EUROPEAN UROLOGY 76 (2019) 732–739

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Neil B. Desai, Kevin Courtney, Rathan M. Subramaniam and Jeffrey A. Cadeddu on pp. 740–742 of this issue

Metastasis-directed Therapy in Treating Nodal Oligorecurrent Prostate Cancer: A Multi-institutional Analysis Comparing the Outcome and Toxicity of Stereotactic Body Radiotherapy and Elective Nodal Radiotherapy

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Article info

Article history:
Accepted July 5, 2019

Associate Editor:
T Morgan

Statistical Editor:
Emily Zabor

Abstract

Background: Stereotactic body radiotherapy (SBRT) and elective nodal radiotherapy (ENRT) are being investigated as metastasis-directed treatments in oligorecurrent prostate cancer (PC); however, comparative data are still lacking.
Objective: To compare outcome and toxicity between both treatments. Primary end-point was metastasis-free survival, adjusted for selected variables (aMFS).
Design, setting, and participants: This was a multi-institutional, retrospective analysis of 506 (SBRT: 309, ENRT: 197) patients with hormone-sensitive nodal oligorecurrent PC (five or fewer lymph nodes (LNs; N1/M1a), treated between 2004 and 2017. Median follow-up was 36 mo (interquartile range 23–56).

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https://doi.org/10.1016/j.eururo.2019.07.009

Keywords:
Elective nodal radiotherapy
Metastasis-directed therapy
Oligometastasis
Oligorecurrence
Prostatic neoplasms
Radiotherapy
Recurrence
Stereotactic ablative body radiotherapy
Stereotactic body radiotherapy

Intervention: SBRT was defined as a minimum of 5 Gy per fraction to each lesion with a maximum of 10 fractions. ENRT was defined as a minimum dose of 45 Gy in up to 25 fractions to the elective nodes, with or without a simultaneous boost to the suspicious node(s). The choice of radiotherapy (RT) was at the discretion of the treating physician, with treatments being unbalanced over the centers.
Outcome measurements and statistical analysis: In total, 506 patients from 15 different treatment centers were included. Primary treatment was radical prostatectomy, RT, or their combination. Nodal recurrences were detected by positron emission tomography/computer tomography (97%) or conventional imaging (3%). Descriptive statistics was used to summarize patient characteristics.
Results and limitations: ENRT was associated with fewer nodal recurrences compared with SBRT ($p < 0.001$). In a multivariable analysis, patients with one LN at recurrence had longer aMFS after ENRT (hazard ratio: 0.50, 95% confidence interval 0.30–0.85, $p = 0.009$). Late toxicity was higher after ENRT compared with that after SBRT (16% vs. 5%, $p < 0.01$). Limitations include higher use of hormone therapy in the ENRT cohort and nonstandardized follow-up.
Conclusions: ENRT reduces the number of nodal recurrences as compared with SBRT, however at higher toxicity. Our findings hypothesize that ENRT should be preferred to SBRT in the treatment of nodal oligorecurrences. This hypothesis needs to be evaluated in a randomized trial.
Patient summary: This study investigated the difference between stereotactic and elective nodal radiotherapy in treating limited nodal metastatic prostate cancer. Nodal relapse was less frequent following elective nodal radiotherapy than following stereotactic body radiotherapy, and thus elective nodal radiotherapy might be the preferred treatment.

1. Introduction

Following primary treatment of prostate cancer (PC), 20–50% of patients present with biochemical recurrence depending on the stage and grading [1]. In this setting, choline, prostate-specific membrane antigen (PSMA) or ^{18}F-fluciclovine positron emission tomography/computer tomography (PET/CT), and whole-body magnetic resonance imaging (MRI) are improving the identification of sites of recurrence early at a low disease burden [2–4]. Low-volume disease has better prognosis than higher-volume disease and might require a different treatment approach [5,6]. However, till now, the treatment approach for these patients remained unchanged, and they are currently treated by means of systemic agents, with immediate or delayed androgen deprivation therapy (ADT) as the cornerstone of treatment, despite important side effects [7,8]. Since the recognition of the oligometastatic state in 1995, growing interest exists in treating these patients differently by means of metastasis-directed therapy (MDT) [9]. Several retrospective studies and two prospective single-arm studies suggest a possible delay in initiating ADT and even a favorable effect on progression-free survival (PFS) for patients treated with MDT [10–12]. The recent phase II, randomized Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP) trial confirmed prolonged ADT-free survival with the use of MDT [13]. Nevertheless, it is still unclear which method of MDT is preferred. Following local therapy, the most dominant sites of recurrence are lymph nodes (LNs), which can be targeted with radiotherapy (RT) in two ways: focally, targeting the detected LN using stereotactic body radiotherapy (SBRT), or more comprehensively, including noninvolved nodal regions using elective nodal radiotherapy (ENRT) [14–16]. Various studies have shown favorable results for SBRT; however, only one limited recent study has reported the comparison of SBRT with ENRT [17,18]. In this multi-institutional, retrospective study, we want to explore the differences in toxicity and efficacy profiles of SBRT and ENRT as an MDT option for oligorecurrent nodal PC in a large patient cohort.

2. Patients and methods

2.1. Patient selection

We performed a retrospective analysis, focusing on patients with hormone-sensitive nodal oligorecurrent (five or fewer LNs) PC, following local therapy with curative intent, between 2004 and 2017. In total, 506 patients from 15 different treatment centers were included. Primary treatment was radical prostatectomy (RP), RT, or a combination of both. Both regional (N1) and distant (M1a) LN metastases were included. Patients presenting with synchronous prostate relapse, and bone and/or visceral metastasis at recurrence were excluded, as were patients having a testosterone level of <50 ng/dl at the time of metastatic recurrence. Patients presenting with oligometastasis at primary diagnosis were excluded. Nodal recurrences were detected by PET/CT (choline: $n = 428$; PSMA: $n = 46$; fluorodeoxyglucose: $n = 17$) or conventional imaging (MRI: $n = 5$; CT: $n = 10$).

2.2. RT approaches

SBRT was defined as the administration of a high dose of RT (minimum 5 Gy per fraction) directed to the suspicious node(s) in maximum 10 fractions. ENRT was defined as RT to suspicious and elective nodes with a minimum dose of 45 Gy in 25 fractions (or a biological equivalent), with or

without a simultaneous integrated boost to the suspicious nodes. Both the choice of RT and the addition of temporary ADT to the therapy were at the discretion of the treating physician. The clinical target volume to planning target volume margins used were center dependent, and ranged from 2 to 6 mm for SBRT cases and from 5 to 7 mm for ENRT cases. The field design for ENRT was not standardized and included the prostate bed in 60 patients, who had not previously been treated with salvage RT (60/67 patients). As no guidelines exist regarding SBRT or ENRT, adjuvant ADT use was very variable between both treatments. In order to keep patient groups as balanced as possible, patients receiving ADT for longer than 1 yr were excluded. Supplementary Fig. 1 shows an overview of the applied treatment modality per treatment center.

2.3. Endpoints

The primary endpoint was metastasis-free survival (MFS), defined as time to development of any M1 lesion or death. Secondary endpoints included castration-resistant prostate cancer (CRPC)-free survival (CRPC-FS), defined as time to CRPC or death, and pattern of progression, defined as the first clinical relapse observed following MDT. Progression could be at the prostatic fossa, nodal (N+), or metastatic (M+), and was based on imaging. Toxicity-free survival was defined as time to any toxicity or death. Toxicity was defined based on the Common Terminology Criteria for Adverse Events (CTCAE) or Radiation Therapy Oncology Group (RTOG) grading system. All endpoints were defined as time to an endpoint starting from the start of MDT. In all centers, reimaging following MDT was driven by prostate-specific antigen (PSA) increases.

2.4. Statistical analysis

Descriptive statistics were used to summarize patient characteristics. For MFS and CRPC-FS, statistical analysis included two steps. The following variables were evaluated as possible predictors of the outcomes: age at diagnosis, time from diagnosis to recurrence (based on age difference between diagnosis and recurrence), European Association of Urology (EAU) risk group (local vs. locally advanced) [19], primary treatment (RP vs. RT vs. RP + RT), extent of nodal disease (N1 vs. M1a), number of nodes at recurrence (1 vs. >1), type of RT (SBRT vs. ENRT), PSA at recurrence ($\leq$4 vs. >4) [20], and adjuvant ADT at the time of MDT (no vs. yes).

First, variable selection was performed using the least absolute shrinkage and selection operator (LASSO), including all main effects and interactions of all variables with the type of RT. This was to investigate whether particular patient groups benefit more from a specific RT modality by exploring its interactions with other selected variables. Second, the selected variables were entered in a multivariable Cox proportional hazard analysis, where interactions were pruned at alpha = 0.1 to enhance interpretability. The final model reporting on the difference between RT modalities and other selected variables (interactions) was reported as adjusted MFS (aMFS) and was depicted as an adjusted Cox model plot. The null hypothesis that "RT is not associated with time to new metastases or death, after adjustment for confounders" was tested using a likelihood ratio test comparing the final model with the same model, discarding the interactions with and the main effect of RT. The same test was used to test the null hypothesis that time to CRPC or death was comparable between the two types of RT. Stability of this result was tested using bootstrap analysis (Supplementary Fig. 2). A more detailed explanation of the used statistical analysis can be found in the Supplementary material. All p values of <0.05 were considered statistically significant. Statistical analysis was performed using R. Pattern of progression and toxicity were evaluated using SPSSv.25.0. A comparison of the pattern of progression and toxicity between both treatment groups was performed using the Fisher's exact test. The null hypothesis stated that the pattern of progression and toxicity were comparable between both groups.

3. Results

3.1. Patient and tumor characteristics

Patient and disease characteristics are summarized in Table 1. In total, 764 LNs were treated with RT. Median time between PC diagnosis and oligorecurrence was 53 mo (interquartile range [IQR] 30–85). The use of adjuvant ADT at the time of MDT varied across the different treatment modalities ($p < 0.001$; Table 1).

3.2. Oncological results

Median follow-up after MDT was 36 mo (IQR 23–56). In total, 35 patients died (SBRT: 16, ENRT: 19), in 16 of whom the cause of death was PC.

3.2.1. Metastasis-free survival

The 3-yr MFS was 68% (95% confidence interval [CI] 61–73) for SBRT and 77% (95% CI 69–82) for ENRT ($p = 0.01$). A total of 352 patients did not show any metastasis with a median follow-up of 33 mo.

For the multivariable analysis, the association between RT and MFS was statistically significant (likelihood ratio test 7.24, df = 2, $p = 0.03$). In the analysis, the interaction of the number of nodes with RT modality was selected. The multivariable model containing variables and interactions selected by LASSO can be consulted in Supplementary Table 1. For patients presenting with only one node at recurrence ($n = 341$, 67%), ENRT resulted in longer aMFS than SBRT (hazard ratio [HR]: 0.50, 95% CI 0.30–0.85, $p = 0.009$; Fig. 1). There was no difference in aMFS for patients presenting with more than one LN (HR: 0.92, 95% CI 0.54–1.59, $p = 0.8$). The difference in effect between patients presenting with more than one LN and those presenting with one LN is depicted as the ratio of the two HRs (1.84, 95% CI 0.87–3.86, $p = 0.1$; Supplementary Table 1).

Table 1 – Patient and tumor characteristics.

Patient characteristic	SBRT (*n* = 309, 61%)	ENRT (*n* = 197, 39%)
Age at PCa diagnosis (yr), median (IQR)	63 (58–68)	63 (59–68)
PSA at PCa diagnosis (ng/ml), median (IQR)	9.3 (6.7–14.0)	9.2 (6.7–16)
EAU risk group classification, n (%)		
Localized disease	125 (40)	69 (35)
Locally advanced	178 (58)	128 (65)
Unknown	6 (2)	0 (0)
Type of primary treatment, n (%)		
RP only	87 (28)	67 (34)
RT only	66 (21)	29 (15)
RP and RT	156 (50)	101 (51)
RT field, *n* (%)	*n* = 222	*n* = 130
Prostate bed only	204 (92)	120 (92)
Whole pelvis RT	18 (8)	10 (8)
PLND at primary treatment, *n* (%)		
No	168 (54)	100 (51)
Yes	141 (46)	97 (49)
Median no. of nodes removed (IQR)	8 (5–12)	8 (4–14)
pN0	122 (87)	85 (88)
pN1	19 (13)	12 (12)
Median no. of nodes positive if pN1 (IQR)	1 (1–3)	2 (2–4)
ADT at primary treatment, *n* (%)		
No	159 (51)	130 (66)
Yes	120 (39)	63 (32)
Unknown	30 (10)	4 (2)
Age at recurrence (yr), median (IQR)	69 (64–74)	68 (64–72)
PSA at recurrence (ng/ml), median (IQR)	2.7 (1.3–5.6)	2.5 (1.2–4.9)
PSA-DT at recurrence (mo),[a] median (IQR)	6.0 (4.0–10.9)	5.0 (3.0–8.6)
Metastatic site, *n* (%)		
Pelvic	222 (72)	143 (73)
Extrapelvic	69 (22)	29 (15)
Pelvic + extrapelvic	18 (6)	25 (13)
No. of positive nodes at imaging, *n* (%)		
1 metastasis	243 (79)	98 (50)
2 metastases	50 (16)	55 (28)
3 metastases	13 (4)	23 (12)
4 metastases	2 (1)	13 (7)
5 metastases	1 (<1)	8 (4)
Adjuvant ADT at time of recurrence, *n* (%)		
No	237 (77)	78 (40)
Yes	71 (23)	119 (60)
Unknown	1 (<1)	0 (0)
Median duration of ADT, mo (IQR)	6 (3–11)	6 (6–9)

ADT = androgen-deprivation therapy; ENRT = elective nodal radiotherapy; IQR = interquartile range; PLND = pelvic lymph node dissection; pN0 = pathologically confirmed N0 state after PLND; pN1 = pathologically confirmed N1 state after PLND; PSA = prostate-specific antigen; PSA-DT = prostate-specific antigen doubling time; RP = radical prostatectomy; RT = radiotherapy; SBRT = stereotactic body radiotherapy.

[a] In the SBRT group, we note 100 (32%) missing values compared with 29 (15%) missing values in the ENRT group.

3.2.2. *Pattern of progression following MDT*

Local progression was observed in 50 patients following SBRT and in nine cases following ENRT ($p < 0.001$). The median follow-up of the 447 patients who did not show progression was 35 mo.

After RT, 259 patients developed a new N1 or M1 lesion. The median follow-up of the 247 patients who did not show progression was 29 mo. In 78% ($n = 201$) of patients, the relapses were less than five lesions. The pattern of distant progression can be seen in Table 2. LN progression was observed more frequently following SBRT than following ENRT ($p < 0.001$), especially in the pelvis ($p < 0.001$). Bone, prostate, or visceral progression was comparable between both groups ($p = 0.6$, $p = 0.6$, and $p > 0.9$, respectively). In total, relapse following SBRT (177 patients) was significantly higher than that following ENRT (74 patients; $p < 0.001$).

3.2.3. *Castration-resistant PC-free survival*

The 3-yr CRPC-FS was comparable for both treatment groups (88% [95% CI 84–93] after SBRT and 87% [95% CI 81–92] after ENRT, $p = 0.5$). A total of 419 patients did not develop CRPC and had a median follow-up of 34 mo. None of the variables were retained to build a multivariable analysis.

3.3. *Toxicity*

Fig. 2 shows an overview of the observed toxicities. As seen in the figure, no early or late grade 3 or higher toxicity was observed following SBRT, which is in contrast to the five events for the ENRT group ($p = 0.009$). Early toxicity was observed in 15 cases and was significantly higher after ENRT (SBRT: 3 vs. ENRT: 12, $p = 0.002$). After ENRT, the observed late toxicity was significantly higher ($n = 31$) compared with

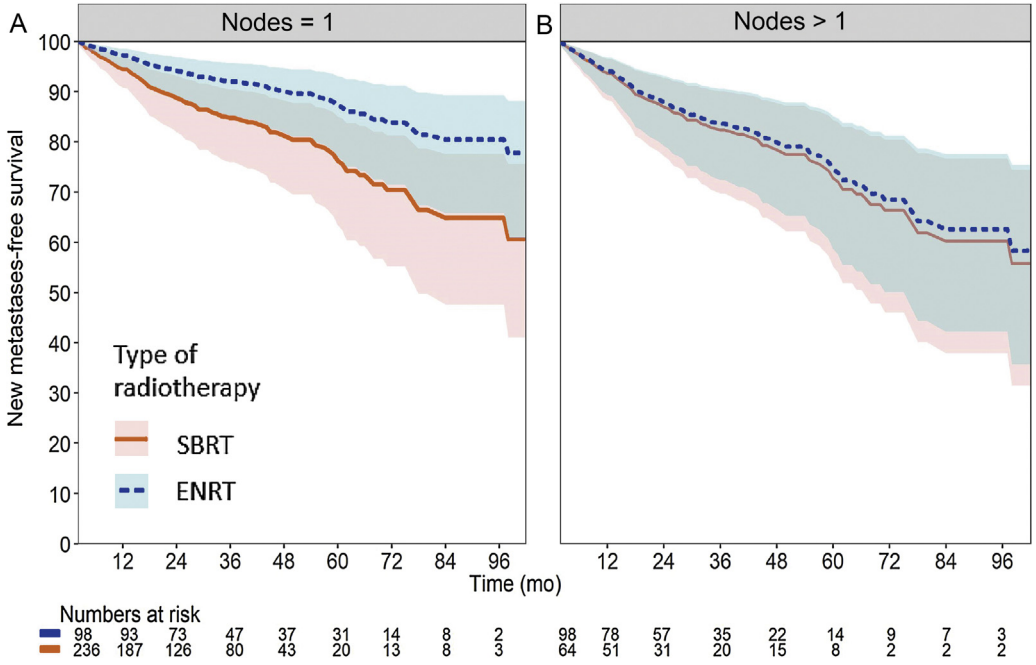

Fig. 1 – Cox model plots showing the difference in adjusted metastasis-free survival following SBRT and ENRT. The specific survival curves are for patients with median age at diagnosis (63 yr), median age difference between diagnosis and recurrence (5 yr), local prostate cancer (according to EAU risk assessment) treated by radical prostatectomy at diagnosis and presenting with N1 disease at recurrence, no adjuvant ADT at MDT, and PSA ≤ 4 at recurrence. (A) The difference between both treatment modalities for patients presenting with only one lymph node. (B) The comparison between SBRT and ENRT for patients presenting with more than one lymph node at recurrence. ADT = androgen deprivation therapy; EAU = European Association of Urology; ENRT = elective nodal radiotherapy; MDT = metastasis-directed treatment; PSA = prostate-specific antigen; SBRT = stereotactic body radiotherapy.

Table 2 – Pattern of progression following SBRT or ENRT.

Metastatic location	SBRT (n = 309, 61%)	ENRT (n = 197, 39%)	p value
Node, n	**131**	**40**	**<0.001**
Pelvic	55	3	
Extrapelvic	34	32	
Pelvic + extrapelvic	42	5	
Bone, n	**35**	**26**	**0.6**
Axial	17	12	
Nonaxial	13	7	
Axial + nonaxial	5	7	
Prostate bed, n	**1**	**2**	**0.6**
Visceral, n	**10**	**6**	**>0.9**
Total, n	**177**	**74**	**<0.001**

ENRT = elective nodal radiotherapy; SBRT = stereotactic body radiotherapy.
In case of a combination (M1a–b–c), the highest metastatic definition is applied. The main sites of recurrence are highlighted in bold.

SBRT (n = 16; $p < 0.001$). A detailed description of the observed toxicity can be found in Supplementary Table 2.

4. Discussion

To our knowledge, this is the largest study comparing SBRT with ENRT in oligorecurrent nodal PC. Both RT strategies are not mentioned in the current treatment guidelines [7], but represent a potential treatment option for these patients according to an expert consensus meeting [21]. In this setting, the OLIGOPELVIS-2 trial (NCT03630666), comparing ADT with ADT + ENRT, and the Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases (STORM) trial (NCT03569241), comparing salvage lymph node dissection (sLND)/SBRT + ADT versus ENRT + ADT, could provide more evidence for these strategies in the upcoming 5 yr. In the meanwhile, several findings in our study are of interest.

First, distant progression observed following SBRT (n = 177) was significantly higher than that following ENRT (n = 74, $p < 0.001$). Interestingly, following SBRT, patients tend to relapse more often in the LNs, in particular in the pelvic LNs ($p < 0.001$ and $p < 0.001$, respectively; Table 2). These findings are in line with the available literature [22]

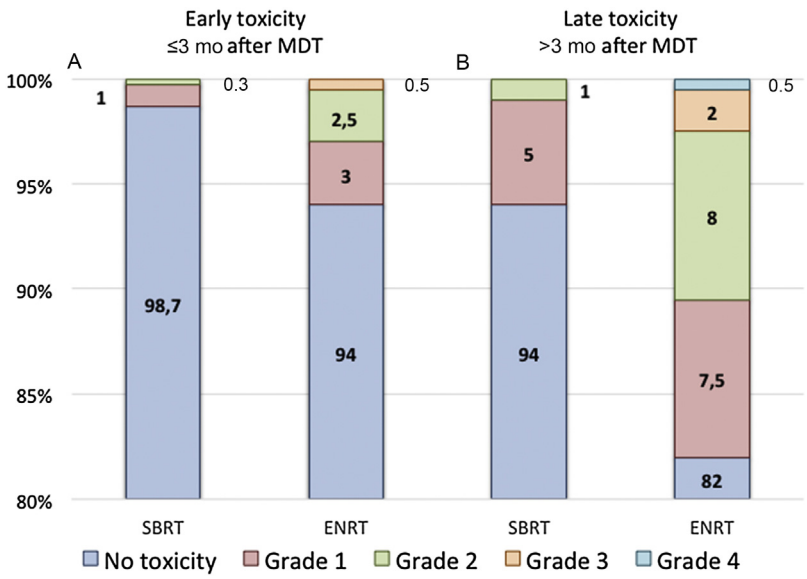

Fig. 2 – General overview of the observed toxicities in both treatment groups: (A) early toxicity and (B) late toxicity. ENRT = elective nodal radiotherapy; MDT = metastasis-directed therapy; SBRT = stereotactic body radiotherapy.

and probably reflect the limited sensitivity of imaging in detecting microscopic nodal invasion [23]. In the recent sLND series by Fossati et al. [24], quarter of patients had three or more positive spots on choline or PSMA PET/CT at the time of recurrence, while this number doubled after pathological confirmation (54%), confirming the well-recognized limited sensitivity of choline and PSMA PET/CT.

Adjusted MFS was superior following ENRT for patients with one LN (HR: 0.50, 95% CI 0.30–0.85, $p = 0.009$). In contrast, for patients presenting with more than one LN, aMFS was not significantly different (HR: 0.92, 95% CI 0.54–1.59, $p = 0.8$). The latter result should be interpreted with caution as the confidence intervals are large, and a possible significant effect cannot be excluded if the sample size would have been larger. From a biological perspective, it might be that patients with a single positive node are reflective of a disease early in the spectrum of dissemination and potentially salvageable if microscopic disease is eradicated. For patients with an increasing number of nodes, there is a higher likelihood of undetected metastatic spread, and it could be hypothesized that the use of local therapies does not impact time to metastasis, independent of the type of local therapy used.

Second, when making a decision between both treatments, toxicity should be of importance in the selection. Early and late toxicities following ENRT were significantly higher than those following SBRT ($p = 0.002$ and $p < 0.001$, respectively). However, most side effects with ENRT were limited to grade 2 or lower, with only five patients developing grade 3–4 toxicity. Since this was a retrospective study, it is presumable that the recorded toxicity was under-reported in both treatment groups. Along with toxicity, patient convenience and health economics aspects (in terms of waiting lists and resource collocation) should also be considered.

Third, the evidence on the role of ADT in this setting remains inconclusive. The TOAD trial concluded that immediate ADT did not result in superior overall survival (OS) for patients with biochemical recurrence as compared with delayed ADT [25]. In the 2019 EAU guidelines, delayed ADT should still be offered for well-informed asymptomatic patients with biochemical recurrence [26]. In the current series, the majority of patients were negative for conventional imaging, but with PET-positive findings. Nevertheless, we know that ADT in addition to RT even for microscopic disease holds a benefit in terms of PFS (Genitourinary Group GETUG16 and Radiation Therapy Oncology Group RTOG9601) and MFS (RTOG9601) [27,28]. Recent data indicated that there are specific interactions between RT and ADT, suggesting that ENRT should be avoided without neoadjuvant ADT [29]. Consequently, it seems logical to combine RT with temporary ADT, as suggested in other settings [7]. However, further exploration of the use of adjuvant ADT in combination with these treatments is necessary.

Finally, sLND has also been reported as a treatment option for oligorecurrent PC [30]. Fossati et al. [24] recently published their results of a multi-institutional analysis of sLND at recurrence. They reported 3-yr clinical recurrence-free survival of approximately 50%, which is lower than the 3-yr MFS of 71% in our cohort. Nevertheless, differences in patient selection, adjuvant treatment use, and endpoint definition might explain this difference. Back in 2014, Rischke et al. [31] showed that the percentage of patients free of next relapse was significantly better if the patients received adjuvant RT after sLND compared with sLND alone (free of next relapse for 5 yr, 34.3% vs. 15.4%; $p = 0.01$). However, no difference in cancer-specific survival was identified ($p = 0.8$).

4.1. Limitations

Inevitably, this study has important limitations. First, this study was associated with a number of missing values and differences in patient characteristics. To adjust for these limitations, we used multivariable analyses to identify independent risk factors for the different endpoints. However, compared with randomized controlled trials, this study lacks sufficient evidence to make treatment recommendations. In addition, the process of variable selection inevitably results in inflated estimates and overly optimistic *p* values. Still, we believe that a thorough investigation of interactions with the treatment was warranted and valid in this hypothesis-generating context. Second, patients were treated and followed in different centers in the world. Choice of treatment and follow-up regimes were not standardized and differed between centers. The field of ENRT was not standardized between different centers, and restaging imaging occurred at different PSA levels, giving rise to heterogeneous patient and tumor characteristics. Additionally, in the multivariable setting, center effects were examined. Accounting for center effects by a stratified analysis would result in a significant loss of data. However, when, as an alternative, a center is added as a covariate in the multivariable Cox model, the treatment-related estimates are very similar. Third, staging was conducted with PSMA or choline PET/CT or conventional imaging, all of which are known to have different sensitivity in diagnosing recurrent disease, inevitably influencing all endpoints. Finally, the use of adjuvant ADT was not standardized for these patients, with a substantial difference in use of adjuvant ADT between both treatment groups (SBRT: 23% vs. ENRT: 60%). To minimize further differences, we limited the duration of ADT for both groups to a maximum of 12 mo, as this is typically used in combination with SBRT. Fourth, we have chosen time to metastases as the primary endpoint in analogy with the recent findings that MFS is a surrogate for OS in localized PC [32]. Whether this is the case in this specific setting is unknown. Nevertheless, MFS is considered to be a relevant endpoint for agencies such as the Food and Drug Administration, as pointed out by the recent approval of three novel drugs, improving this endpoint, in the setting of nonmetastatic CRPC [33]. Finally, it is important to state that these MDTs remain investigational. However, we suggest that the outcomes of this international collaboration, which is the largest retrospective study to date, support ongoing trials investigating this topic.

5. Conclusions

ENRT reduces the number of nodal recurrences as compared with SBRT; however, toxicity was higher following ENRT. In this study, patients presenting with a single node showed improved aMFS when treated with ENRT as compared with SBRT. Our findings hypothesize that ENRT should be preferred to SBRT in the treatment of nodal oligorecurrences. However, this hypothesis should be addressed in a randomized trial.

The results of this study were presented at the 2019 EAU congress.

Author contributions: Elise De Bleser had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ost, De Bleser.
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Drafting of the manuscript: De Bleser, Ost.
Critical revision of the manuscript for important intellectual content: Jereczek-Fossa, Pasquier, Zilli, Van As, Siva, Fodor, Dirix, Gomez-Iturriaga, Trippa, Detti, Ingrosso, Triggiani, Bruni, Alongi, De Meerleer, Surgo, Loukili, Miralbell, Silva, Chander, Di Muzio, Maranzano, Francolini, Lancia, Tree, Deantoni, Ponti, Marvaso Reynders, Goetghebeur.
Statistical analysis: De Bleser, Reynders, Goetghebeur, Ost.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Ost.
Other: None.

Financial disclosures: Elise De Bleser certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Elise De Bleser: travel expenses and congress sponsoring by Ferring, Astellas, and Ipsen. Barbara Alicja Jereczek-Fossa: research funding—Accuray (institutional grant) and AIRC Italian Association for Cancer Research (grants); travel expenses or honoraria—Janssen, Ferring, Bayer, Roche, Astellas, Elekta, Carl Zeiss, and Ipsen. Shankar Siva: research funding and speaker honoraria from Varian for Research unrelated to this work. Andrei Fodor: received honoraria for presentations at congresses from Accuray (AERO Academy) and Janssen (Janssen Academy) Conferences; was a member in the advisory board of Sandoz Italia; and had travel and accommodation for congresses from AB Medica, Ipsen, and Astellas. Alfonso Gomez-Iturriaga: advisory board—Janssen, Astellas, and Bayer. Nadia Gisella Di Muzio: received honoraria for a congress presentation from Accuray (AERO Academy), and had travel and accommodation for a congress from Ipsen. Alison Tree: research funding—Elekta, Accuray, and MSD; travel expenses or honoraria—Elekta, Janssen, Ferring, Bayer, and Genesis Healthcare. Piet Ost: institute research funding—Merck; consultancy honoraria or advisory board (institute)—Ferring, BMS, Janssen, and Bayer.

Funding/Support and role of the sponsor: This paper represents work supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2019.07.009.

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