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 (PCN+) 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 PCN+, with the aim to explore options for improved nodal target definition.

Methods and materials: Data of all patients treated with curative intent EBRT for PCN+ 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 PCN+ 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.

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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 (PCN+) 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)
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 disease-free survival could be extended with optimization of RT to the hypothesis that disease-free survival could be extended with optimization of RT to new insights related to nodal disease spread. Detected regional disease-free survival could be extended with optimization of RT to new insights related to nodal disease spread. Detected regional disease-free survival could be extended with optimization of RT to new insights related to nodal disease spread. Detected regional disease-free survival could be extended with optimization of RT to new insights related to nodal disease spread. Detected regional disease-free survival could be extended with optimization of RT to new insights related to nodal disease spread. 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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. Of 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.

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-
Patients with only nodal recurrence on PET/CT. (mean 39.8 ng/ml versus 27.4 ng/ml), or clinical T-stage (88% versus 78%), initial PSA level in their diagnostic work-up, 4/7 had nodal recurrences (57%), and 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.

### Table 3

| Patient | Treatment | 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    | 13.31         | 73                         | Aortic bifurcation           | No      |
| 18      | sRT        | T2N1           | PLND                     | NA NA         | 10.31   | 54            | 40                         | Aortic bifurcation           | No      |
| 27      | Primary RT | T3bN1          | SNP                      | 7 36          | 15.75   | 29            | 12                         | Common iliac at level L4     | No      |
| 33      | sRT        | T3bN1          | PLND                     | 9 36          | 15.53   | 12            | 4.2                        | Aortic bifurcation + inguinal | No      |
| 34      | sRT        | T3bN1          | PLND                     | 8 0           | 4.2     | 32            | 1.0                        | Common iliac at level L5     | No      |
| 38      | sRT        | T3aN1          | PLND                     | 7 6           | 0.56    | 13            | 29                         | External Iliac               | Yes     |
| 42      | sRT        | T3aN1          | PLND                     | 9 6           | 3.5     | 1            | 24                         | 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.

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**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 PCP, 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 outweigh 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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