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Patterns of Recurrence Following Post-Prostatectomy Fossa Radiotherapy Identified by C-11 Choline PET/CT

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Abstract

Purpose—To evaluate C-11 choline PET/CT (CholPET) in staging and determining patterns of recurrence in prostate cancer patients with rising PSA post prostatectomy radiotherapy (RT).

Materials and Methods—The study includes patients with biochemical failure following post-prostatectomy RT who underwent CholPET between 2008 and 2015. Patient and disease characteristics were examined in relation to sites of recurrence. All RT dosimetry records were reviewed, and recurrences were mapped on a representative CT dataset with their relationship relative to the irradiated fossa field as out-of-field (OOF), edge-of-field (EOF; recurrence within <45Gy isodose lines), or in-field (IF; recurrence within 45 Gy isodose lines).

Results—Forty-one patients were identified with 121 sites of recurrence (median 2 sites; IQR 1–4). The median PSA at CholPET was 3.1 (IQR 1.9–5.6) ng/mL. Median interval from RT to biochemical failure was 24 (IQR: 10–46) months, with recurrence identified on CholPET at a median of 15 (IQR 7–28) months from biochemical failure. Histologic confirmation of recurrence was obtained in 20 (49%) patients; with the remainder confirmed by treatment response. Five patients (12%) had IF recurrences, 10 patients (24%) had EOF recurrences (median dose 10 Gy; IQR 5–30 Gy), and 36 patients (88%) had OOF recurrences. Ten patients had combination failures: 6 (15%) EOF/OOF and 4 (10%) IF/OOF. Fifty-seven (47%) of recurrences were pelvic nodal sites inferior to the L5–S1 interspace of which 52 (43%) are within a pelvic RT field. Eighty-one (67%) of recurrences were nodal and inferior to the aortic bifurcation.

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Conclusions—Using CholPET, we found that the majority of patients evaluated for biochemical failure recurred outside of the post-prostatectomy RT field. Furthermore, most recurrence sites were nodal and inferior to the aortic bifurcation. These results provide data which may be useful for examining strategies that include elective lymph node irradiation in post-prostatectomy patients.

Keywords

Prostate cancer; radiotherapy; recurrence; PET/CT; radiation field

Introduction

Post-prostatectomy radiotherapy (RT), given as either adjuvant therapy for adverse pathologic features or as salvage for a rising prostate-specific antigen (PSA), has been shown to improve oncologic outcomes in select patients with prostate cancer (CaP) (1-5). However, between 26-68% of patients who undergo post-prostatectomy RT will suffer biochemical failure within 5 to 6 years of treatment (1, 2, 6). For these men who have failed maximal local treatment a frequently employed management strategy is androgen deprivation therapy (ADT).

Unfortunately for men who suffer biochemical failure, the paradigm of androgen deprivation obligates men to the side effects of hormonal ablation (7, 8) and is often followed by subsequent progression to metastatic and castration resistant disease (9). Additionally, the rationale for management of such recurrences with ADT alone is predicated on the assumption that recurrences after multi-modal local therapy are not amenable to any further targeted intervention, and is likely a reflection of our relative inability to detect potentially salvageable recurrences using standard imaging techniques (10, 11). However, new imaging modalities – such as C-11 choline PET/CT (CholPET) – are increasingly being utilized for patients with CaP, resulting in improved localization of recurrence at a lower disease burden and, therefore, potentially guiding directed therapies for recurrence (12-16).

We hypothesized that CholPET could identify sites of recurrence in biochemically recurrent post-prostatectomy RT patients, which could be correlated with their location relative to the previously delivered dose to the prostatic fossa. We aimed to construct an anatomic map of recurrences as identified on CholPET, and to delineate clinical characteristics associated with recurrences relative to the post-prostatectomy RT field.

Materials and Methods

After obtaining Institutional Review Board approval, we identified patients who were found to have a site of recurrence on CholPET performed between 2008 and 2015 for the evaluation of biochemical failure (PSA ≥ 0.4 ng/mL) (17) in the setting of prior post-prostatectomy fossa-only RT. Patients were excluded if they had received elective nodal RT and if they were receiving ADT or were castration-resistant at the time of evaluation with CholPET. Castration-resistant prostate cancer was defined as continued PSA increase or progression of lesions identified radiographically in the setting of ongoing ADT with documented castrate testosterone levels (< 50 ng/dL) (18).

The methods of obtaining CholPET and multiparametric magnetic resonance imaging (mpMRI) in this study have been previously described (19). PET images were acquired from the mid-thigh to the orbits after the bolus administration of a median of 696 MBq of C-11 choline (IQR 666 – 710) and fused with conventional CT images. For the purpose of this analysis, the radiology report which originally described the results of the CholPET and mpMRI were used.

Clinical variables studied included age at diagnosis of prostate cancer, PSA at diagnosis of prostate cancer, pathologic Gleason score, 2010 AJCC pathologic T-stage (20), age at prostatectomy, time from prostatectomy to RT, post-RT PSA nadir, time to PSA nadir, PSA at biochemical failure, time to biochemical failure from date of RT completion, PSA at positive CholPET, time to positive CholPET, and location of recurrence(s). RT was classified as adjuvant (performed in the setting of an undetectable post-operative PSA within 4 months of surgery) or salvage (detectable PSA post-prostatectomy). For patients treated at our institution (n=21), the original radiation dosimetry was evaluated in the planning system employed (Eclipse V 8.0, Varian, Palo Alto, CA). For patients who received RT elsewhere (n=20), the radiation plan was either recreated in our system using the outside facility's radiotherapy records or uploaded directly into the system from DICOM RT data in electronic format.

For patients with identified sites of recurrence on CholPET, the number and location of lesions were documented. Pelvic lymph node recurrences were defined as the presence of nodal disease within the true pelvis inclusive of perirectal, presacral, internal iliac, obturator, and external iliac lymph nodes. Common iliac nodal recurrences were considered separately from retroperitoneal recurrences (defined as recurrence within a retroperitoneal site cephalad to the aortic bifurcation). Representative lesions identified on CholPET were localized on the corresponding CT image dataset and co-registered with the RT planning CT images to characterize recurrences using Eclipse treatment planning software (Varian, Palo Alto). Sites of recurrence were mapped with respect to each patient's post-prostatectomy RT isodose lines as either in-field (IF), edge-of-field (EOF), or out-of-field (OOF) by a radiation oncologist (XXX, XXX, XXX; all were reviewed by XXX for consistency in reporting). IF recurrences were defined as those occurring within the 45Gy isodose line whereas EOF recurrences were any recurrences occurring within an isodose volume receiving <45Gy (21). OOF recurrences were defined as recurrences occurring in a region which did not receive any dose. Finally, standard pelvic nodal RT (L5-S1 interface) (21) and extended nodal RT (to the aortic bifurcation) (22) treatment volumes were superimposed on the representative CT image dataset containing sites of recurrence. An isometric 0.5 cm clinical target volume (CTV) expansion to planning target volume (PTV) was used. Sites were characterized as either included (inside the PTV) or not included (outside the PTV) within these fields.

Categorical variables were summarized using frequencies and percentages. Continuous variables were summarized using medians and interquartile range (IQR). The linear relationship between number of sites of recurrence and PSA at evaluation was performed and summarized with Pearson's product moment correlation (ρ). To test the association of recurrence location with clinical features, the data was evaluated both by patient and by lesion. Differences were assessed using Fisher's exact chi-squared analyses and non-

parametric 1-way ANOVA testing (Kruskal-Wallis tests) without adjustment for multiple testing (hypothesis generating analyses only). Finally, an exploratory analysis of recurrence site as a function of pelvis-only nodal RT and extended nodal RT (21, 22) was performed to describe recurrences relative to these anatomic distributions. All analyses were performed using R version 3.2.3 (R-Foundation, Vienna, Austria) with two sided p-values reported and a p-value of <0.05 considered statistically significant.

Results

Between 2008 and 2015, a total 2,842 patients underwent CholPET at our institution of which 391 patients were previously treated with RT including definitive, adjuvant, salvage, and palliative RT for prostate cancer. Of these patients, we identified 41 patients with a site of recurrence on CholPET during the evaluation of biochemical failure after post-radical prostatectomy RT and who also met other exclusion criteria as described. Clinical features of the cohort are summarized in Table 1. While one patient had missing pathologic data, the majority of patients (38/41; 93%) had documented Gleason scores ≥ 7 and 66% (27/41) had pT3a or pT3b. Following prostatectomy, an undetectable PSA was achieved in 24 (59%) patients. In our cohort, post-prostatectomy RT was completed between 1996 and 2014, with a median dose of 68.4 (IQR 64.8 – 70.2) Gy in conventional 1.8 or 2.0 Gy fractions, delivered at a median of 17 (IQR 8 – 41) months following surgery.

In total, 121 sites of recurrence were identified in the 41 patients (median 2 lesions per patient; IQR 2 – 4) at a median of 40 (IQR 23 – 64) months from RT and a median of 24 (IQR 10 – 46) months from diagnosis of biochemical failure (Table 2). The median PSA at detection of recurrence was 3.1 (IQR 1.9 – 5.6) ng/mL, which correlated weakly with the number of lesions ($\rho=0.37$, $p=0.02$). The median PSA level per lesion was 1.4 (IQR 0.9 – 2.7) ng/mL. Of these 41 patients, 33 (81%) also underwent evaluation with mpMRI, of whom 16/33 (49%) had at least one identified site of recurrence concordant with CholPET findings. The remainder either did not identify recurrence ($n=7$, 21%) or had indeterminate findings ($n=10$, 30%). Figure 1 demonstrates a representative image of an indeterminate MRI finding, which was PET avid and biopsy confirmed as recurrence.

Sites of recurrence and their relationship to RT planning fields are summarized in Table 2 and Figure 2 for the 41 patients. In total, 20 (49%) patients had histologic confirmation of their disease. The majority of recurrence sites were within the pelvis ($n_{\text{fossa}}=5$ and $n_{\text{pelvis to L5-S1}}=57$ for a total of 62 non-osseous sites inferior to L5-S1 of 121; 51%). Notably, recurrences were limited to the prostatic fossa only in 1 (2%) patient, the other 4 (10%) patients with IF recurrences had additional sites of recurrence out of the treated field (IF + OOF). Recurrences limited to the non-osseous pelvis below L5/S1 were seen in 17 (41%) patients. An additional 9 (22%) patients had maximal cephalad disease extension to the common iliac lymph nodes (below aortic bifurcation). With respect to the post-prostatectomy RT field treated, 5/41 (12%) patients had an IF recurrence and 10/41 (24%) patients had an EOF recurrence, with maximal extent of recurrence limited to either IF or EOF in 5 (12%) patients. Twenty-six patients (63%) experienced OOF recurrence exclusively. When assessed by CholPET avid site ($n=121$), there were 5 (4%) IF, 12 (10%) EOF, and 104 (86%) OOF recurrences. Notably, 70% (40/57) of pelvic nodal recurrences

were OOF, including 67% (6/9) of perirectal and presacral nodal recurrences. When type of recurrence was assessed by lesion, the only statistical difference in clinical characteristics observed was the PSA at biochemical failure (Table 3), which was not observed when assessed by patient.

Table 4 summarizes the location of recurrences with respect to different pelvic nodal RT fields to either the L5-S1 interface or to the aortic bifurcation (with and without the fossa RT field). Notably, 52/121 (43%) and 76/121 (63%) of nodal recurrences would be included within the PTV for L5-S1 fields and aortic bifurcation fields, respectively (Figure 2). When combined with fossa radiation fields, the L5-S1 nodal fields would include all sites of recurrences in 16 (39%) patients, whereas RT volumes to the aortic bifurcation would be fully inclusive for 24 (59%) patients.

Discussion

Using a large institutional experience in CholPET imaging, we report our findings in a select group of patients with biochemical failure after post-prostatectomy RT of the prostatic fossa. We identified 121 sites of recurrence in 41 patients – 73 % of whom had more than 1 lesion, highlighting the multifocal nature of recurrences in this patient cohort. Furthermore, we found that only a minority, 17 of 121 (14%), of recurrences were within (n=5) or at the margin of the post-prostatectomy RT field (n=12), with the majority (86%) occurring OOF, primarily as nodal recurrences. The identification of osseous metastases was uncommon in our cohort and only one patient was identified with visceral metastatic disease. When we evaluated the relationship between anatomic landmarks typically used to establish the superior border of nodal RT fields and the recurrences identified here, we found that 67% of recurrence sites and 59% of patients would have disease encompassed using pelvic nodal fields that extend cephalad to the aortic bifurcation.

The definition of recurrence among advanced imaging studies varies dramatically, ranging from histologic confirmation to reliance on deviation from physiologic levels of radiotracer uptake alone (23). We chose a conservative approach to define recurrence – using either histologic evaluation (49% of patients) or ADT driven treatment response confirmed by serial imaging – which is consistent with studies evaluating CholPET in prostate cancer patients (12, 19, 24). Furthermore, during the study period patients were treated with conventional fields and doses consistent with those used in RTOG clinical trials (25) and/or by the RTOG consensus for post-prostatectomy RT (26) and were restricted to those not receiving ADT at the time of evaluation. Our exclusion of patients on ADT is supported by Graziani *et al*, who demonstrated that ongoing ADT at the time of CholPET influenced the PSA level at which recurrences were detected and their anatomic distribution (27).

The incidence and anatomic distribution of primary therapy failure vary (28, 29). In the current era of multimodality therapy for prostate cancer, it is increasingly understood that the extent of disease at primary treatment not only informs prognosis, but also guides the selection of adjuvant therapies. For example, some series have shown that patients with lymph node involvement at the time of prostatectomy appear to benefit from adjuvant RT given in addition to ADT compared to ADT alone (30-32). Similarly, 18-fluorocholine has

been used in prostate cancer to tailor therapy in both the primary and salvage therapy setting with promising early results (33). As such, the identification and distribution of lymph node involvement at presentation and recurrence is of interest as it relates to efforts designed to maximize long-term control of disease.

Previous investigations have established the role for CholPET in the evaluation of biochemical recurrence after either RP or RT (24, 27, 34). The National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) (35, 36) recognize the use of CholPET in the identification of sites of metastatic disease, but acknowledge that additional study is needed to define best practices. In a recent report of over 4,000 CholPET re-staging scans (27), the authors found that a PSA cut-off of 1.16ng/mL optimized the operational characteristics of CholPET, with a median PSA of 3.6ng/mL among patients with positive scans. Notably, the median PSA at detection was 3.1ng/mL reported here, similar to previous reports from our institution (24). Other institutions have shown a limited sensitivity of CholPET when the PSA is <2.0ng/mL (37), which may reflect the lower doses of C-11 choline used in other series relative to the protocol employed here. Indeed, reports from our institution where operative characteristics are available have shown a detection rate of 64% among patients with a PSA <2.0ng/mL (34), compared to 45% as reported in the aforementioned study of 4,000 restaging scans (27).

While we report on our experience with CholPET among patients with recurrent disease after post-prostatectomy RT, it is important to acknowledge that other radiopharmaceuticals, such as 68Ga-PSMA, have been shown to also detect recurrence at a low PSA, even among patients with a PSA <0.5ng/mL (38). While the majority of CholPET reports appear to confirm that C-11 choline is less sensitive at low PSA levels than 68Ga-PSMA, the sensitivities reported by our institution (24) are comparable to some of the 68Ga-PSMA studies, which may be reflective of our higher dose protocol. Future studies directly comparing these two agents, and others, in the same patient population may serve to further define the comparative sensitivity and specificity of these agents. Regardless, the common finding among all studies evaluating CholPET and other molecular imaging modalities (23) – including our own – is the relatively low PSA detection thresholds compared to conventional imaging modalities (11, 38). Importantly, by detecting recurrence at a lower PSA, the majority of patients are identified with fewer than 3 sites of disease with low rates of osseous and visceral metastases (27, 39).

As outlined in the EAU guidelines, the choice to evaluate a patient with CholPET is predicated by the assumption that a salvage therapy is being considered. Recently, Fodor and colleagues reported their experience with CholPET for salvage RT of lymph node recurrences following primary treatment in which 42 patients (~50%) had undergone RP followed by either adjuvant or salvage RT (39). Their approach to salvage RT included nodal RT to 51.8 Gy with an integrated boost of 65.5 Gy (in 28 fractions) to previously un-irradiated sites of recurrence. Using this approach with adjuvant systemic therapy (58% of patients), the 3-year biochemical recurrence-free survival was 42%, with grade II/III rectal and genitourinary toxicity limited to 4% and 6% of patients, respectively. These rates of GU

and GI toxicity are comparable to other reports on pelvic RT in the post-operative setting using intensity modulated approaches (40, 41).

CholPET has the potential to identify the anatomic sites of tumor recurrence when disease burden is lower – potentially at a point when clinical outcomes may be improved. We observed a significant portion (85%) of recurrences outside standard prostatic fossa only RT fields in this select study population. These findings are useful if the study of additional salvage therapy is contemplated. Others have reported that salvage of recurrent disease has the potential to prolong survival (16, 39, 42, 43). Data presented here indicate that a large number of patients' recurrences may be amenable to additional nodal irradiation using typical pelvic or extended pelvic fields. Interestingly, multiple patients evaluated (n=9) had deep pelvic nodal recurrences in perirectal and presacral sites, which are typically not included in traditional IMRT-based pelvic nodal RT. At the present time it is not clear whether these findings have implications with respect to elective nodal RT at the time of adjuvant or salvage RT, when pathologic staging at the RP showed no evidence of nodal involvement. The recently completed RTOG 05-34 (NCT00567580) should further define the role of pelvic nodal RT in these patients. Our finding with respect to the location of recurrences relative to nodal treatment volumes adds to this evolving area of clinical inquiry and should be considered hypothesis-generating only.

We acknowledge limitations to our methods and findings. Although we utilized dedicated image fusion software to guide the localization of recurrence with respect to RT treatment fields, this may not have resulted in an exact co-registration of images. We manually assessed the fusion to correct any error in registration; however, there is the potential that the mapped sites may be subject to slight error in location. Thus, we elected to include edge-of-field as a recurrence category as opposed to simply in-field or out-of-field. Furthermore, this series represents only patients in which CholPET identified recurrences, and while a significant number had histologic confirmation, not all recurrences classified by treatment response may harbor pathologic disease (44). Therefore, inferences drawn from the distribution of clinical features among recurrence sites – particularly with respect to recurrence within a RT field – must be limited to hypothesis generation only, as we cannot account for the overall rate of negative scans among other patients with these same clinical characteristics. Thus, these data should not be interpreted as a comment on the operational sensitivity and specificity of CholPET in this clinical setting. Furthermore, our exclusion of patients with castration resistant disease limits the generalizability of these anatomic descriptions to patients with primary failure after post-prostatectomy RT; however, we feel that this restriction resulted in a sample of patients where the influence of the pre-treatment state on their recurrence distribution would be minimized. Lastly, our description of recurrence sites as a function of pelvic RT fields should not be considered as our assertion that additional RT would have prevented these recurrences and subsequent survival. Indeed, even within our series, a small subset of patients with adequate radiation coverage of the prostatic fossa still recurred within the RT field. Despite these limitations, we maintain that this series provides useful data on patients evaluated with C-11 choline PET/CT for recurrence following post-prostatectomy RT.

Conclusion

C-11 choline PET/CT is a useful modality for the identification of sites of recurrence following post-prostatectomy RT. We found that recurrences within a treated RT field were uncommon – only 4% of all sites, and were predominantly nodal (89%). Additionally, we identified that most recurrences were not only out of a treated prostatic fossa RT field, but would be encompassed by either a pelvic (superior border at L5-S1 interface) or extended pelvic (superior border at aortic bifurcation) nodal RT field. These data provide information regarding the role of advanced imaging in the evaluation of biochemically recurrent CaP patients. These data may also be useful in clinical trial formulation and examination of treatment guidelines which include elective lymph node RT in post-prostatectomy patients.

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Summary

C-11 Choline PET/CT identified 121 sites of recurrence in 41 patients evaluated for biochemical failure after post-prostatectomy radiotherapy. Patient median PSA at time of detection was 3.1 ng/mL (IQR; 1.9 – 5.6). Histologic confirmation was obtained in 20 (49%) patients; the remainder were confirmed by treatment response. Recurrences were; 89% nodal, 6% osseous and 1% visceral. Most recurrences (86%) were outside of prostatic-fossa radiation fields; 5 were within field and 12 were on the edge-of-field.

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Figure 1.

Example of an out-of-field right internal iliac nodal recurrence which was (A) equivocal on MRI (short axis 6mm), (B) positive on Choline PET, and (C) biopsy confirmed. PSA at diagnosis was 7.8 ng/mL.

Figure 2.

Radiation treatment volumes superimposed on sites of recurrence identified at Choline PET in AP (A) and Lateral (B). Fields to the L5-S1 interface are denoted by green, whereas fields to the aortic bifurcation are denoted by blue. Sites of recurrence are either IF (purple), EOF (yellow), and OOF (blue). Histologic confirmation of sites denoted by red in AP (C) and Lateral (D). Note: Right pleural nodule, left rib and left supraclavicular nodal sites not shown.

Table 1
Clinical features of patients with detected recurrence following post-prostatectomy radiotherapy

	N or Median	% or IQR
Age at radical prostatectomy (years)	60	55 – 66
Pre-Treatment PSA (ng/mL)	7.7	5.4 – 11.3
Prostatectomy Gleason score (n=40)*		
6	2	5
7	23	56
8-10	15	37
Missing	1	2
Prostatectomy pathologic T- and N-stage (n=40)*		
pT2a-c	13	32
pT3a	14	34
pT3b	13	32
pN0	40	98
Missing	1	2
Undetectable post-prostatectomy PSA	24	59
Time from prostatectomy to RT (months)	17	8 – 41
RT type		
Adjuvant RT	2	5
Salvage RT	39	95
Hormone therapy during RT	17	42
RT dose (Gy)	68.4	64.8 – 70.2
Number of fractions	36	34 – 37
PSA nadir after RT (ng/mL)	< 0.1	< 0.1 – 0.28
Time to biochemical failure (months)	24	10 – 46
PSA at positive CholPET (ng/mL)	3.1	1.9 – 5.6
Time to positive CholPET from RT (months)	40	23 – 64
Time to positive CholPET from biochemical failure (months)	15	7 – 28
Number of CholPET prior to first identifiable recurrence site		
0	30	73
1	7	17
2	3	7
3	1	2

Table 2
Characterization of CholPET findings

	N or Median	% or IQR
Multiparametric MRI (n=33)		
Negative	7	21
Indeterminate	10	30
Concordant	16	49
Confirmation		
Histologic	20	49
Treatment response	21	51
Number of recurrence sites per patient		
Median number	2	1 – 4
1	11	27
2	12	29
3	5	12
4	6	15
5	2	5
6 or more	5	12
PSA per lesion (ng/mL)	1.4	1.0 – 2.6
Location of recurrence sites (n=121)		
Prostatic fossa	5	4
Pelvic lymph node sites	57	47
Perirectal lymph nodes	6	5
Presacral lymph nodes	3	2
Internal iliac lymph nodes	15	12
Obturator lymph nodes	6	5
External iliac lymph nodes	27	22
Common iliac lymph node sites	24	20
Retroperitoneal lymph node sites	26	21
Pelvic osseous sites	2	2
Extrapelvic osseous sites	5	4
Distant nodal site (Left supraclavicular node)	1	<1
Visceral site (Right pleural nodule, biopsy proven)	1	<1
Maximal cephalad extent of recurrence by patient (n=41)		
Prostatic fossa	1	2
Pelvic lymph nodes	17	41
Common iliac lymph nodes	9	22
Retroperitoneal lymph nodes	8	20
Osseous *	5	12
Visceral	1	2
Field of recurrence by lesion (n=121)		
IF	5	4

	N or Median	% or IQR
EOF	12	10
OOF	104	86
Field of recurrence by patient (n=41)		
IF only	1	2
IF + OOF	4	10
EOF only	4	10
EOF + OOF	6	15
OOF only	26	63

* One patient had both an osseous site and a left supraclavicular lymph node site.

Table 3

Characterization of lesions as a function of prior radiation field

	Per Lesion				Per Patient		
	IF (n=5)	EOF (n=12)	OOE (n=104)	p-value	No OOE (n=5)	Any OOE (n=36)	p-value
Median PSA at diagnosis (ng/mL) (IQR)	9.9 (7.4-14.7)	6.0 (5.5-10.8)	8.0 (5.6-9.9)	0.22	11.4 (10.4-14.7)	7.4 (5.3-9.6)	0.07
Gleason score (%)[†]				0.11			
6	0 (0.0)	2 (4.0)	3 (6.0)		0 (0)	2 (6)	>0.9
7	2 (3)	7 (10)	62 (88)		4 (8.0)	19 (53)	
8-10	3 (8)	2 (5)	35 (88)		1 (2.0)	14 (39)	
Pathologic Stage (%)[‡]				0.62			>0.9
pT2a-c	1 (3)	5 (14)	30 (83)		1 (2.0)	12 (34)	
pT3a	2 (7)	3 (10)	24 (83)		2 (4.0)	12 (34)	
pT3b	2 (4)	3 (6)	48 (91)		2 (4.0)	11 (31)	
Undetectable PSA post-RP (%)	2 (3)	9 (14)	52 (83)	0.21			
Median dose (Gy) (IQR)	66.6 (64.8-68.6)	67.3 (66.1-68.4)	68.4 (66.6-72.0)	0.11	68.4 (64.8-68.4)	68.0 (65.7-70.7)	0.76
Median EOF dose	--	10 (5-30)	--	--	--	--	--
Median fractions of RT (IQR)	36 (36-36)	36 (36-37)	36 (34-37)	0.76	38 (38-38)	36 (34-36)	<0.01
Median PSA nadir (ng/mL) (IQR)	0.1 (0.1-0.1)	0.2 (0.1-0.3)	0.1 (0.1-0.4)	0.11	0.1 (0.1-0.3)	0.1 (0.1-0.3)	0.90
Median PSA at biochemical failure (ng/mL) (IQR)	1.2 (0.9-1.2)	0.8 (0.5-1.2)	0.5 (0.4-0.8)	0.03	1.0 (0.6-1.2)	0.5 (0.4-0.8)	0.22
Median time to biochemical failure (months) (IQR)	34 (29-44)	25 (11-49)	22 (5-42)	0.39	40 (9-74)	24 (10-44)	0.58
Median PSA at ChOlPET (ng/mL) (IQR)	2.5 (2.0-3.1)	3.1 (2.3-4.7)	3.4 (2.0-7.9)	0.77	2.8 (2.1-3.1)	3.2 (1.9-5.7)	0.68
Median time from recurrence to positive ChOlPET (months) (IQR)	14 (10-18)	7 (4-13)	14 (9-27)	0.052	15 (3-42)	15 (7-28)	0.78
Location (% of all sites at each location)				--*			--*
Prostate fossa	5 (100)	0 (0)	0 (0)		1 (20)	4 (80)	
Pelvic lymph nodes	0 (0)	12 (21)	45 (79)		4 (7)	53 (93)	
Perirectal/Presacral lymph nodes	0 (0)	3 (33)	6 (67)		1 (11)	8 (89)	
Internal iliac lymph nodes	0 (0)	2 (13)	13 (87)		0 (0)	15 (100)	
Obturator lymph nodes	0 (0)	3 (50)	3 (50)		3 (50)	3 (50)	
External iliac lymph nodes	0 (0)	4 (15)	23 (85)		0 (0)	27 (100)	
Common iliac lymph nodes	0 (0)	0 (0)	24 (100)		0 (0)	24 (100)	

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	Per Lesion			Per Patient		
	IF (n=5)	EOF (n=12)	EOF (n=104)	p-value	No OOF (n=5)	Any OOF (n=36)
Retropertitoneal lymph nodes	0 (0)	0 (0)	26 (100)		0 (0)	26 (100)
Distant lymph nodes	0 (0)	0 (0.0)	1 (100)		0 (0)	1 (100)
Pelvic osseous sites	0 (0)	0 (0)	2 (100)		0 (0)	2 (100)
Extrapelvic osseous sites	0 (0)	0 (0)	5 (100)		0 (0)	5 (100)
Visceral site	0 (0)	0 (0)	1 (100)		0 (0)	1 (100)

* As location of recurrence is directly related to IF, EOF, or OOF recurrence, statistically assessing differences in this variable is not statistically appropriate.

[†]Excludes 1 patient with missing pathologic data.

Table 4
Recurrences as a function of different radiation fields

	L5-S1 interface	Aortic bifurcation
<i>Pelvic nodal fields only</i>		
Number of patients entirely covered (n=41) (%)	11 (27)	19 (46)
Number of recurrences covered (n=121) (%)	52 (43)	76 (63)
<i>Fossa and pelvic nodal fields</i>		
Number of patients entirely covered (n=41) (%)	16 (39)	24 (59)
Number of recurrences covered (n=121) (%)	57 (47)	81 (67)