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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Abstract

Background: Stereotactic body radiotherapy (SBRT) and elective nodal radiotherapy (ENRT) are being investigated as metastasis-directed treatments (MDT) in oligorecurrent prostate cancer (PC), however comparative data are still lacking.

Objective: To compare outcome and toxicity between both treatments. Primary endpoint 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 (≤5 lymph nodes (LN), N1/M1a) treated between 2004 and 2017. Median follow-up was 36 months (IQR 23-56).

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 RT was at the discretion of the treating physician with treatments being unbalanced over the centers.

Results and limitations: ENRT was associated with fewer nodal recurrences compared to SBRT ($p<0.001$). In multivariable analysis, patients with 1 LN at recurrence, had a longer aMFS after ENRT (HR:0.50, 95%CI 0.30-0.85, $p=0.009$). Late toxicity was higher after ENRT compared to SBRT (16% versus 5%, respectively, $p<0.01$). Limitations include higher use of hormone therapy in the ENRT cohort and non-standardized follow-up.

Conclusions: ENRT reduces the number of nodal recurrences as compared to SBRT, however at higher toxicity. Our findings hypothesize that ENRT should be preferred over 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. Following elective nodal radiotherapy, nodal relapse was less frequent compared to stereotactic body radiotherapy and might be the preferred treatment.

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 compared to higher volume disease and might require a different treatment approach[5,6]. However, up 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 a prolonged ADT-free survival with the use of MDT[13]. Nevertheless, it is still unclear what method of MDT is preferred. Following local therapy, the most dominant site of recurrence are lymph nodes (LN), which can be targeted with radiotherapy (RT) in two ways: focally, targeting the detected LN using stereotactic body radiotherapy (SBRT), or more comprehensively, including non-involved 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 to 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.

Materials and methods

Patient selection

We performed a retrospective analysis, focusing on patients with hormone-sensitive nodal oligorecurrent (≤5) 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, bone and/or visceral metastasis at recurrence were excluded, as were patients having a testosterone level below 50 ng/dl at 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 (FDG), n=17) or conventional imaging (MRI n=5, CT n=10).

Radiotherapy approaches

SBRT was defined as the administration of a high dose of RT (minimum 5Gy 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 45Gy in 25 fractions (or a biological equivalent) with or without a simultaneous integrated boost to the suspicious nodes. Both the choice of RT as well as the addition of temporary ADT to the therapy was at the discretion of the treating physician. The clinical target volume to planning target volume margins used were center-dependent and ranged from 2-6 mm for SBRT cases and for ENRT from 5-7 mm. 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 one year were excluded. Supplementary figure 1 shows an overview of the applied treatment modality per treatment center.

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-free survival (CRPC-FS) defined as time to CRPC or death and pattern of progression which was defined as the first clinical relapse observed following MDT. Progression could be either at the prostatic fossa, nodal (N+) or metastatic (M+) and was based on imaging. Toxicity-free survival (TFS) 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 endpoint starting from start of MDT. In all centers, re-imaging following MDT was driven by PSA increases.

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 versus locally advanced)[19], primary treatment (RP versus RT versus RP+RT), extent of nodal disease (N1 versus M1a), number of nodes at recurrence (1 versus >1), type

of RT (SBRT versus ENRT), PSA at recurrence (≤4 versus >4)[20] and adjuvant ADT at time of MDT (no versus yes).

First, variable selection was performed using Least Absolute Shrinkage and Selection Operator (LASSO), including all main effects and interactions of all variables with type of RT. This was to investigate if 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 adjusted Cox model plot. The null hypothesis '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 figure 2). A more detailed explanation of the used statistical analysis can be found in the supplementary material. P-values <0.05 were considered statistically significant. Statistical analysis was performed using R. Pattern of progression and toxicity were evaluated using SPSSv.25.0. Comparison of pattern of progression and toxicity between both treatment groups was performed using the Fisher's Exact-test. The null hypothesis stated that pattern of progression and toxicity were comparable between both groups.

Results

Patient and tumor characteristics

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

Oncological results

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

Metastasis-free survival

The 3-year MFS was 68% (95%CI 61-73) and 77% (95%CI 69-82) for SBRT and ENRT, respectively (p=0.01). 352 patients did not show any metastasis with a median follow-up of 33 months.

For the multivariable analysis, the association between RT and MFS was statistically significant (LR test 7.24, df=2, p=0.03). In the analysis, the interaction of 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 a longer aMFS as compared to SBRT (HR:0.50, 95%CI 0.30-0.85, p=0.009) (figure 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 >1 LN compared to 1 LN is depicted as the ratio of the two HR's (1.84, 95% CI 0.87-3.86, p=0.1) (supplementary table 1).

Pattern of progression following MDT

Local progression was observed in 50 patients following SBRT and in 9 cases following ENRT (p<0.001). Median follow-up of the 447 patients that did not show progression was 35 months.

After RT, 259 patients developed a new N1 or M1 lesion. The median follow-up of the 247 patients that did not show progression was 29 months. In 78% (n=201), the relapses were less than five lesions. The pattern of distant progression can be consulted in table 2. Following SBRT, LN progression was observed more frequently as compared to ENRT (p<0.001), especially in the pelvis compared to ENRT (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 compared to ENRT (74 patients) (p<0.001).

Castration-resistant prostate cancer-free survival

The 3-year 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). 419 patients did not develop CRPC and had a median follow-up of 34 months. None of the variables were retained to build a multivariable analysis.

Toxicity

Figure 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 5 events for the ENRT group (p=0.009). Early toxicity was observed in 15 cases and was significantly higher after ENRT (SBRT:3 versus ENRT:12, p=0.002). After ENRT, the observed late toxicity was significantly higher (n:31), compared to SBRT (n:16) (p<0.001). A detailed description of the observed toxicity can be consulted in supplementary table 2.

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 five years. In the meanwhile, several findings in our study are of interest.

First, distant progression observed following SBRT (n=177) was significantly higher compared to ENRT (n=74, p<0.001). Interestingly, following SBRT, patients tend to relapse in the lymph nodes more often, and in particular in the pelvic lymph nodes (p<0.001 and p<0.001, respectively) (table 2). These findings are in line with the available literature[22] and probably reflect the limited sensitivity of imaging in detecting microscopic nodal invasion[23]. In the recent sLND-series by Fossati et al., quarter of patients had ≥3 positive spots on choline or PSMA PET/CT at time of recurrence, while this number doubled after pathological confirmation (54%), confirming the well-recognized limited sensitivity of choline and PSMA PET/CT[24].

aMFS 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 >1LN, 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 all 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.

Secondly, when making a decision between both treatments, toxicity should be of importance in the selection. Following ENRT, early and late toxicity was significantly higher compared to SBRT ($p=0.002$ and $p<0.001$, respectively). However, most side-effects with ENRT were limited to grade 2 or lower, with only 5 patients developing grade 3-4 toxicity. Since this was a retrospective study, it is presumable that the recorded toxicity was underreported 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 a superior overall survival (OS) for patients with biochemical recurrence as compared to 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 conventional imaging negative, 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 suggested that there are specific interactions between RT and ADT suggesting

that ENRT should be avoided without neo-adjuvant 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. recently published their results of a multi-institutional analysis of sLND at recurrence. They reported a 3-year clinical recurrence-free survival of approximately 50%, which is lower than the 3-year MFS of 71% in our cohort [24]. Nevertheless, differences in patient selection, adjuvant treatment use and differences in endpoint definition might explain this difference. Back in 2014, Rischke et al. showed that the percentage free of next relapse was significantly better if patients received adjuvant RT after sLND compared to sLND alone (5-year free of next relapse 34.3% versus 15.4%, respectively, p=0.01)[31]. However, no difference in cancer-specific survival was identified (p=0.8).

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 to 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. Secondly, 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 stratified analysis would result in a significant loss of data. However, when, as an alternative, 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, 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% versus ENRT:60%). To minimize further differences, we limited the duration of ADT for both groups to a maximum of 12 months, 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 prostate cancer [32]. Whether this is the case in this specific setting is unknown. Nevertheless, MFS is considered to be a relevant endpoint for agencies like the Food and Drug Administration (FDA) as pointed out by the recent approval of three novel drugs, improving this endpoint, in the setting of non-metastatic CRPC [33]. Finally, it is important to state that these MDT's 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.

Conclusion

ENRT reduces the number of nodal recurrences as compared to 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 to SBRT. Our findings hypothesize

that ENRT should be preferred over SBRT in the treatment of nodal oligorecurrences. However, this hypothesis should be addressed in a randomized trial.

Conflict of interest

Elise De Bleser: Travel expenses and congress sponsoring by Ferring, Astellas, Ipsen

Barbara Alicja Jereczek-Fossa: Research funding: Accuray (institutional grant), AIRC Italian Association for Cancer Research (grants). Travel expenses or honoraria: Janssen, Ferring, Bayer, Roche, Astellas, Elekta, Carl Zeiss, Ipsen

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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 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

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Nadia Gisella Di Muzio: Received honoraria for a congress presentation from Accuray (AERO Academy) and had travel and accommodation for a congress from Ipsen

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Previous Presentation or Release of Information

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

Data sharing policy

Data are available for bona fide researchers who request it from the authors

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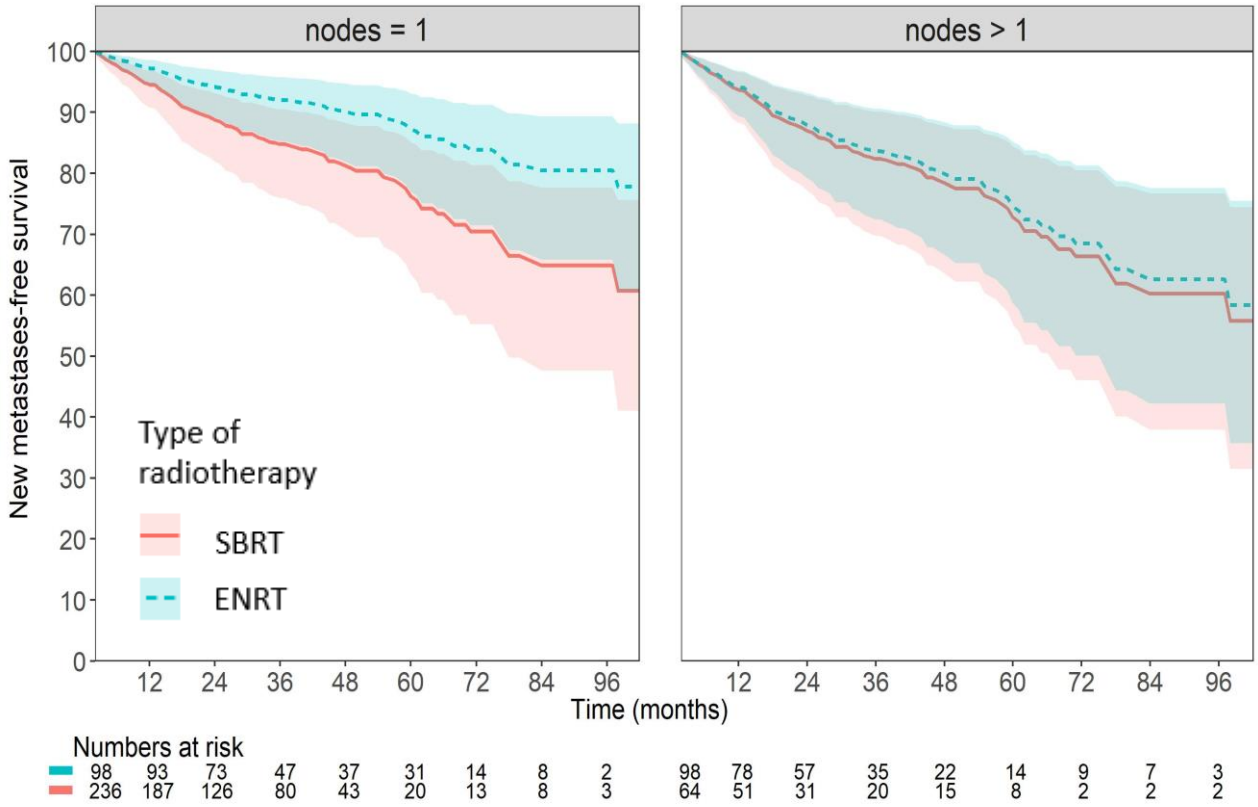


Figure 1. *Cox model plots showing the difference in metastasis-free survival following SBRT and ENRT. The specific survival curves are for patients with median age at diagnosis (63 y), median age difference between diagnosis and recurrence (5y), local prostate cancer (according to EAU risk assessment), treated by radical prostatectomy at diagnosis and presenting with N1 disease at recurrence, no adjuvant ADT at MDT and PSA at recurrence of ≤4. Left curve shows the difference between both treatment modalities for patients presenting with only one lymph node. Right curve illustrates the comparison between SBRT and ENRT for patients presenting with more than one lymph node at recurrence. ENRT: elective nodal radiotherapy; SBRT: stereotactic body radiotherapy*

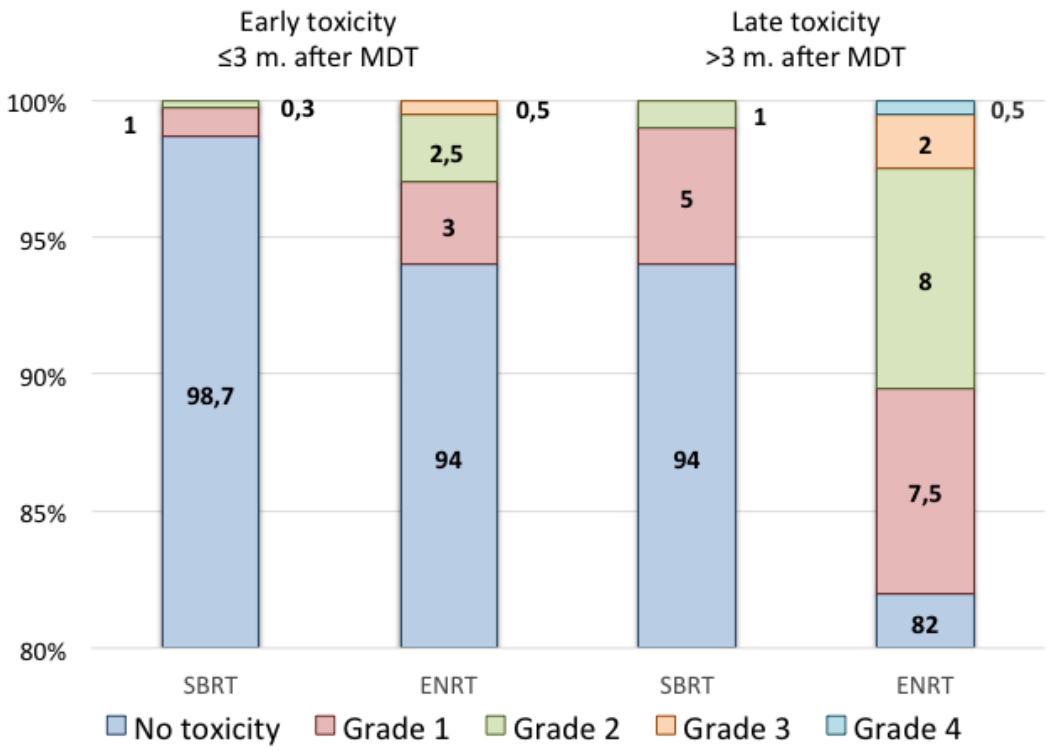


***Figure 2**: General overview of the observed toxicities in both treatment groups. A: early toxicity. B: late toxicity. ENRT: elective nodal radiotherapy; MDT: metastasis-directed therapy; SBRT: stereotactic body radiotherapy*

Tables

Table 2. *Patient and tumor characteristics.*

Patient characteristic	**SBRT**	**ENRT**
	n= 309, 61%	**n=197, 39%**
Age at PCa diagnosis, years		
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 n of nodes		

removed, (IQR)	8 (5-12)	8 (4-14)
pN0	122 (87)	85 (88)
pN1	19 (13)	12 (12)
Median n 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, years		
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, months*		
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)
N 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, months (IQR)	6 (3 – 11)	6 (6 – 9)

** in the SBRT group we note 100 (32%) missing values compared to 29 (15%) missing values in the ENRT group. 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*

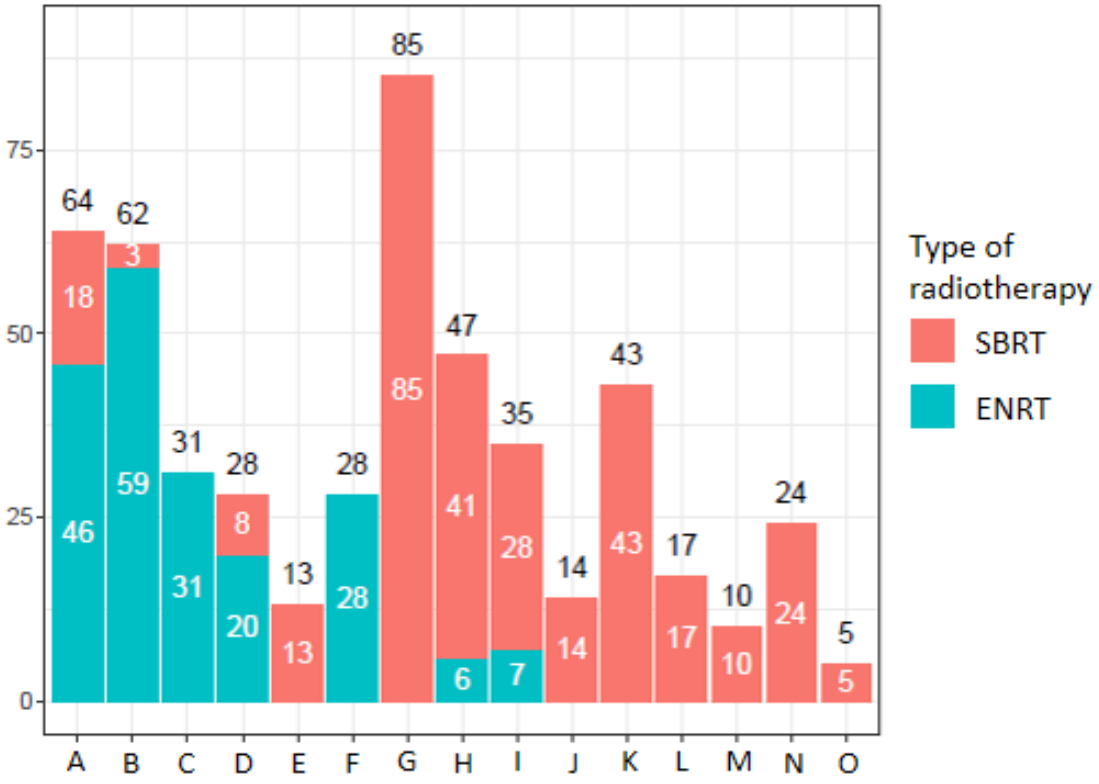
Table 3: pattern of progression following SBRT or ENRT.

Metastatic location	**SBRT**	**ENRT**	**p-value**
	n=309, 61%	**n=197, 39%**	
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	
Non-axial	13	7	
Axial + non-axial	5	7	
Prostate bed, n	**1**	**2**	**0.6**
Visceral, n	**10**	**6**	**>0.9**
Total, n	**177**	**74**	**<0.001**

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

Supplementary material

Supplementary figure 1: Overview of the applied treatment modalities in the different treatment centers



Each letter represents one center with the radiotherapy modality type indicated in color (red: SBRT, blue: ENRT).

Statistical analysis

Bootstrap analysis

Following a bootstrap evaluation of the LASSO procedure for variable selection, we found that the full set of selected variables was quite variable, but in 75% of the cases the LASSO added the interaction between RT and lymph nodes amongst the variables selected, as on the original data. When fitting the parsimonious model involving all main effects plus this interaction across 2000 bootstrap samples, a positive interaction effect was estimated in more than 95% of the bootstrap samples. Together this leads us to propose to examine the hypothesis of the existence of such interaction in a future RCT. A more detailed description of the used method can be found below.

The stability of the analyses was tested as follows:

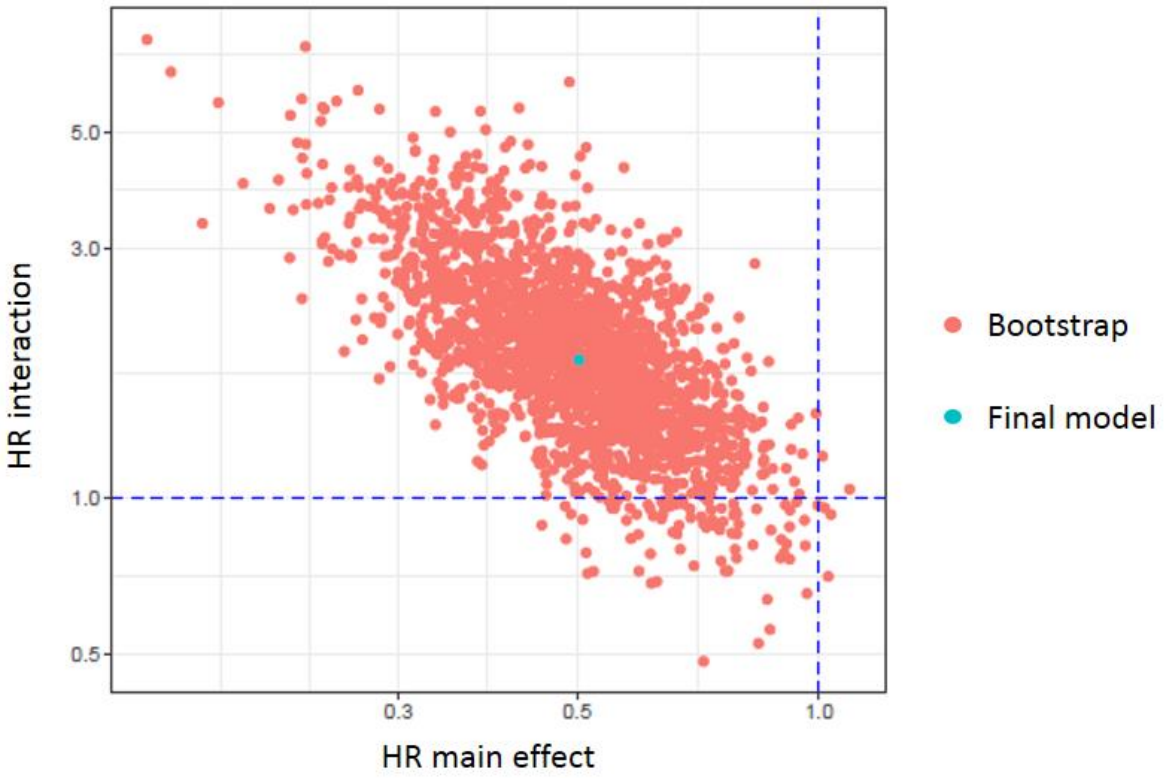
1. A bootstrap on the complete procedure (LASSO/Coxph/Pruning of interactions)

2. A bootstrap with the thus selected variable set, i.e. `final model', only (all main effects plus the interaction between RT and number of nodes)

3. Forward selection of interactions, starting with a model including all main effects. Interactions between RT and a confounder were only examined if the main effects for the confounder was statistically significant

In the first bootstrap-analysis, the interaction between RT and number of nodes, is retained in 45% of the bootstraps (75% if only LASSO is considered and pruning is not performed).
However, the model fitted with the retained set of variables (all main effects plus interaction between RT and number of nodes), does provide a stable image over the different bootstrap samples. In more than 95% of the bootstrap samples, the estimate for the coefficient of the interaction is positive (see supplementary figure 2). Thus, the qualitative image that the final model provides, does hold over the different bootstrap samples.
Exploring forward selection of interactions with RT starting from a model including all main effects and only testing interactions with RT for statistically significant confounders, leads to the same final model.

Supplementary figure 2: graphic representation of 2000 bootstraps where the cox-model with all main effects plus an interaction between RT and number of nodes is fitted in each bootstrap.



The x-axis represents the HR of the main effect of type of radiotherapy. The y-axis represents the HR of the interaction of type of radiotherapy and number of nodes. Remark the logarithmic scale on both axes. The blue dashed lines indicate a HR of 1. The blue dot represents the final model with the HR for the main effect of 0.5 and the HR for the interaction of 1.84. As seen in the figure, 95% of the bootstraps are in the same quadrant of the final model, indicating comparable results in the same direction with a HR of the main effect lower than 1 in combination with a HR of the interaction higher than 1. HR: hazard ratio

Supplementary table 1: Multivariable analysis of metastasis-free survival

Variable		**HR (95% CI)**
Type of RT	SBRT versus **ENRT**	0.5 (0.3-0.85)
Age at time of diagnosis	Median age (63y)	1.01 (0.98-1.04)
Age difference*	Median difference (5y)	0.99 (0.94-1.04)
EAU risk group	Local versus **locally advanced**	1.26 (0.88-1.8)
Primary treatment	RP versus **RT**	1.82 (1.06-3.13)
Primary treatment	RP versus **RP+RT**	2.03 (1.31-3.15)
Extent of nodal disease	N1 versus **M1a**	1.22 (0.85-1.75)
Adjuvant ADT	No versus **yes**	0.85 (0.6-1.21)
PSA at recurrence	≤4 versus **>4**	1.42 (0.99-2.04)
Number of nodes	1 versus **>1**	1.17 (0.72-1.91)
Interactions		
Type of RT and number of nodes°	SBRT versus **ENRT** and 1 versus **>1**	1.84 (0.87-3.86)

due to missing values, only 496 observations were retained.

The variables not accentuated in bold correspond to the baseline values. The variables accentuated in bold are the variables that correspond with the HR. ° The HR of the interactions are calculated by multiplying the HR of the individual variables. For patients presenting with more than 1 node, the HR for ENRT versus SBRT is 0.5x1.84=0.92

*Age difference between diagnosis and recurrence; represents time from diagnosis to recurrence

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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Abstract

Background: Stereotactic body radiotherapy (SBRT) and elective nodal radiotherapy (ENRT) are being investigated as metastasis-directed treatments (MDT) in oligorecurrent prostate cancer (PC), however comparative data are still lacking.

Objective: To compare outcome and toxicity between both treatments. Primary endpoint 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 (≤5 lymph nodes (LN), N1/M1a) treated between 2004 and 2017. Median follow-up was 36 months (IQR 23-56).

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 RT was at the discretion of the treating physician with treatments being unbalanced over the centers.

Results and limitations: ENRT was associated with fewer nodal recurrences compared to SBRT ($p<0.001$). In multivariable analysis, patients with 1 LN at recurrence, had a longer aMFS after ENRT (HR:0.50, 95%CI 0.30-0.85, $p=0.009$). Late toxicity was higher after ENRT compared to SBRT (16% versus 5%, respectively, $p<0.01$). Limitations include higher use of hormone therapy in the ENRT cohort and non-standardized follow-up.

Conclusions: ENRT reduces the number of nodal recurrences as compared to SBRT, however at higher toxicity. Our findings hypothesize that ENRT should be preferred over 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. Following elective nodal radiotherapy, nodal relapse was less frequent compared to stereotactic body radiotherapy and might be the preferred treatment.

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 compared to higher volume disease and might require a different treatment approach[5,6]. However, up 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 a prolonged ADT-free survival with the use of MDT[13]. Nevertheless, it is still unclear what method of MDT is preferred. Following local therapy, the most dominant site of recurrence are lymph nodes (LN), which can be targeted with radiotherapy (RT) in two ways: focally, targeting the detected LN using stereotactic body radiotherapy (SBRT), or more comprehensively, including non-involved 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 to 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.

Materials and methods

Patient selection

We performed a retrospective analysis, focusing on patients with hormone-sensitive nodal oligorecurrent (≤5) 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, bone and/or visceral metastasis at recurrence were excluded, as were patients having a testosterone level below 50 ng/dl at 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 (FDG), n=17) or conventional imaging (MRI n=5, CT n=10).

Radiotherapy approaches

SBRT was defined as the administration of a high dose of RT (minimum 5Gy 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 45Gy in 25 fractions (or a biological equivalent) with or without a simultaneous integrated boost to the suspicious nodes. Both the choice of RT as well as the addition of temporary ADT to the therapy was at the discretion of the treating physician. The clinical target volume to planning target volume margins used were center-dependent and ranged from 2-6 mm for SBRT cases and for ENRT from 5-7 mm. 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 one year were excluded. Supplementary figure 1 shows an overview of the applied treatment modality per treatment center.

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-free survival (CRPC-FS) defined as time to CRPC or death and pattern of progression which was defined as the first clinical relapse observed following MDT. Progression could be either at the prostatic fossa, nodal (N+) or metastatic (M+) and was based on imaging. Toxicity-free survival (TFS) 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 endpoint starting from start of MDT. In all centers, re-imaging following MDT was driven by PSA increases.

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 versus locally advanced)[19], primary treatment (RP versus RT versus RP+RT), extent of nodal disease (N1 versus M1a), number of nodes at recurrence (1 versus >1), type

of RT (SBRT versus ENRT), PSA at recurrence (≤4 versus >4)[20] and adjuvant ADT at time of MDT (no versus yes).

First, variable selection was performed using Least Absolute Shrinkage and Selection Operator (LASSO), including all main effects and interactions of all variables with type of RT. This was to investigate if 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 adjusted Cox model plot. The null hypothesis '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 figure 2). A more detailed explanation of the used statistical analysis can be found in the supplementary material. P-values <0.05 were considered statistically significant. Statistical analysis was performed using R. Pattern of progression and toxicity were evaluated using SPSSv.25.0. Comparison of pattern of progression and toxicity between both treatment groups was performed using the Fisher's Exact-test. The null hypothesis stated that pattern of progression and toxicity were comparable between both groups.

Results

Patient and tumor characteristics

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

Oncological results

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

Metastasis-free survival

The 3-year MFS was 68% (95%CI 61-73) and 77% (95%CI 69-82) for SBRT and ENRT, respectively (p=0.01). 352 patients did not show any metastasis with a median follow-up of 33 months.

For the multivariable analysis, the association between RT and MFS was statistically significant (LR test 7.24, df=2, p=0.03). In the analysis, the interaction of 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 a longer aMFS as compared to SBRT (HR:0.50, 95%CI 0.30-0.85, p=0.009) (figure 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 >1 LN compared to 1 LN is depicted as the ratio of the two HR's (1.84, 95% CI 0.87-3.86, p=0.1) (supplementary table 1).

Pattern of progression following MDT

Local progression was observed in 50 patients following SBRT and in 9 cases following ENRT (p<0.001). Median follow-up of the 447 patients that did not show progression was 35 months.

After RT, 259 patients developed a new N1 or M1 lesion. The median follow-up of the 247 patients that did not show progression was 29 months. In 78% (n=201), the relapses were less than five lesions. The pattern of distant progression can be consulted in table 2. Following SBRT, LN progression was observed more frequently as compared to ENRT (p<0.001), especially in the pelvis compared to ENRT (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 compared to ENRT (74 patients) (p<0.001).

Castration-resistant prostate cancer-free survival

The 3-year 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). 419 patients did not develop CRPC and had a median follow-up of 34 months. None of the variables were retained to build a multivariable analysis.

Toxicity

Figure 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 5 events for the ENRT group (p=0.009). Early toxicity was observed in 15 cases and was significantly higher after ENRT (SBRT:3 versus ENRT:12, p=0.002). After ENRT, the observed late toxicity was significantly higher (n:31), compared to SBRT (n:16) (p<0.001). A detailed description of the observed toxicity can be consulted in supplementary table 2.

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 five years. In the meanwhile, several findings in our study are of interest.

First, distant progression observed following SBRT (n=177) was significantly higher compared to ENRT (n=74, p<0.001). Interestingly, following SBRT, patients tend to relapse in the lymph nodes more often, and in particular in the pelvic lymph nodes (p<0.001 and p<0.001, respectively) (table 2). These findings are in line with the available literature[22] and probably reflect the limited sensitivity of imaging in detecting microscopic nodal invasion[23]. In the recent sLND-series by Fossati et al., quarter of patients had ≥3 positive spots on choline or PSMA PET/CT at time of recurrence, while this number doubled after pathological confirmation (54%), confirming the well-recognized limited sensitivity of choline and PSMA PET/CT[24].

aMFS 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 >1LN, 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 all 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.

Secondly, when making a decision between both treatments, toxicity should be of importance in the selection. Following ENRT, early and late toxicity was significantly higher compared to SBRT ($p=0.002$ and $p<0.001$, respectively). However, most side-effects with ENRT were limited to grade 2 or lower, with only 5 patients developing grade 3-4 toxicity. Since this was a retrospective study, it is presumable that the recorded toxicity was underreported 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 a superior overall survival (OS) for patients with biochemical recurrence as compared to 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 conventional imaging negative, 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 suggested that there are specific interactions between RT and ADT suggesting

that ENRT should be avoided without neo-adjuvant 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. recently published their results of a multi-institutional analysis of sLND at recurrence. They reported a 3-year clinical recurrence-free survival of approximately 50%, which is lower than the 3-year MFS of 71% in our cohort [24]. Nevertheless, differences in patient selection, adjuvant treatment use and differences in endpoint definition might explain this difference. Back in 2014, Rischke et al. showed that the percentage free of next relapse was significantly better if patients received adjuvant RT after sLND compared to sLND alone (5-year free of next relapse 34.3% versus 15.4%, respectively, p=0.01)[31]. However, no difference in cancer-specific survival was identified (p=0.8).

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 to 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. Secondly, 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 stratified analysis would result in a significant loss of data. However, when, as an alternative, 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, 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% versus ENRT:60%). To minimize further differences, we limited the duration of ADT for both groups to a maximum of 12 months, 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 prostate cancer [32]. Whether this is the case in this specific setting is unknown. Nevertheless, MFS is considered to be a relevant endpoint for agencies like the Food and Drug Administration (FDA) as pointed out by the recent approval of three novel drugs, improving this endpoint, in the setting of non-metastatic CRPC [33]. Finally, it is important to state that these MDT's 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.

Conclusion

ENRT reduces the number of nodal recurrences as compared to 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 to SBRT. Our findings hypothesize

that ENRT should be preferred over SBRT in the treatment of nodal oligorecurrences. However, this hypothesis should be addressed in a randomized trial.

Conflict of interest

Elise De Bleser: Travel expenses and congress sponsoring by Ferring, Astellas, Ipsen

Barbara Alicja Jereczek-Fossa: Research funding: Accuray (institutional grant), AIRC Italian Association for Cancer Research (grants). Travel expenses or honoraria: Janssen, Ferring, Bayer, Roche, Astellas, Elekta, Carl Zeiss, Ipsen

Nicholas Van As: 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.

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 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

Pedro Silva: 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.

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, MSD, Travel expenses or honoraria: Elekta, Janssen, Ferring, Bayer, Genesis Healthcare. 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.

Piet Ost: Institute research funding: Merck. Consultancy honoraria or advisory board (institute): Ferring, BMS, Janssen, Bayer.

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Previous Presentation or Release of Information

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

Data sharing policy

Data are available for bona fide researchers who request it from the authors

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Tables and figures

Table 4. *Patient and tumor characteristics.*

Figure 1. *Cox model plots showing the difference in adjusted metastasis-free survival following SBRT and ENRT .*

Table 2: *Pattern of progression following metastasis-directed therapy*

Figure 2*: General overview of the observed toxicities in both treatment groups.*

Supplementary material

Supplementary figure 1: *Overview of the applied treatment modalities in the different treatment centers*

Supplementary information regarding statistical analysis of the endpoints

Supplementary figure 2: *graphic representation of 2000 bootstraps where the cox-model with all main effects plus an interaction between RT and number of nodes is fitted in each bootstrap.*

Supplementary table 1: *Multivariable analysis of metastasis-free survival*

Supplementary table 2: *Detailed overview of the observed toxicities*

Illustrations

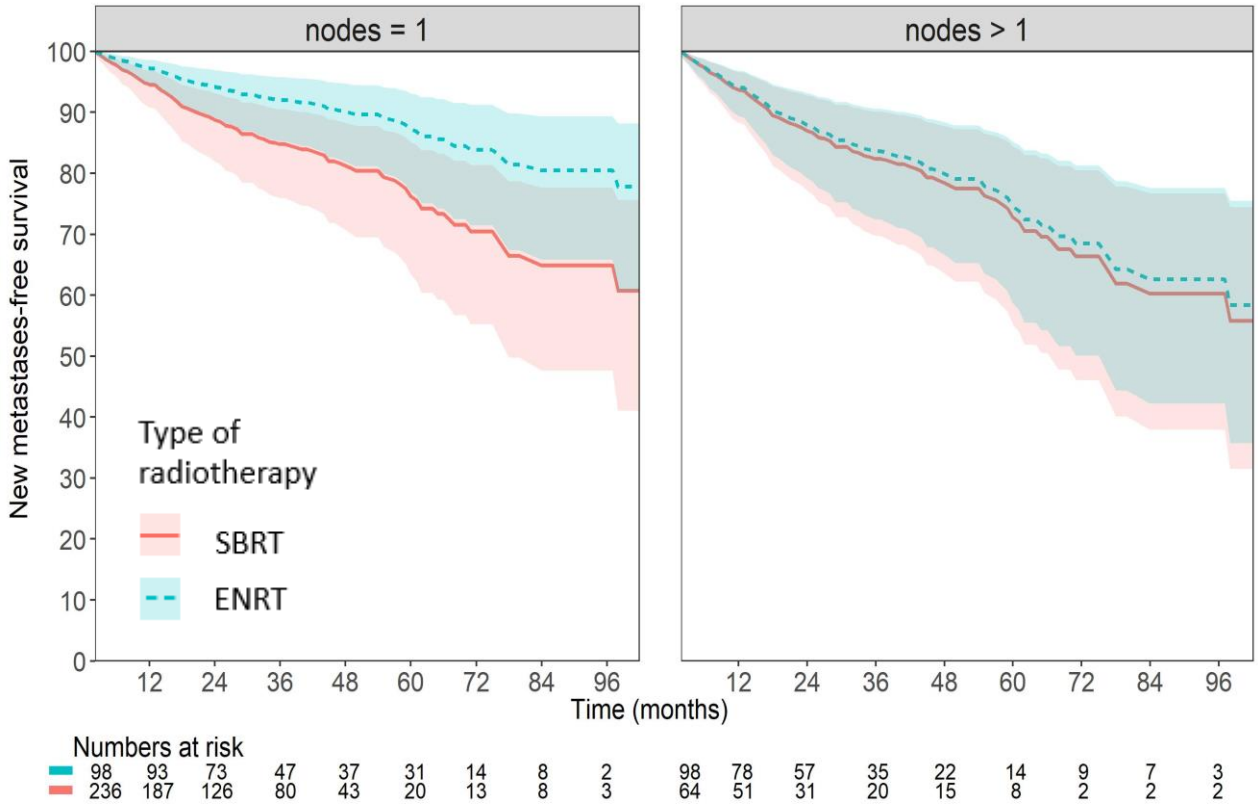


Figure 1. *Cox model plots showing the difference in metastasis-free survival following SBRT and ENRT. The specific survival curves are for patients with median age at diagnosis (63 y), median age difference between diagnosis and recurrence (5y), local prostate cancer (according to EAU risk assessment), treated by radical prostatectomy at diagnosis and presenting with N1 disease at recurrence, no adjuvant ADT at MDT and PSA at recurrence of ≤4. Left curve shows the difference between both treatment modalities for patients presenting with only one lymph node. Right curve illustrates the comparison between SBRT and ENRT for patients presenting with more than one lymph node at recurrence. ENRT: elective nodal radiotherapy; SBRT: stereotactic body radiotherapy*

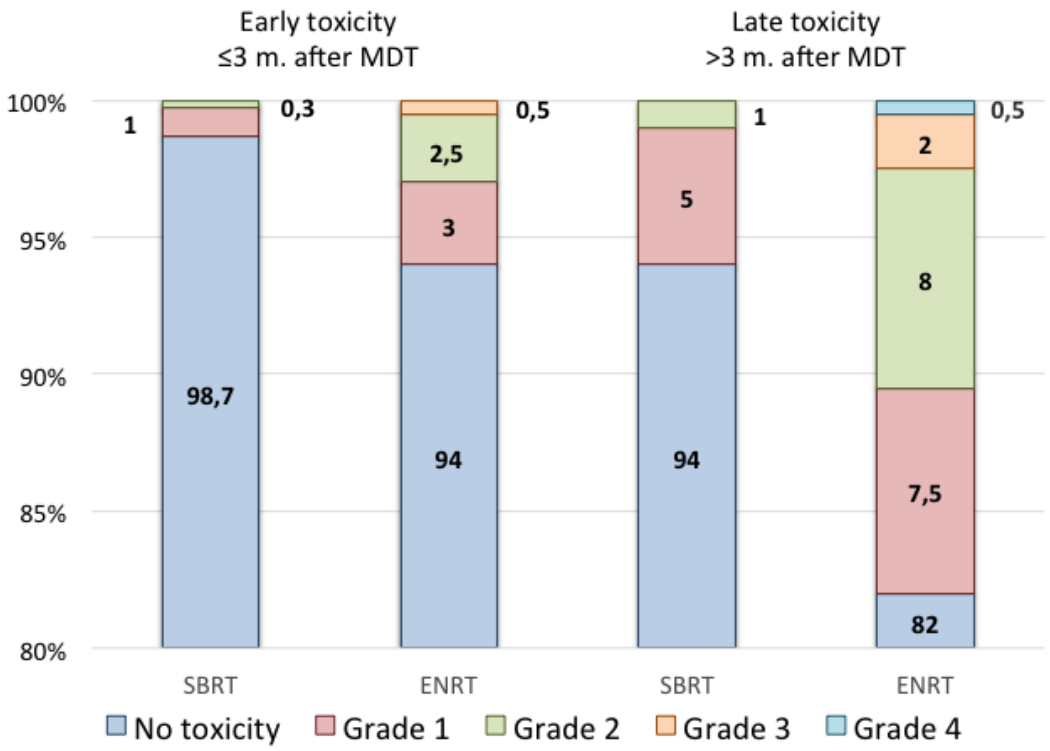


***Figure 2**: General overview of the observed toxicities in both treatment groups. A: early toxicity. B: late toxicity. ENRT: elective nodal radiotherapy; MDT: metastasis-directed therapy; SBRT: stereotactic body radiotherapy*

Tables

Table 5. *Patient and tumor characteristics.*

Patient characteristic	**SBRT**	**ENRT**
	n= 309, 61%	**n=197, 39%**
Age at PCa diagnosis, years		
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 n of nodes		

removed, (IQR)	8 (5-12)	8 (4-14)
pN0	122 (87)	85 (88)
pN1	19 (13)	12 (12)
Median n 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, years		
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, months*		
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)
N 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, months (IQR)	6 (3 – 11)	6 (6 – 9)

** in the SBRT group we note 100 (32%) missing values compared to 29 (15%) missing values in the ENRT group. 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*

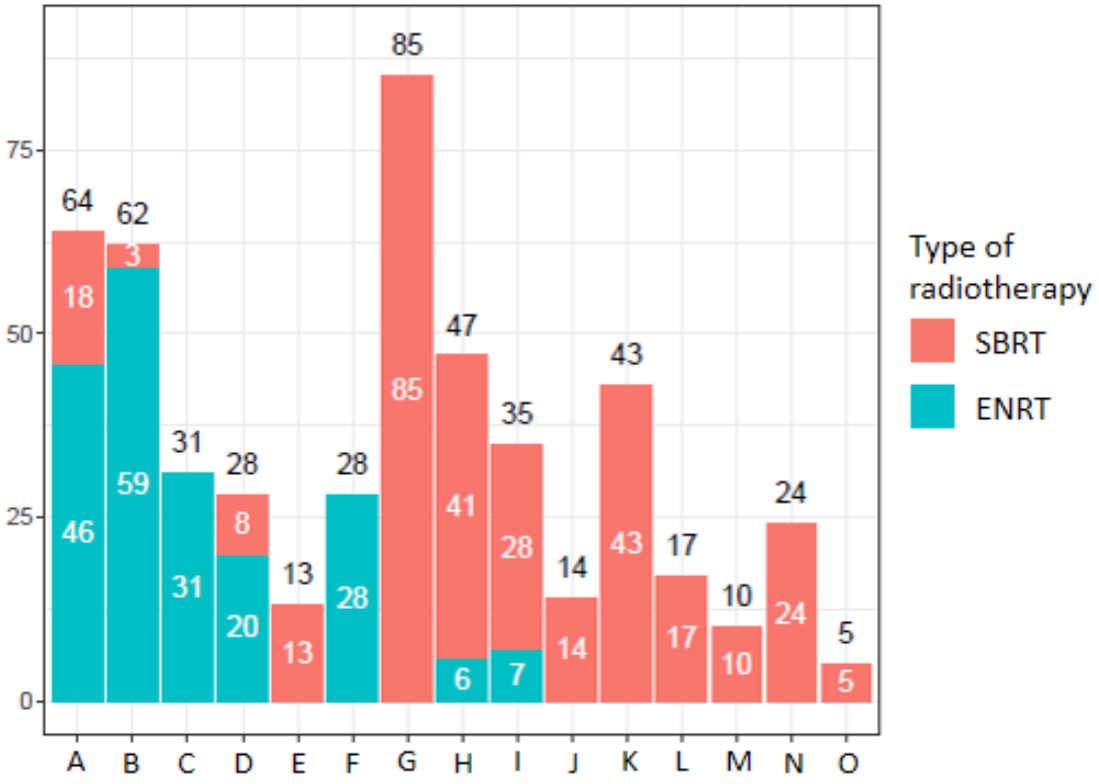
Table 6: pattern of progression following SBRT or ENRT.

Metastatic location	**SBRT**	**ENRT**	**p-value**
	n=309, 61%	**n=197, 39%**	
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	
Non-axial	13	7	
Axial + non-axial	5	7	
Prostate bed, n	**1**	**2**	**0.6**
Visceral, n	**10**	**6**	**>0.9**
Total, n	**177**	**74**	**<0.001**

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

Supplementary material

Supplementary figure 1: Overview of the applied treatment modalities in the different treatment centers



Each letter represents one center with the radiotherapy modality type indicated in color (red: SBRT, blue: ENRT).

Statistical analysis

Bootstrap analysis

Following a bootstrap evaluation of the LASSO procedure for variable selection, we found that the full set of selected variables was quite variable, but in 75% of the cases the LASSO added the interaction between RT and lymph nodes amongst the variables selected, as on the original data. When fitting the parsimonious model involving all main effects plus this interaction across 2000 bootstrap samples, a positive interaction effect was estimated in more than 95% of the bootstrap samples. Together this leads us to propose to examine the hypothesis of the existence of such interaction in a future RCT. A more detailed description of the used method can be found below.

The stability of the analyses was tested as follows:

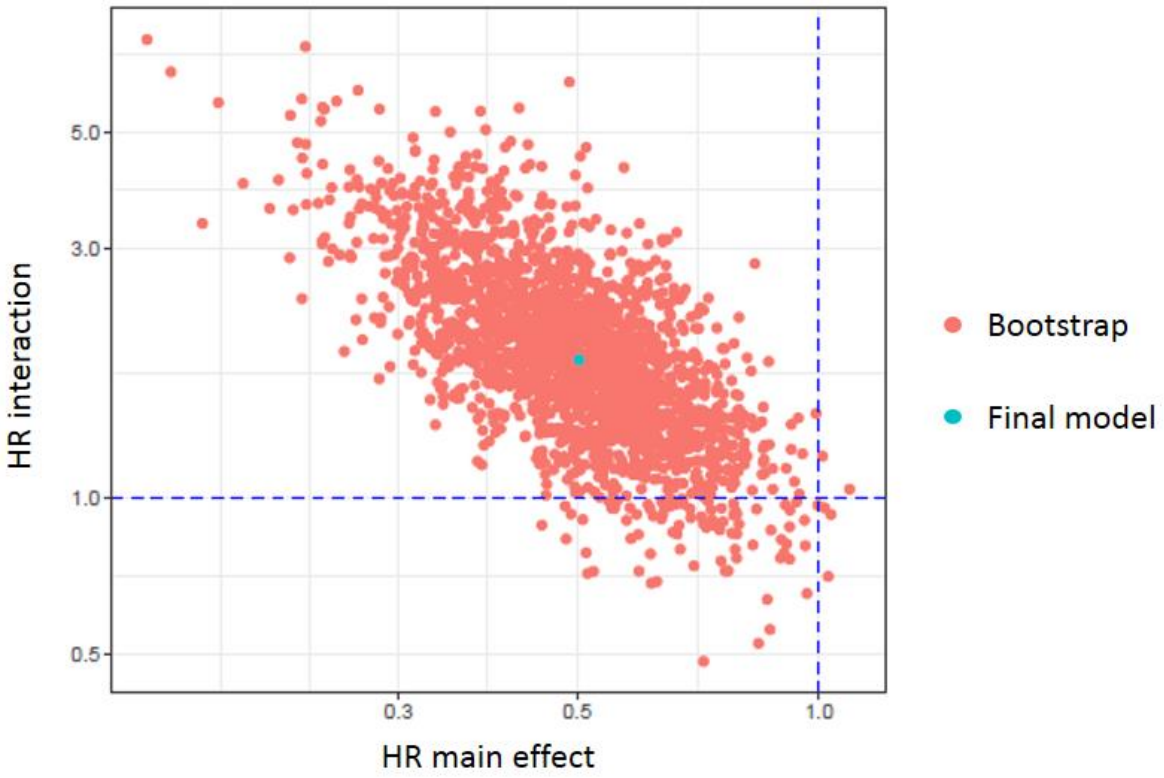
1. A bootstrap on the complete procedure (LASSO/Coxph/Pruning of interactions)

2. A bootstrap with the thus selected variable set, i.e. `final model', only (all main effects plus the interaction between RT and number of nodes)

3. Forward selection of interactions, starting with a model including all main effects. Interactions between RT and a confounder were only examined if the main effects for the confounder was statistically significant

In the first bootstrap-analysis, the interaction between RT and number of nodes, is retained in 45% of the bootstraps (75% if only LASSO is considered and pruning is not performed).
However, the model fitted with the retained set of variables (all main effects plus interaction between RT and number of nodes), does provide a stable image over the different bootstrap samples. In more than 95% of the bootstrap samples, the estimate for the coefficient of the interaction is positive (see supplementary figure 2). Thus, the qualitative image that the final model provides, does hold over the different bootstrap samples.
Exploring forward selection of interactions with RT starting from a model including all main effects and only testing interactions with RT for statistically significant confounders, leads to the same final model.

Supplementary figure 2: graphic representation of 2000 bootstraps where the cox-model with all main effects plus an interaction between RT and number of nodes is fitted in each bootstrap.



The x-axis represents the HR of the main effect of type of radiotherapy. The y-axis represents the HR of the interaction of type of radiotherapy and number of nodes. Remark the logarithmic scale on both axes. The blue dashed lines indicate a HR of 1. The blue dot represents the final model with the HR for the main effect of 0.5 and the HR for the interaction of 1.84. As seen in the figure, 95% of the bootstraps are in the same quadrant of the final model, indicating comparable results in the same direction with a HR of the main effect lower than 1 in combination with a HR of the interaction higher than 1. HR: hazard ratio

Supplementary table 1: Multivariable analysis of metastasis-free survival

Variable		**HR (95% CI)**
Type of RT	SBRT versus **ENRT**	0.5 (0.3-0.85)
Age at time of diagnosis	Median age (63y)	1.01 (0.98-1.04)
Age difference*	Median difference (5y)	0.99 (0.94-1.04)
EAU risk group	Local versus **locally advanced**	1.26 (0.88-1.8)
Primary treatment	RP versus **RT**	1.82 (1.06-3.13)
Primary treatment	RP versus **RP+RT**	2.03 (1.31-3.15)
Extent of nodal disease	N1 versus **M1a**	1.22 (0.85-1.75)
Adjuvant ADT	No versus **yes**	0.85 (0.6-1.21)
PSA at recurrence	≤4 versus **>4**	1.42 (0.99-2.04)
Number of nodes	1 versus **>1**	1.17 (0.72-1.91)
Interactions		
Type of RT and number of nodes°	SBRT versus **ENRT** and 1 versus **>1**	1.84 (0.87-3.86)

due to missing values, only 496 observations were retained.

The variables not accentuated in bold correspond to the baseline values. The variables accentuated in bold are the variables that correspond with the HR. ° The HR of the interactions are calculated by multiplying the HR of the individual variables. For patients presenting with more than 1 node, the HR for ENRT versus SBRT is 0.5x1.84=0.92

*Age difference between diagnosis and recurrence; represents time from diagnosis to recurrence

Supplementary table 2: Detailed overview of the observed toxicities

	SBRT (n=309)				***ENRT (n=197)***			
Toxicity	***GU***	***GI***	***GU & GI***	***Other***	***GU***	***GI***	***GU & GI***	***Other***
Early, n (%)								
Grade 1	*1 (0.3)*	*0 (0)*	*0 (0)*	*1 (0.3)*	*4 (2)*	*2 (1)*	*0 (0)*	*0 (0)*
Grade 2	*1 (0.3)*	*0 (0)*	*0 (0)*	*0 (0)*	*2 (1)*	*3 (2)*	*0 (0)*	*0 (0)*
Grade 3	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*1 (0.5)*	*0 (0)*	*0 (0)*	*0 (0)*
Grade 4	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*
Late, n (%)								
Grade 1	*6 (2)*	*5 (2)*	*0 (0)*	*3 (1)*	*6 (3)*	*2 (1)*	*1 (0.5)*	*2 (1)*
Grade 2	*1 (0.3)*	*2 (0.6)*	*0 (0)*	*0 (0)*	*7 (4)*	*6 (3)*	*0 (0)*	*3 (2)*
Grade 3	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*3 (2)*	*0 (0)*	*0 (0)*	*0 (0)*
Grade 4	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*1 (0.5)*	*0 (0)*
Total	*9 (3)*	*7 (2)*	*0 (0)*	*4 (1)*	*23 (12)*	*13 (7)*	*2 (1)*	*5 (3)*

ENRT: elective nodal radiotherapy; GI: gastro-intestinal; GU: genito-urinary; SBRT: stereotactic body radiotherapy