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Original Research Article

Nodal recurrence patterns on PET/CT after RTOG-based nodal radiotherapy for prostate cancer

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ABSTRACT

Purpose: Biochemical failure after external beam radiotherapy (RT) for node-positive prostate cancer (PC_{N+}) frequently involves nodal recurrences, in most cases out of field. This raises the question if current RTOG-based elective nodal fields can still be considered optimal. Modern diagnostic tools like PSMA PET/CT and choline PET/CT can visualize nodal recurrences with unprecedented accuracy. We evaluated recurrence patterns on PET/CT after RT for PC_{N+}, with the aim to explore options for improved nodal target definition.

Methods and materials: Data of all patients treated with curative intent EBRT for PC_{N+} in NKI-AVL from 2008 to 2018 were retrospectively reviewed. EBRT comprised 70 Gy to the prostate or 66–70 Gy to the prostate bed, 60 Gy to involved nodes, and 52,5–56 Gy (46 Gy EQD2) to RTOG-based elective nodal fields, in 35 fractions. Locations of recurrences on PET/CT were noted, and nodal locations were correlated with the applied EBRT fields.

Results: 42 patients received PSMA (28) or choline (14) PET/CT at biochemical recurrence. 35 patients (83%) had a positive scan. At their first positive scan 17 patients had nodal metastasis, in some cases together with a local recurrence or distant disease. In-field nodal recurrences were uncommon (n = 3). Out-field nodal recurrences occurred more frequently (n = 14), with the majority (n = 12) just above the elective nodal field. These nodes were the single area of detectable failure in 6 patients (14%).

Conclusions: Current RT with RTOG-based nodal fields for PC_{N+} provides good in-field tumour control, but frequent out-field nodal recurrences suggest missed microscopic locations. Expanding elective fields to include the aorta bifurcation may prolong recurrence-free survival. Future research must address whether the potential benefits of this strategy outbalance additional toxicity.

1. Introduction

The presence of lymph node metastases is an important independent negative prognostic factor in prostate cancer [1,2]. Over 30–40% of patients with high risk prostate cancer show lymph node metastasis at staging with pelvic lymph node dissection [3].

Node-positive prostate cancer (PC_{N+}) is often treated with external beam radiotherapy (RT) of the prostate and pelvic nodes, preferably concurrent with long-term androgen deprivation treatment (ADT) [4,5]. Besides a high dose to macroscopically involved nodes, the consensus guideline of the RTOG (2009) is commonly used to decide which pelvic node at risk for involvement volumes require elective treatment [6]. The upper limit of the elective nodal field in this guideline extends to the L5/S1 interspace (the level of the distal common iliac and proximal presacral lymph nodes). The techniques that were used to guide decisions on this radiation field included prostatic lymphography, extended pelvic lymph node dissection (ePLND) and pelvic MRI. However, more recently, new staging methods such as PET/CT using radiolabeled choline analogs [7] or ligands to the prostate-specific membrane antigen (PSMA)

Abbreviations: BCR, biochemical recurrence; ePLND, extended pelvic lymph node dissection; GS, Gleason Score; IMRT, Intensity-Modulated Radiation Therapy; IRB, Institutional Review Board; LND, Lymph Node Dissection; NKI-AVL, Nederlands Kanker Instituut Antoni van Leeuwenhoek; PC_{N+}, node-positive prostate cancer; PET/CT, positron emission tomography / computed tomography; PSMA, Prostate-Specific Membrane Antigen; rLND, retroperitoneal lymph node dissection (rLND); RP, radical prostatectomy; RT, external beam radiotherapy; RTOG, Radiation Therapy Oncology Group; SNB, Sentinel Node Biopsy; SNP, Sentinel Node Procedure; sRT, Salvage Radiotherapy; VMAT, Volumetric Arc Therapy.

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have been developed [8]. These imaging modalities are now increasingly used for restaging of biochemical recurrence (BCR), and have high accuracies for identification of metastases that are relevant for RT and that could previously not be detected with conventional imaging [9].

The practical value of modern diagnostic PET/CT imaging to detect nodal involvement and to guide target volume decisions or dose escalation areas is increasingly recognized [10–13]. The introduction of new PET/CT techniques allows increasingly accurate detection of nodal metastases at low PSA-values. In two studies, extrapelvic nodes were detected depending on PSA-level at BCR after radical prostatectomy ranging from 5 to 44% of patients [14,15]. These observations have been confirmed by a mapping study in which ePLND and retroperitoneal lymph node dissection (rLND) were performed in 19 patients with high risk prostate cancer, where 77.8% had involved retroperitoneal nodes [16].

The increased awareness of nodal involvement and potential recurrences outside RTOG volumes leads to the hypothesis that disease-free survival could be extended with optimization of RT to new insights related to nodal disease spread. Detected regional nodal metastases with PET/CT are included in high-dose fields. However, which areas should be added to elective fields to reduce recurrences remains unclear. Hereby, we report nodal recurrence patterns on PET/CT after RT for PC_{N+}, with the aim to start debate about the accuracy of historically based target volumes for pelvic irradiation in the present era.

2. Methods

2.1. Patient selection

We retrospectively identified patients who received curative intent RT (+/− ADT) for PC_{N+} (primary diagnosed or in salvage setting after radical prostatectomy) in NKI-AVL in the 10 years prior to evaluation (June 2008 – June 2018). Patients were restaged in NKI-AVL with at least one choline PET/CT or PSMA PET/CT upon BCR. All data was pseudonymized prior to evaluation, and the local IRB of NKI-AVL waived the need for informed consent for this retrospective cohort study (reference IRBd18035).

2.2. Prior treatment

Patients received RT of the prostate or prostatic fossa combined with pelvic lymph node regions. For staging prior to treatment, the majority of the patients (81%) received either an ePLND (50%) or a sentinel node biopsy procedure (SNB) (33%), 1 patient received both (2%) and the remaining 17% received no surgical nodal staging. Pelvic lymph node regions were contoured based on the RTOG guidelines [6]. In the evaluated period, radiation dose was 75.25–77 Gy to the prostate and 52.5–56 Gy to pelvic lymph nodes in 35 fractions, or in salvage setting 66–70 Gy to the prostatic fossa and 52.8–56 Gy to the pelvic lymph nodes in 33–35 fractions. Pathologically enlarged or otherwise suspicious lymph nodes received an integrated boost up to 60 Gy. Treatment was delivered using an IMRT technique until June 2014, and using VMAT thereafter. In general, concurrent and adjuvant ADT was advised.

2.3. Follow-up

Patients were followed after treatment with blood PSA level measurements regularly, according to Dutch guidelines. The common definition of BCR was either a rising PSA at multiple consecutive occasions, a PSA above 2 ng/mL above PSA nadir, or a short PSA doubling time, although it was to clinicians' discretion which of the abovementioned definitions was used. Upon BCR, a PET/CT scan was performed to determine the location of recurrence and to evaluate options for salvage treatment. In case of a negative PET/CT, the scan could be repeated upon further rise of PSA at the discretion of the referring physician (generally after one or two PSA-doublings). When a negative PET/CT was later followed by one or more positive scans, the first positive PET/CT was selected for evaluation in this study.

2.4. PET/CT imaging

Positron Emission Tomography/Computed Tomography (PET/CT) imaging was performed using a Gemini TF-II or Gemini TF Big Bore PET/CT scanner (Philips, Maryland, USA). First a non-contrast enhanced low dose CT scan was acquired for attenuation correction and anatomical correlation (120–140 kV, 40–80 mAs with dose modulation, reconstruction in 2 mm slices, scan range from proximal femora to skull base). This was immediately followed by PET acquisition of the same scan range. Patients were prepared for imaging by adequate oral hydration before administration of the tracer. Patients were imaged with choline PET/CT until June 2016, and from then on with PSMA PET/CT.

For choline PET/CT, ^{18}F-fluormethylcholine (BV Cyclotron, Amsterdam, the Netherlands) was administered as an intravenous bolus injection of 190 MBq (240 MBq if the body mass index was > 28). PET images were acquired directly after tracer administration, with 3 min per bed position for pelvis/abdomen and 1,5 min per bed position for the remainder of the scan range.

For PSMA PET/CT, either ^{68}Ga-PSMA-11 or ^{18}F-DCFPyL were used as tracers. ^{68}Ga-PSMA-11 was radiolabelled in-house using a fully automated system (Scintomics GmbH, Germany). A fixed dose of 100 MBq was administered to patients as an intravenous bolus. Scanning commenced after an incubation period of 45 +/− 5 min, with 3 min per bed position for pelvis/abdomen and 2 min per bed position for the remainder of the scan range. ^{18}F-DCFPyL (BV Cyclotron, Amsterdam, the Netherlands) was administered as an intravenous bolus injection with a fixed dose of 200 MBq. Scanning commenced after an incubation period of 60 +/− 5 min, with 2 min per bed position over the complete scan range.

All images had been interpreted for clinical decision making by nuclear medicine physicians experienced in prostate cancer PET imaging and reporting, and were reviewed a second time by an independent observer in the scope of this retrospective evaluation. Discrepancies were resolved by discussion until consensus was reached. Reports included detailed description regarding possible local, regional and distant sites of prostate cancer recurrence.

2.5. Correlation with treatment

The locations of detected nodal recurrences were correlated visually based on anatomy with the dose distribution of the prior treatment, to classify the recurrence as in-field (overlapping with high dose or elective dose) or out-field (visually beyond the 50% isodose of the delivered fields). Descriptive statistics were used to present and interpret the resulting data, including the relation with the use of the sentinel node procedure (SNP) or LND to diagnose node-positive disease, the use of PET/CT for restaging, and tumour characteristics.

3. Results

3.1. Selected patients

Between June 2008 and June 2018, a total of 436 patients received the described treatment. These patients were matched with patient IDs from 2411 choline PET/CT or PSMA PET/CT scans

that were acquired in the same period. This identified 48 evaluable patients who had at least one PET/CT for BCR in the NKI-AVL after their primary treatment. Six patients were excluded after further evaluation: one patient was excluded from the analysis because of more extensive lymph node irradiation than recommended by RTOG guidelines, one patient received multiple years of androgen deprivation treatment upon detection of node positive disease, one patient did not receive local therapy of prostate or prostatic fossa upon pelvic radiotherapy and three patients were excluded because they received a PET/CT at low PSA values as response to treatment evaluation. The remaining 42 patients were selected for evaluation (28 with PSMA PET/CT and 14 with choline PET/CT). The patient identification procedure is illustrated in Fig. 1.

3.2. Patient characteristics

The characteristics of the 42 evaluated patients are listed in Table 1. The majority of the patients was between 60 and 70 years old at time of their primary treatment (median 64.5 years; mean 6 years). They predominantly had high-risk tumours, with at least 2 high-risk factors in 25 patients. The median initial PSA was 17 μg/L (mean 32.4 μg/L). More patients were treated to the prostate than to the prostatic fossa, and in the majority of cases this was combined with ADT (advised duration up to 36 months; reported in 19 patients).

3.3. Recurrences

The distribution of detected recurrences in all patients is listed in Table 2. There were 7 patients (17%) in whom no recurrence was detected with PET/CT despite BCR (PSA range at that time 0.17–1.71) ng/ml). At their first positive scan, 13 patients (31%) showed local recurrence, 17 (40%) nodal metastasis, and 16 (38%) distant disease. Of the 17 patients with nodal recurrences, 9 had involved nodes as the only location of detected disease. From the rest, 3 had nodal recurrence plus local recurrence and 5 in combination with distant metastasis. Of the locations of nodal recurrences in respect to irradiation fields; 3 were in-field and 14 out-field. An overview of the anatomical locations of all detected nodal recurrences is provided in Fig. 2.

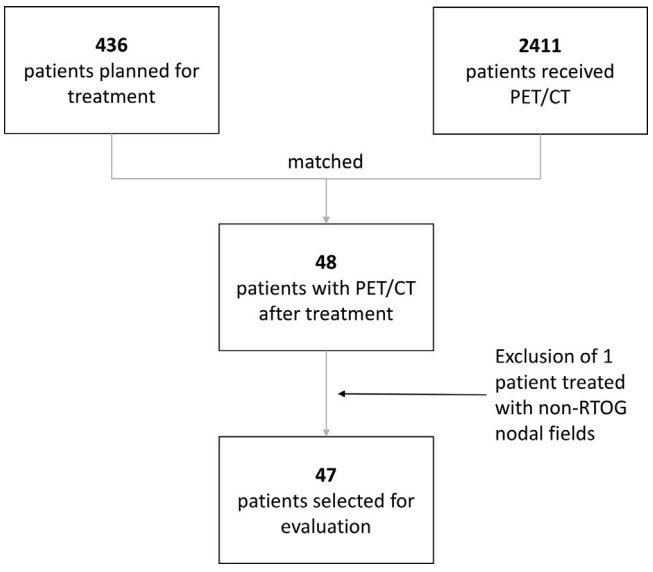

Fig. 1. Overview of patient selection.

Table 1
Characteristics of included patients.

42 patients included	Total
Age	
40–50	1
50–60	8
60–70	27
70–80	6
≥80	0
T-stage	
T1	2
T2	3
T3	33
T4	4
N-stage	
cN0	1
cN1	41
Gleason sum score	
6	3
7	21
8	8
9	8
10	1
Missing	1
PSA at first diagnosis	
<10	13
≥10 and <20	10
≥20 and <40	10
>40	8
Missing	1
PSA at PET CT at BCR	
Median	3.15
Range	0.17–64 μg/L
Treatment	
Prostate + pelvis	26
Prostatic fossa + pelvis	16
Dose	
Prostate + pelvis	
75,25 + 52,5 Gy	20
77 + 52,5 Gy	2
77 + 56 Gy	2
Other	2
Prostatic fossa + pelvis	
66 + 52,8 Gy	5
70 + 56 Gy	11
Androgen deprivation treatment	
Yes	25
No	9
Not reported	8

Table 2
Locations of all detected recurrences on PET/CT.

Recurrences on PET/CT	N = 42
None detected	7
Local only	7
Nodal only	9
Distant only	8
Local + nodal	3
Local + distant	3
Nodal + distant	5

3.4. Factors related to nodal recurrences

There was no clear difference in nodal recurrences between patients originally diagnosed with N1 disease by the SNP, LND or imaging. From the patients diagnosed N1 using SNP, 4/14 had nodal recurrences (29%). From the patients diagnosed with LND, 10/21 had nodal recurrences (48%). From the patients who had evi-

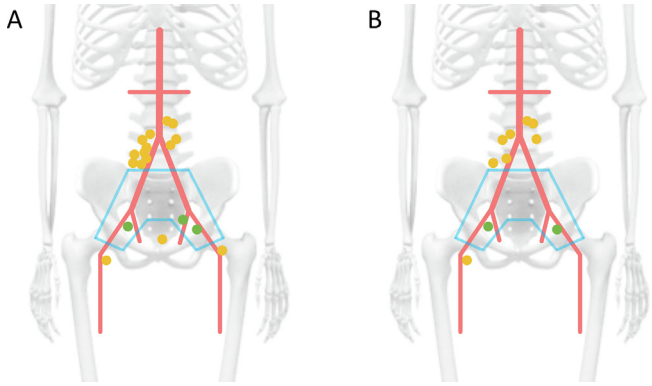

Fig. 2. Schematic distribution of nodal recurrences. Schematic overview of anatomical locations of nodal recurrences (A) in all patients and (B) in patients with only nodal recurrence. Red = large arteries for anatomical reference. Blue box = RTOG-based elective nodal radiotherapy field. Green dot = in-field nodal recurrence. Yellow dot = out-field nodal recurrence, indicating the node closest to the elective field for each involved anatomical region. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dent nodal involvement at diagnostic imaging and did not receive any surgical confirmation, 3/8 had nodal recurrences (38%).

From the patients who received PET/CT for restaging purposes in their diagnostic work-up, 4/7 had nodal recurrences (57%), and without PET/CT staging 13/35 had nodal recurrences (37%).

There were no large differences in Gleason score, (47% of the patients with nodal recurrence with GS > 7 versus 40% of the patients without nodal recurrence with a GS > 7), initial PSA level (mean 39.8 ng/ml versus 27.4 ng/ml), or clinical T-stage (88% versus 88% stage T3 or higher) between the patients that experienced nodal recurrence versus patients who did not. There was also no large difference in the use of concurrent ADT (59% versus 60%).

3.5. Patients with only nodal recurrences

The details of the 9 patients who had only nodal recurrence, without any evidence of local recurrence or distant metastasis, were explored further (Table 3). This group had no clear common characteristics of either their initial or recurrent disease, with recurrent PSA range 0.56–15.75, initial primary tumours cT2–cT3b, and initial Gleason scores 7–9. Most of these patients (8/9) were detected with PSMA PET/CT, and only one with choline PET/CT. Interestingly, 7 of these 9 patients had only out-field recurrences, with the most proximal metastasis located in the common iliac or lower para-aortal areas just cranially to the elective nodal field. Initially, the majority of these patients had nodal disease in the para-iliac nodes. Also, in all but one of these patients the recurrent nodal disease was limited to the area below the renal veins. Example images of out-field nodal recurrences in two representative patients are provided in images 3 and 4.

4. Discussion

To our knowledge, this is the first publication that describes nodal recurrence patterns for prostate cancer after RT with elective nodal fields, based on the high sensitivity, high specificity and good anatomical localization provided by current PET/CT techniques. The very low number of in-field nodal recurrences illustrates the efficacy of current nodal RT for PC_{N+}. However, frequent out-field nodal recurrences might suggest missing of microscopic locations by current RTOG-based elective nodal fields.

The RTOG recommendations for elective nodal fields date from 2009, and were based on knowledge on nodal spread and recurrence patterns as determined with less accurate tools [6]. As discussed earlier, new and improved staging techniques such as PSMA PET/CT can detect lymph nodes metastasis beyond the pelvic lymph node regions that are generally evaluated with lymph node dissections [17]. Better evaluable regions may include for example the paravesical, para-rectal, retroperitoneal and mediastinal nodes. Our results specifically indicate the risk of nodal progression/recurrence in the nodes just above the current RTOG-based fields, along the common iliac arteries above the level of the promontory, around the aortic bifurcation, and in the lower para-aortic area.

Literature determining which patients are likely to benefit from adjuvant radiotherapy of lymph node metastasis are based on a wide variety of pathologic and radiographic staging techniques with varying sensitivity and specificity, similar to the development of the RTOG recommendations. Two things could be hypothesized from this. First, the patient categories that are most likely to benefit from radiotherapy of lymph node areas may need to be re-evaluated. In current literature, only patients with limited nodal disease ($\leq$4 positive nodes) are likely to benefit from radiotherapy to nodal regions [18]. However, these patients may have been understaged in the era prior to PET/CT. In patients with more extensive nodal disease, distant disease may traditionally have been understaged. Therefore, current patients with extensive nodal disease could potentially be cured with optimized radiation fields, or at least their recurrence free survival might be prolonged, while a proportion of patients with better staged distant disease could possibly refrain from an ineffective locoregional treatment.

Second, the target areas of elective nodal irradiation may need to be reconsidered. A larger proportion of the patients are nowadays identified with para-aortal and retroperitoneal lymph node metastasis, at primary presentation as well as recurrent disease. Since elective nodal regions were based on historical knowledge on disease spread, it seems logical to re-evaluate the nodal regions now that disease spread is shown in other locations. Several studies have already shown lymph node metastasis outside the current RTOG volume [19–21]. First, Calais et al. reported recurrence patterns after prostatectomy prior to salvage radiotherapy. 33 patients experienced extrapelvic lesions, of which 15% could have had superior extension of the nodal CTVs to encompass the para-aortic disease [20]. Second, De Bari et al. studied PSMA PETCT scans

Table 3
Patients with only nodal recurrences on PET/CT.

Patient	Treatment sRT vs Primary RT	Primary tumour	Initial N-staging method	Gleason Score	ADT (M)	PSA at PET/CT	Time to recurrence (months)	Area of first nodal metastasis	In-field
8	Primary RT	T4N1	PLND	7	36	3.24	82	Aortic bifurcation	No
13	Primary RT	T3bN1	Imaging	9	36	6.68	86	Aortic bifurcation	No
18	sRT	T2N1	PLND	NA	NA	13.31	73	Aortic bifurcation	No
27	Primary RT	T3bN1	SNP	7	36	10.31	54	Aortic bifurcation	No
33	sRT	T3bN1	PLND	9	36	15.75	40	Common iliac at level L4	No
34	sRT	T3bN1	PLND	8	0	15.53	12	Aortic bifurcation + inguinal	No
36	sRT	T3aN1	PLND	7	NA	4.2	32	Common iliac at level L5	No
38	sRT	T3bN1	PLND	7	0	1.0	29	External Iliac	Yes
42	sRT	T3aN1	PLND	9	6	0.56	13	Obturator	Yes

for BCR after prostatectomy. A large number of these operated patients experienced nodal relapses outside the current RTOG volume (68.8%) and also both inside and outside the RTOG volume (6.2%). Their suggestion is to adopt even larger target volumes (up to the level of Th12/L1), to treat at least 95% of the lymph node regions at risk for occult relapse [21]. Our data illustrate the relevance of the upper nodal field limit in the population of patients who received external beam radiotherapy. Interestingly, almost all patients with nodal recurrence alone reported in this study had their most proximal nodal metastasis just above the cranial border of the elective field at the paraaortic level. A similar pattern was demonstrated by Spratt et al., but with less sensitive detection of nodal recurrences using anatomical criteria on CT or MRI [19]. Further supporting evidence may be derived from the RTOG 0924 trial, which recommends limited cranial expansion of the field border to the level of L4-L5. Results of this study are awaited [22].

An important question that remains is whether lymphatic spread of prostate cancer develops exclusively in a linear pattern from one node station to the next or whether non-linear patterns occur as well. Briganti et al. showed that patients with common iliac nodes in the para-aortal and retroperitoneal node dissection specimen all had also positive nodes in the external or internal iliac area [16]. This suggests an ascending lymphatic spread in a linear pattern. Therefore, it may be possible to halt lymphatic spread with limited expansion of elective fields. However, expanded fields may fail when linear lymphatic spread is already further than imaging can detect, or when lymphatic spread follows a non-linear pattern with skip metastasis, such as is described in several other cancer types [23,24]. For example, the case illustrated in Fig. 3 suggests potential prolonged recurrence free survival with a limited expansion. In contrast, the case illustrated in Fig. 4 likely would have had less chances on such a benefit given the extensive nodal spread at recurrence.

Further research will be needed to determine whether a potential benefit in recurrence free survival outweighs the assumed added toxicity, and which patients to select that benefit most.

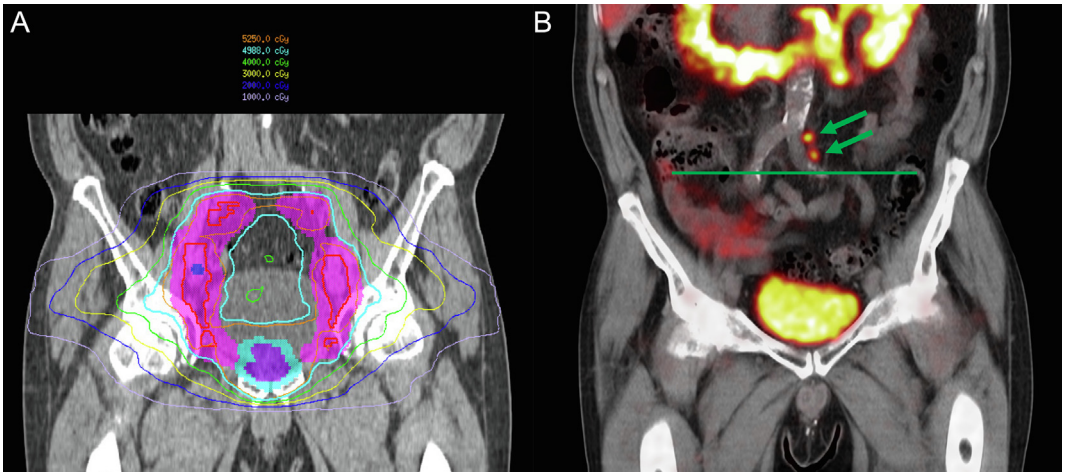

Fig. 3. Example of limited out-field nodal recurrence. Coronal slices of patient 13, of the treatment plan in 2011 (A) and of PSMA PET/CT at biochemical recurrence with PSA 6.68 in 2017 (B). The plan shows the delineated elective nodal field (pink) with isodose lines indicating its cranial border. The PET/CT scan shows two nodal metastases (green arrows) just above elective field, at the of the aortic bifurcation. There were no signs of distant metastasis. Stereotactic treatment of these two nodes resulted in biochemical response, with a duration of 1.5 years. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

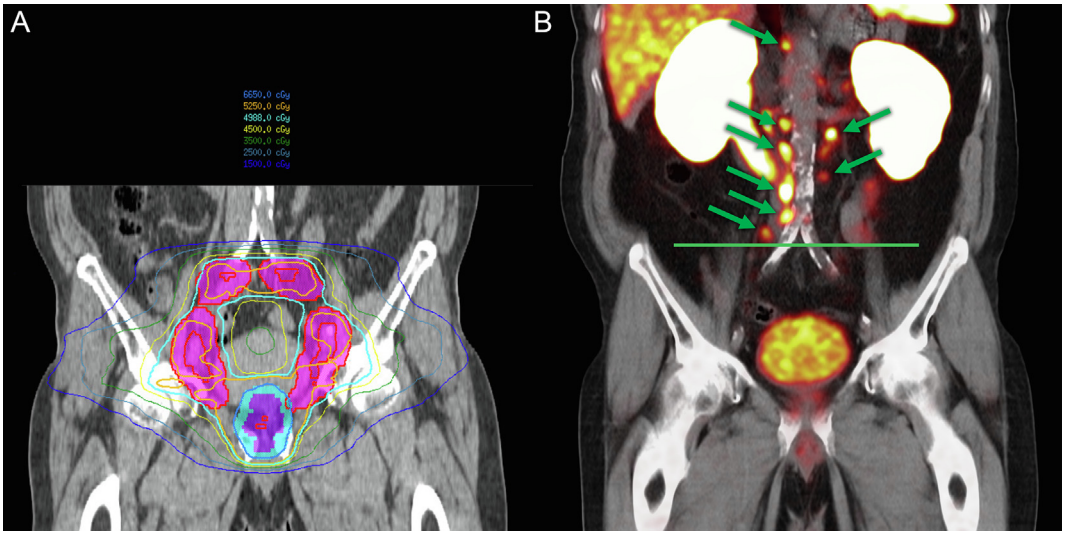

Fig. 4. Example of extensive out-field nodal recurrence. Coronal slices of patient 27, of the treatment plan in 2012 (A) and of PSMA PET/CT at biochemical recurrence with PSA 10.31 in 2017 (B). The plan shows the delineated elective nodal field (pink) with isodose lines indicating its cranial border. The PET/CT scan shows extensive nodal metastases (green arrows) from just above elective field, up to the renal vessels and one node above. The patient started ADT, with ongoing biochemical response at the time of evaluation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

There is also no clear answer whether nodal metastasis influence the risk of developing distant metastasis later on and therefore overall survival or prostate cancer specific survival.

An important limitation of this study is the retrospective nature of the evaluation, with a relatively low percentage of treated patients who received PET/CT for BCR in the same centre (11%). The evaluated cohort involved patients with different treatment strategies (e.g. prior prostatectomy versus primary radiotherapy). Although this could be relevant for treatment decisions in individual patients, this is expected to have limited effect on evaluation of the spatial distribution of nodal recurrences after nodal radiotherapy. A fair share of patients with BCR may have received re-staging in referring hospitals, and some other patients with may have not received any imaging or only imaging with limited value for nodal recurrence instead of a PET/CT. This study may therefore be subject to selection bias. Some small nodal recurrences may have been missed, despite the relatively high sensitivity of current PET/CT techniques. This may have lowered the number of evaluable patients, but this does not affect the interpretation of the positive PET/CT scans reported in this study. Another limitation is the variable timing of PET/CT, using different radiopharmaceuticals, at varying PSA levels and for various reasons. In the recent years, definitions of BCR and the indications for PET/CT are increasingly being standardized, supported by clinical evidence [17]. Despite these limitations, the patients in the evaluated cohort demonstrate recurrence patterns with a distribution between local, nodal and distant recurrences comparable with other publications [25,26]. As such, these results may contribute to justification of prospective research, preferably with better standardized tracer selection and timing of PET/CT.

The subgroup evaluations of the patients according to diagnostic work-up, and of the 9 patients with nodal recurrence alone are especially subject to the limitations of a small cohort size, and should be considered as descriptive research that warrant further exploration. With this limitation in mind, there was no clear relation between the occurrence of nodal recurrences and the diagnostic work-up (either SNP, LND or imaging alone), the use of PET/CT for staging or baseline tumour characteristics. This could suggest equal performance of pelvic RT independent of the diagnostic work-up strategy (with application of a nodal boost when deemed appropriate). In addition, the relatively frequent occurrence of isolated nodal recurrences just above the nodal field can be interpreted as an opportunity to optimize treatment.

In conclusion, current RT for PC_{N+} provides good in-field tumour control, but relatively frequent out-field nodal recurrences suggest geographical miss of microscopic locations. An expansion of elective fields to include the aorta bifurcation may avoid nodal recurrences or prolong recurrence-free survival for selected cases, but future research must address whether the potential benefits of this strategy outbalance additional toxicity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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