISUP grade, PSA and PSAdt as predictors of scan positivity (*16*). Ma et al. explored predictors of overall upstaging (nodal and metastatic) by PSMA-PET/CT, constructing nomogram using PSA, percent positive core biopsy, Gleason, and cT-stage; the predictive model only missed 10% of patients, who would have benefitted from PSMA-PET/CT (*17*).

PSA in the post-treatment setting is a reliable indicator of disease volume and PSMA-PET/CT demonstrates a relationship between PSA and extent of disease with ascending percentages of positive scans with higher PSAs. PSA values less than 1.0 ng/ml are associated with local recurrences and pelvic adenopathy, while the proportion of patients with extra-pelvic nodal involvement rises with PSA above 1.0 ng/ml. Bone and visceral metastases become a larger

proportion of cases above 2.0 ng/ml. There is, however, considerable overlap in individual cases, as the rate of PSA production within tumors varies greatly. Thus, these data fit a general model of recurrent PCa that suggest several trajectories for disease. Slowly evolving recurrences tend to be confined to prostate bed, whereas more aggressive tumors propagate to first the pelvic and then retroperitoneal nodes. More aggressive disease tends to rapidly involve bone and visceral organs. Although, there is little doubt that tumors evolve over time, the rate at which this happens depends on the nature of the original tumor. This insight is uniquely provided by PSMA-PETs as previously disease couldn't be detected at this stage with conventional imaging.

The overall ^{18}F-DCFPyL-PET/CT positivity rate was 79.2%, with detection rate of 48.2% at PSA <0.5 ng/mL, in line with previous reports (*10*). Results are equivalent to those by Wondergem et al. (*18*) using ^{18}F-DCFPyL in 248 patients, identifying lesions in 59% of patients at PSA <0.5 ng/ml and in 96% at PSA >2.0 ng/ml. ^{18}F-PSMA-1007-PET/CT exhibited higher detection rate of 62% in patients with low PSAs (0.2–0.5 ng/mL), but similar results to our series for PSA >0.5 ng/mL (*19*). One persistent finding across multiple studies using PSMA-PET is that approximately one quarter of scans are negative, suggesting that these patients either don't express sufficient PSMA to be detected or lesions are simply too small to be identified; these cases are associated with low PSAs and likely represent the threshold for PET detection. Using PET/MRI may help to overcome this potential limited sensitivity for detection within the prostate fossa (*20*). On the other hand, high PSAs (>5.0 ng/ml) are also associated with negative scans; such tumors may represent less differentiated Pca variants or may express other surface markers that might be amenable for different targeted imaging agents. Moreover, disease within the prostate bed may be obscured by radiotracer excretion into the bladder. Other ^{18}F-PSMA-ligands with low urinary excretion, ^{18}F-PSMA-1007 (*21*) and ^{18}F-rhPSMA (*22*), have shown higher local detection rates at

low PSAs since the interpretation of lesions near the urinary bladder may be somewhat easier. Several groups proved the use of diuretics to increase detectability of local recurrence, with improved diagnostic certainty for lesions in proximity to bladder and ureters (*23*,*24*), although forcing diuresis could be an issue for patients with urinary urgency and might require longer waiting time for patients or additional scans.

^{18}F-DCFPyL-positive pelvic lesions were present in 48% of subjects, whereas extra-pelvic disease was found in 30%, almost exclusively when PSA >1.0 ng/mL. This is consistent with the clinical experience that control rates with pelvic radiation therapy start to decline with PSA >1 ng/m (*25*). This agrees with previous data (*26*,*27*) assessing the impact of PSMA-PET on treatment decisions; patients with low PSA and disease confined to pelvis on PSMA-PET might benefit from radiation treatment plan modifications, whereas patients with extra-pelvic lesions may require systemic therapy. In our cohort, at PSA >2.0 ng/mL, PSMA-PET was almost always positive for recurrence, with distant disease seen in about 30% of prostatectomy patients and 45% of post-RT. Furthermore, presence of distant extra-pelvic disease was significantly higher for patients with rapid PSAdt in both post-surgical and post-radiation cohorts, consistent with other prognostic indicators associated with PSAdt (*28*).

Interesting differences were seen in post-surgical and post-radiation recurrences. Negative scans in patients with PSA <0.5 ng/mL after surgery were seen in 24% of patients, whereas only 8% of post-radiation scans were negative. Post-radiation patients tended to show more local recurrences than post-surgical patients. At PSA >2.0 ng/mL recurrences after radiation tended to be extra-pelvic, whereas this trend was less evident in post-surgical patients. The distribution of recurrences was somewhat different for post-surgical and post-radiation patients. PSA threshold values for positive PSMA-PET were substantially higher in post-radiation cohort. When subjects

were primarily treated with radiation, 36% showed positive prostate findings, while recurrences outside the prostate were seen in 56% of patients, similar to prior reports using ^{68}Ga-PSMA-PET/CTs (*29*).

There are limitations to this study. Perhaps most notably, despite using ^{18}F-DCFPyL-PET/CT at both institutions, PET acquisition parameters (e.g. time from injection to imaging) varied between institutions. Although detection rates by PSA were overall similar between institutions scanning at 1 vs 2-h post-injection, differences in detection rates regarding scan time cannot be addressed since individual patients were only scanned at one time point. Further, data harmonization relied on daily quality control procedures using the standard operating procedure provided by the manufacture for each scanner. Such heterogeneity may have affected the results, although reflecting a real-world scenario that make the findings more broadly applicable as ^{18}F-DCFPyL is recently FDA-approved. Further, findings were determined at each institution, followed by a combined analysis, which might lead to heterogeneity in the results, but would recapitulate the use of the PSMA-agent across centers. Another limitation is that no inter-reader variability (kappa) is available for this study. Also, analyses were exploratory in nature and adjustments for multiple comparisons weren't implemented. Lastly, at one institution, patients were accrued into a broader study of the utility of PSMA-PET instead of a dedicated BCR study. As such, this study wasn't prospectively designed to meet a specific endpoint. Furthermore, the detection rate may differ from the true detection rate since histological validation wasn't available for all positive sites. Unfortunately, this is a common problem in studies involving BCR patients where findings are often sub-centimeter, deep within the pelvis, often in unsafe locations or otherwise not feasible to biopsy.

CONCLUSION

^{18}F-DCFPyL-PET/CT successfully identifies sites of recurrence proportional to PSA levels when conventional imaging is negative. ^{18}F-DCFPyL-PET/CT demonstrates a high tumor detection rate even at low PSA (<0.5 ng/mL). Disease recurrence tends to be confined to pelvis in patients with lower PSAs, but at higher values there is visualization of disease outside the pelvis, particularly when PSA >2.0 ng/mL and PSAdt <6 months. The presence of bone and visceral lesions was associated with shorter time after initial treatment and higher PSAs compared to prostate-bed-only recurrences. Clinical nomograms proved that PSA and PSAdt were able to predict scan positivity and disease location in BCR patients. These tools might guide clinicians to select the most suitable candidates for PSMA-PET.

As with other studies, PSMA-PET is not positive in all BCR patients and approximately 15-20% have negative scans at low or high PSAs, likely for different reasons. Low PSA false-negatives are likely due to subthreshold volumes of disease for detection, or overlapping urinary bladder within the pelvis, whereas high PSA false-negatives are likely due to dedifferentiated tumors with low PSMA-expression. ^{18}F-DCFPyL-PET/CT detection efficacy is comparable to previously published results with ^{68}Ga-PSMA compounds and has logistical advantages because of its longer half-life. The general class of PSMA-ligands is destined to significantly change management of BCR patients.

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KEY POINTS

QUESTION: Are there factors predicting PSMA-PET disease location in BCR PCa patients?

PERTINENT FINDINGS: PSA and PSAdt are able to predict PSMA-PET scan positivity and disease location. Presence of bone/visceral lesions are associated with shorter intervals from initial treatment compared to prostate-bed-only recurrences.

IMPLICATIONS FOR PATIENT CARE: These tools might guide clinicians to select suitable candidates for ^{18}F-DCFPyL-PET/CT.

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Table 1: Patients' characteristics

	n
No. patients	245
Primary local therapy	
Radical prostatectomy +/-RT, +/-ADT	195
Radiation therapy +/-ADT	50
Age (y)	
Mean	66
Range	[48-85]
Primary Gleason score	
Gleason ≤6	39
Gleason 7	120
Gleason ≥8	86
PSA (ng/mL)	
Median	1.6
Range	[0.2-35.5]
PSAdt (months)	
Median	6.8
Range	[0.9-75.2]

Figure 1: ^{18}F-DCFPyL-PET overall, intra-pelvic and extra-pelvic detection rates by PSA.

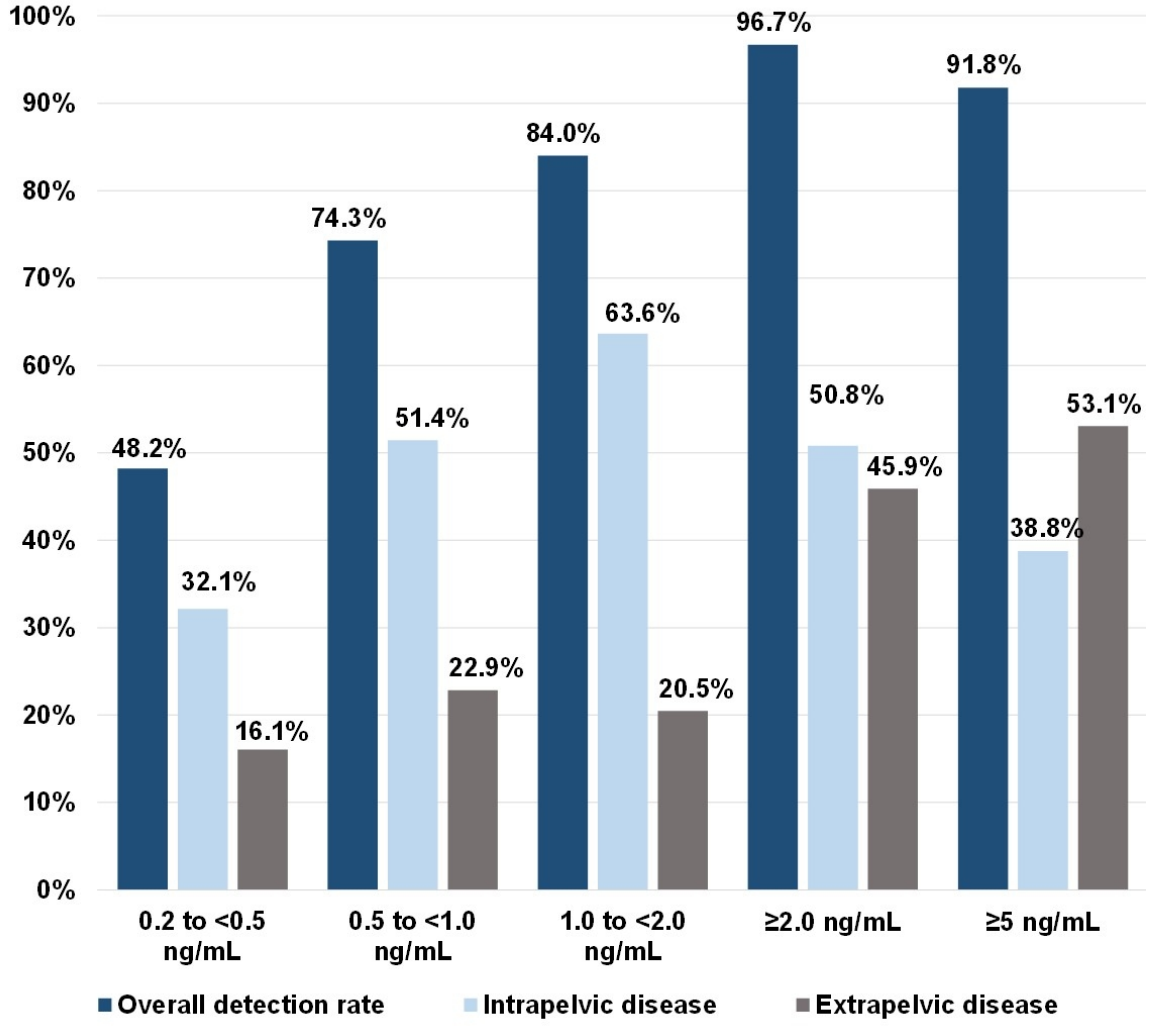


Figure 2: ^{18}F-DCFPyL-positive sites by location and PSA.

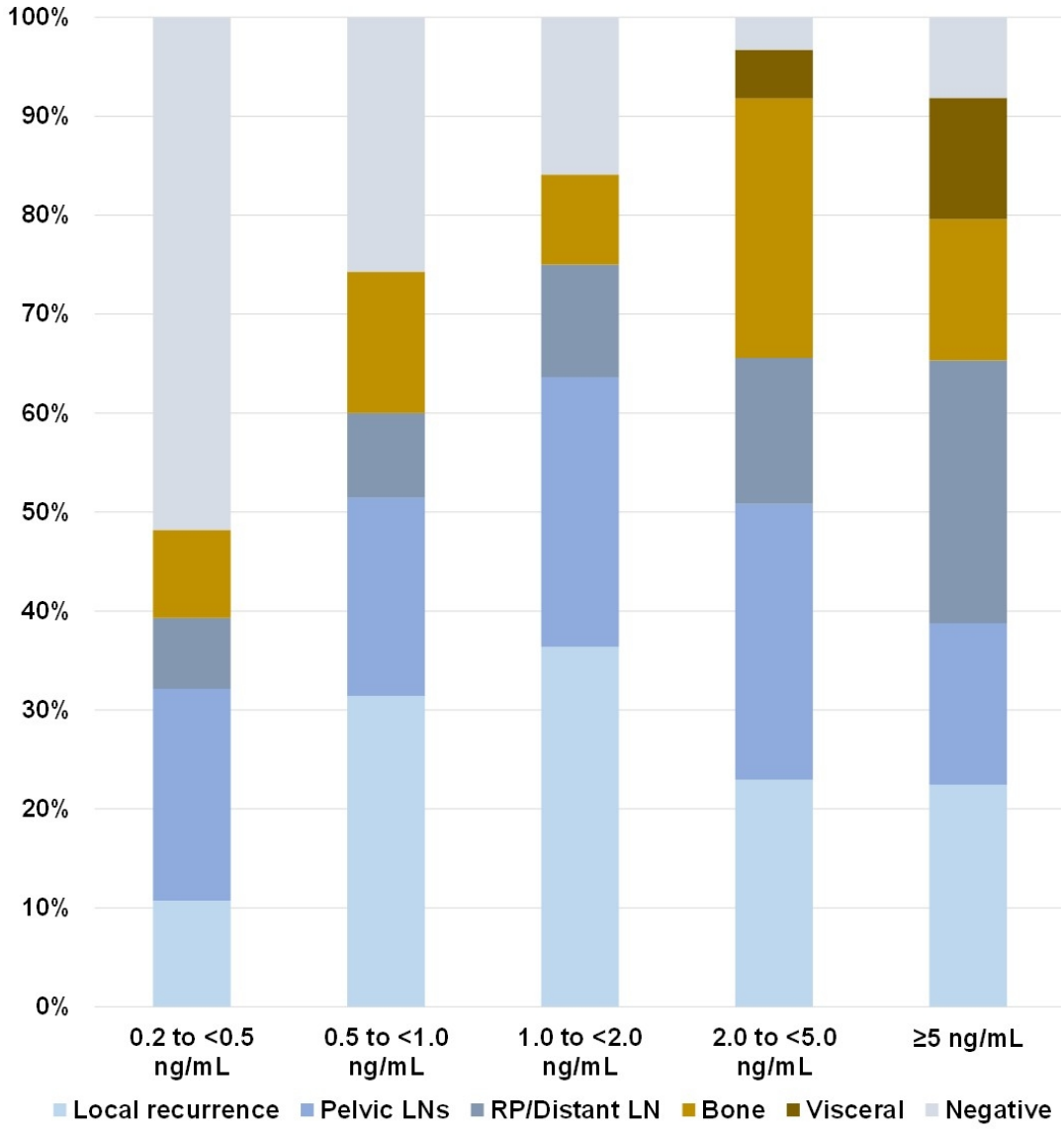


Figure 3: Disease location versus time from prostatectomy (A) and radiation (B).

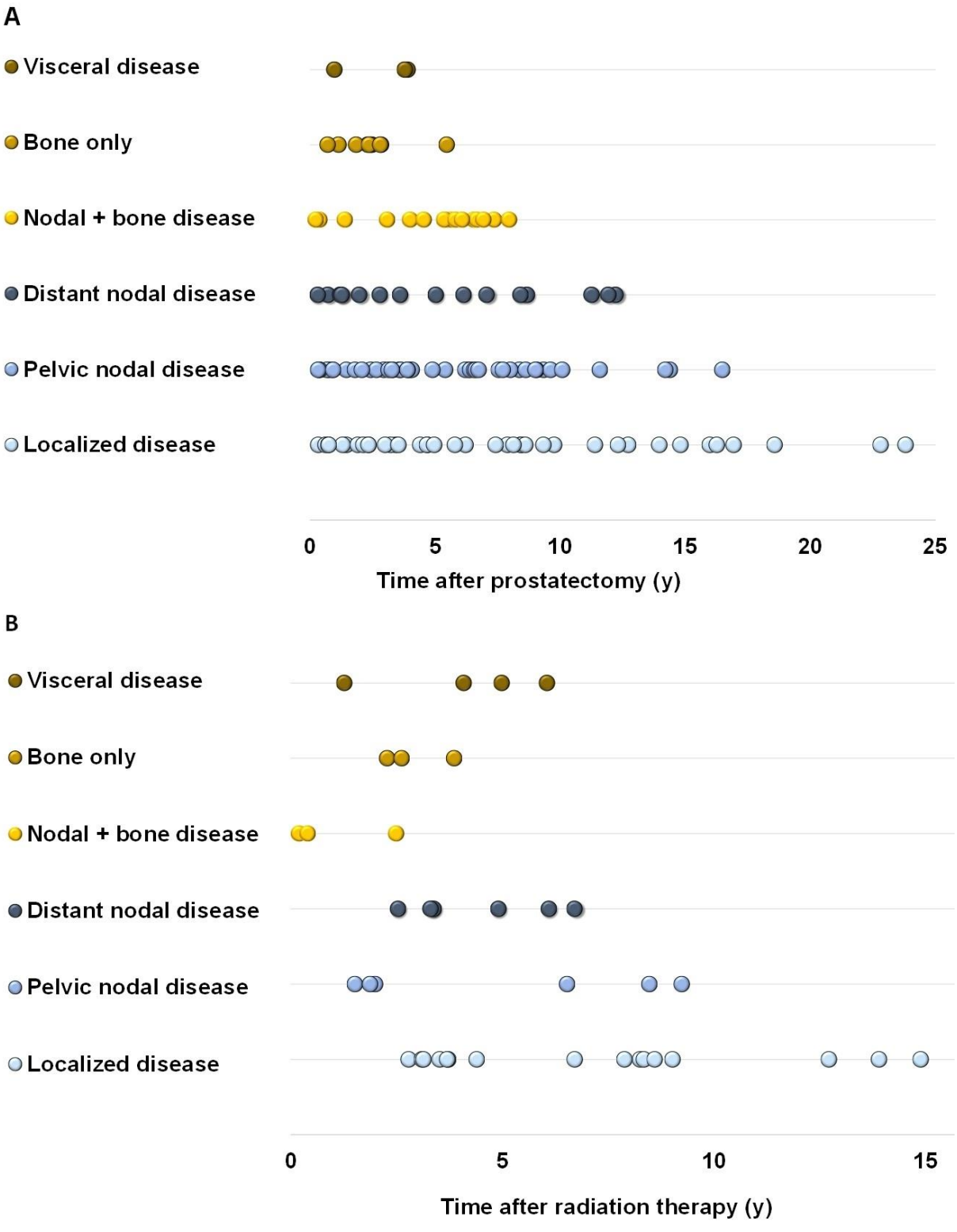


Figure 4: Patterns of recurrence vs. time from therapy and PSAdt in post-prostatectomy (A, B) and post-radiation patients (C, D).

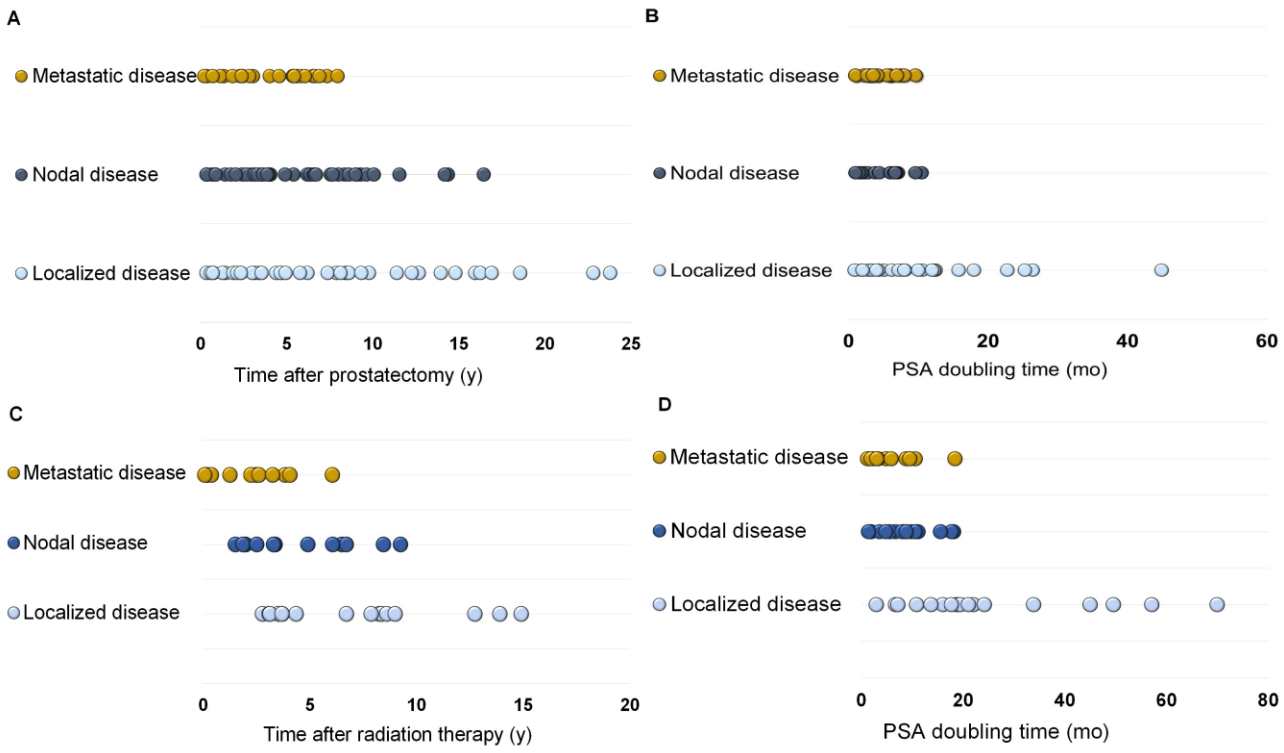


Figure 5: 70-year-old with BCR PCa, primary tumor T4N1, Gleason 4+5, status post-radiation and 2-years of ADT. Time from treatment: 2.5 years; Pre-scan PSA: 2.41 ng/mL; PSAdt: 4.7 months. ^{18}F-DCFPyL-PET/CT shows sub-centimeter pelvic nodes, and foci at T9 and anterior iliac bone. Follow-up biopsy confirmed bone metastasis at the iliac bone.

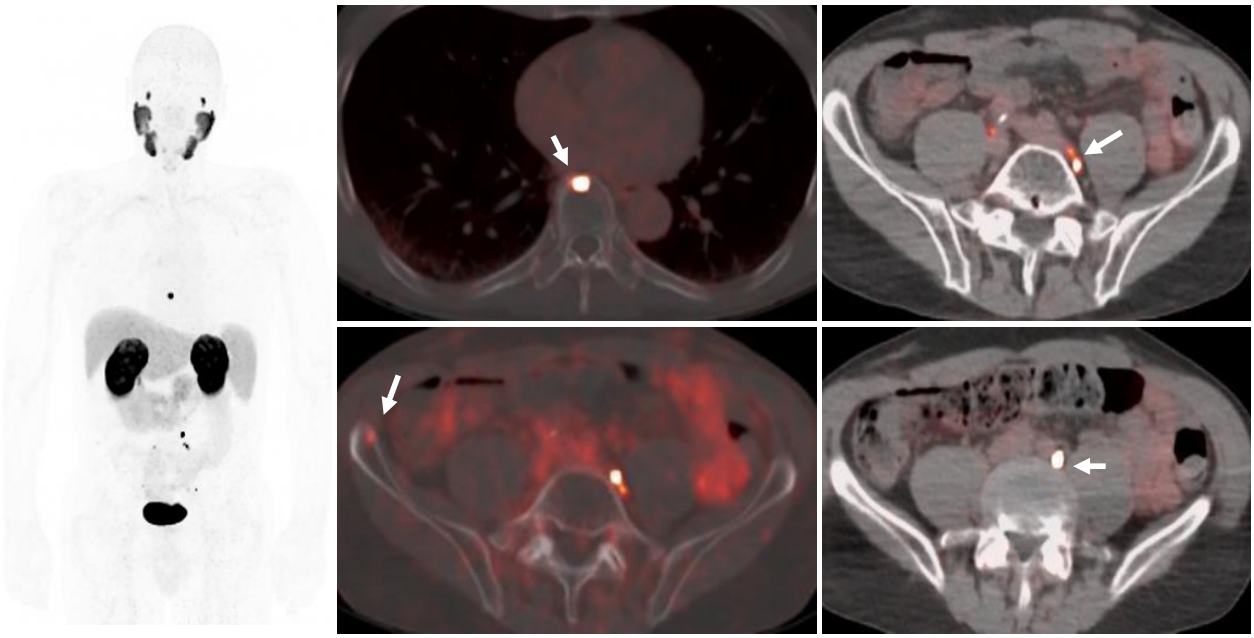


Figure 6: 63-year-old with BCR PCa, primary tumor T3bN1, Gleason 4+5, status post-prostatectomy and 2 years of ADT, reaching undetectable PSA. PSA started to rise 5-years after initial treatment. PSA=0.3ng/mL. PSAdt: 3months. ^{18}F-DCFPyL-PET/CT demonstrates focal uptake in a 0.5-cm left common iliac node. This lesion wasn't biopsied.

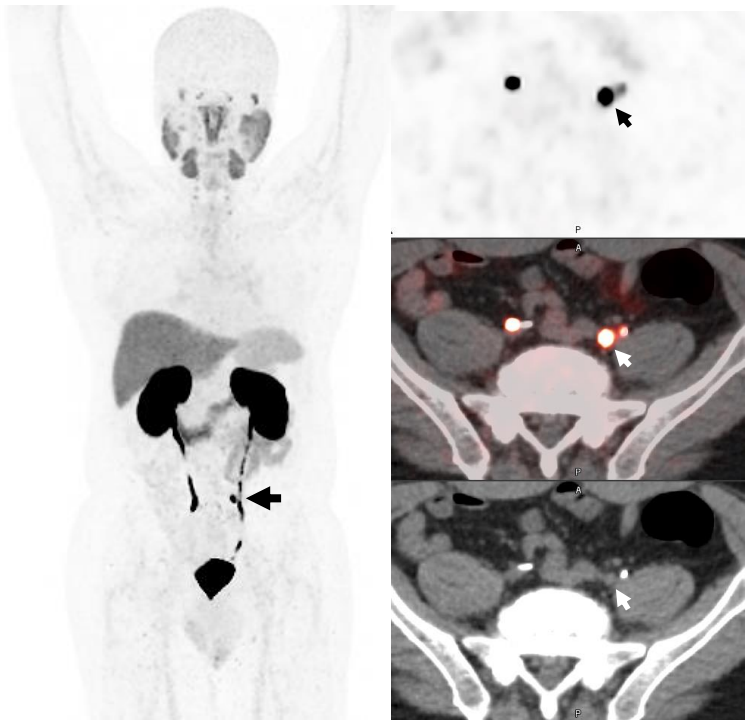
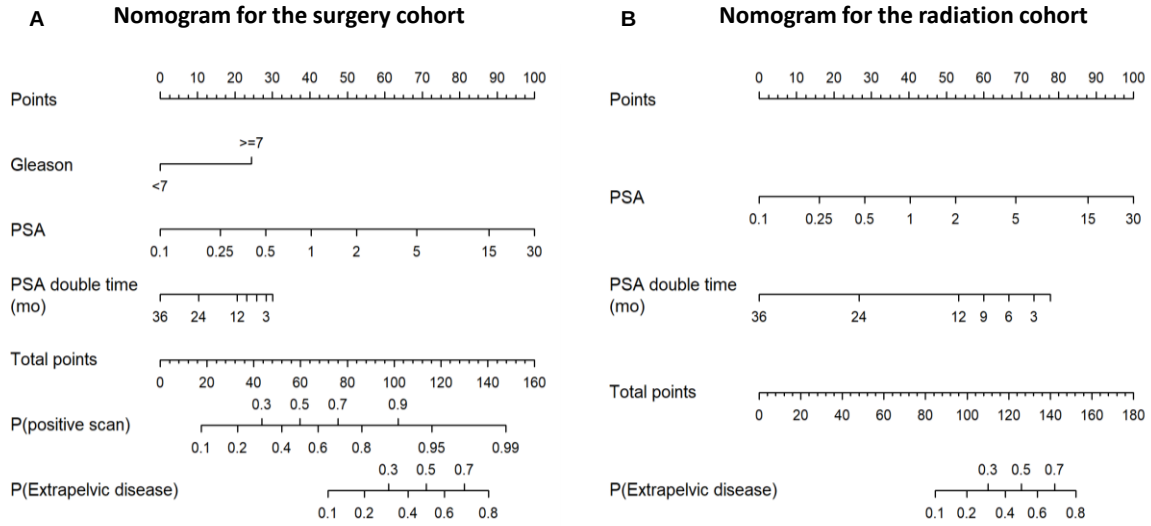


Figure 7: Nomogram predicting the likelihood of ^{18}F-DCFPyL-PET/CT positivity for different settings of BCR patients after prostatectomy (A) or radiation (B). Instructions: locate patient's PSA value and draw a straight line to the Points axis to determinate the amount of points towards the probability of a positive scan. Repeat this process for each variable and sum the points for each predictor. Locate the final sum of points on the Total-point axis and draw a line straight down to find the probability (P) of having a positive scan or having a scan with extra-pelvic lesions.



Graphical Abstract