Pattern of progression following stereotactic body radiotherapy for oligometastatic prostate cancer nodal recurrences.

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Abstract

Introduction:

To report the relapse pattern of stereotactic body radiotherapy (SBRT) for oligorecurrent nodal prostate cancer (PCa).

Materials and methods: PCa patients with ≤3 lymph nodes (N1/M1a) at time of recurrence were treated with SBRT. SBRT was defined as a radiotherapy dose of at least 5 Gy per fraction to a Biological Effective Dose (BED) of at least 80 Gy to all metastatic sites. Distant progression-free survival (DPFS) was defined as the time interval between the first day of SBRT and appearance of new metastatic lesions, outside the high-dose region. Relapses following SBRT were recorded and compared to the initially treated site. Secondary endpoints were local control, time to palliative androgen deprivation therapy and toxicity scored using the Common Terminology Criteria for Adverse Events v4.0.

Results: Overall, 89 metastases were treated in 72 patients. The median DPFS was 21 mo (95% CI: 16-25 mo) with 88% of patients having ≤3 metastases at time of progression. The median time from first SBRT to the start of palliative ADT of 44 mo (95% CI: 17 – 70). The majority of relapses (68%) occurred in nodal regions. Relapses following pelvic nodal SBRT (N=36) were located in the pelvis (N=14), retroperitoneum (N=1), pelvis and retroperitoneum (N=8) or in non-nodal regions (N=13), respectively. Relapses following SBRT for extrapelvic nodes (N=5) were located in the pelvis (N=1) or the pelvis and retroperitoneum (N=4).

Late grade I and II toxicity was observed in 17% (N=12) and 4% of patients (N=3)

Conclusion: SBRT for oligometastatic PCa nodal recurrences is safe. The majority of subsequent relapses are again nodal and oligometastatic.

Introduction

The optimal management of pelvic or retroperitoneal nodal prostate cancer (PCa) recurrences following primary treatment remains largely undefined. These patients are usually treated in the same way as those with distant metastases by means of androgen deprivation therapy (ADT). The detrimental effect of ADT on general health and quality of life [1, 2] has resulted in the exploration of alternative options for these patients [3, 4]. Stereotactic body radiotherapy (SBRT) has been suggested as an alternative, lesion-directed treatment for a subset of patients with a limited number of nodal recurrences (typically ≤3 or ≤5), often called oligometastases. However, this lesion-directed approach might be insufficient as recent data suggest that current imaging modalities underestimate the disease extent on a lesion-based level [5]. However, the small number of patients and heterogeneous use of treatment modalities in the reported SBRT studies limits the strength of conclusions that can be drawn from these reports [3, 4]. The current study is a subset analysis of a previously published cohort [6] and pools the available data of patients treated with stereotactic body radiotherapy (SBRT) for nodal PCa recurrences, allowing a more detailed analysis of the safety and relapse pattern of this approach.

Materials and Methods

Study design

This is a retrospective multicentre analysis of patients diagnosed with ≤ 3 metachronous nodal recurrences treated with SBRT. The study was approved by the central ethics committee of Ghent University Hospital (EC2014/0199) and had local approvals in each hospital where this was required. Inclusion criteria were as follows: histologically proven diagnosis of PCa, biochemical relapse of PCa following radical local prostate treatment (radical prostatectomy, radiotherapy or a combination of both) and the detection of up to 3 N1 or M1a lesions. Patients were excluded in case of M1b or M1c lesions, serum testosterone levels <50ng/ml at time of detection of metastases, neo-adjuvant or concomitant ADT >12 months with SBRT, previous pelvic radiotherapy, biochemical relapse while on active treatment with luteinizing-hormone-releasing hormone (LHRH)-agonists, LHRH-antagonists, anti-androgen, maximal androgen blockade, estrogens or previous treatment with a cytotoxic agent for PCa. Consequently, all patients were in the same disease stage according to the clinical state model: rising PSA and clinically evident metastases in non-castrate patients [7].

Intervention and follow-up

Patients were staged with [18F]-fluorodeoxyglucose (FDG) (n=17) or choline positron emission tomography (PET) (n=54) with co-registered computed tomography (CT) or magnetic resonance imaging (MRI) (N=1) for the detection of metastatic disease. Following re-staging, patients underwent SBRT to all metastatic sites. SBRT was defined as a radiotherapy dose of at least 5 Gy per fraction to a Biological Effective Dose (BED) of at least 80 Gy using an α/β of 3. The metastatic sites were irradiated with the following BEDs: 80-99 Gy (N=18), 100-119 Gy (N=4), 120-139 Gy (N=46) and >140 Gy (N=4). Technical details on SBRT schedule, delineation, planning, quality assurance and follow-up schedules were previously published separately by the authors and are summarized in the supplementary table [8-12].

Endpoints and statistical analysis

The primary endpoint was distant progression free-survival (DPFS) defined as the absence of new metastatic lesions, outside the high-dose region. Local progression (LP) was defined as tumour progression within the irradiated planning target volume (PTV). ADT-free survival (ADTFS) was defined as the time from SBRT to the start of palliative ADT. The reason for starting ADT was recorded, but the decision to start ADT was at the discretion of the referring physician. Late toxicity was evaluated and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [13]. Late effects were designated as events occurring > 3 months following treatment or as an event lasting >3 months after treatment. The Kaplan-Meier method was used to estimate rates of DPFS, local progression-free survival (LPFS), ADTFS, and prostate cancer specific survival (PCSS). Calculations were done from the start of SBRT. Potential prognostic factors were examined using univariate proportional hazards regression from start of SBRT to the time of distant and local progression, respectively. Variables exhibiting a p-value ≤ 0.15 in univariate analysis were entered manually in Cox proportional hazards models in a forward stepwise fashion. Variable retention was based on the likelihood ratio test and change in estimated hazard ratios for variables already present. Potential variable selection for univariate analysis was based on previous papers on noncastrate metastases [14-16]. The total number of metastases was calculated counting all metastatic nodes separately. The following variables were analyzed: risk group at PCa diagnosis [17], interval from PCa diagnosis to metastases, PSA value at time of metastases (≤ 4 vs. >4 ng/ml) [15], number of metastases (1 vs. >1) [14], adjuvant ADT (yes vs no) and BED (≤ 100 Gy vs >100 Gy) to the metastasis. All statistical analyses were performed using SPSS version 21 (SPSS, Chicago, IL) with $p < 0.05$ considered significant.

Results

Patient characteristics

Table 1 summarizes the patient and disease characteristics of 72 patients at time of PCa diagnosis and at time of SBRT. The majority of patients (78%) were treated with a multimodality approach at initial PCa diagnosis. The median interval from PCa diagnosis to oligometastatic recurrence was 3.7 years with a median PSA of 3.4 ng/ml. In total 89 lymph node metastases were treated. The different metastatic subsites are depicted in Table 1. Adjuvant ADT was given in 57% of the patients for a median duration of 1 mo (interquartile range, IQR: 1-6).

Outcomes

Patterns of first progression following SBRT were recorded. Wit a median follow-up of 3 years (IQR: 1.9-3.8 yr), 41 patients (57%) experienced distant progression and 3 patients a local recurrence. The median DPFS was 21 mo (95% confidence interval, CI: 16-25) with 88% of patients having ≤3 metastases at time of progression (Figure 1). The 3- and 5yr-DPFS was 34% and 13%, respectively. None of the variables were significant on univariate analysis (Table 2). No multivariate analysis was performed as none of the other variables in Table 2 had a p-value ≤ 0.15. The detailed pattern of relapse of patients with nodal metastases is depicted in Figure 2. The majority of relapses (68%) occurred in nodal regions. Relapses following pelvic nodal SBRT (N=36) were located in the pelvis (N=14), retroperitoneum (N=1), pelvis and retroperitoneum (N=8) or in non-nodal regions (N=13), respectively. Relapses following SBRT for extrapelvic nodes (N=5) were located in the pelvis (N=1) or the pelvis and retroperitoneum (N=4). The treatment at time of first distant progression was palliative ADT (n=13), a new course of SBRT (n=25) or salvage pelvic nodal dissection (n=2). At time of the current analysis, 30 patients had started with palliative ADT resulting in a median time from first SBRT to the start of palliative ADT of 44 mo (95% CI: 17 – 70). Reasons for starting palliative ADT were biochemical progression (n=1), oligometastatic progression (n=12) or polymetastatic progression (n=17).

The 3y- and 5y-LPFS was 94% and 94%, respectively. Four patients died from PCa and one patient from pancreatic cancer. The 3- and 5-yr overall survival and PCSS was 96% and 96%, respectively.

Toxicity

Late grade I and II toxicity was observed in 17% (N=12) and 4% of patients (N=3). Two patients experienced grade I fatigue and 6 patients experienced gastro-intestinal complaints (grade I: n = 3 and grade II: n = 3). In one patient a grade I rectal haemorrhage was

observed and managed conservatively. One patient experienced sciatic nerve pain grade I. In 5 patients grade I urinary toxicity was observed. No grade 3 toxicity was observed.

Discussion

Following SBRT for nodal PCa oligometastases, the predominant site of further relapse is in the lymph nodes. This suggests that in the majority of patients the extent of nodal disease is underestimated by choline PET-CT, as has been suggested by surgical series [4, 5]. In the current series, 68% of the relapses following SBRT for a nodal recurrence were located in the pelvic and/or retroperitoneal nodes (Figure 2). Rischke et al. reported a 61% relapse rate in the pelvic and/or retroperitoneal nodes following salvage lymph node dissection (SLND) [18]. These data show that microscopic disease is missed, even following template salvage surgical resection.

Our data suggest that the majority of patients relapse again in an oligometastatic fashion, rather than widespread disease, potentially making these patients eligible for repeated SBRT. In the study of the Ghent group, a repeated SBRT strategy was applied for these type of patients [14]. Although the median time to first recurrence following SBRT was 19 mo, the time to a disease stage not salvageable with SBRT was 25 mo.

Another potential solution put forward by Rischke et al. is the addition of prophylactic nodal irradiation following salvage lymph node dissection [18]. The percentage of nodal recurrences dropped to 39% with the majority of relapses located in the retroperitoneum (35%), which was not always included in the prophylactic radiotherapy field. This treatment strategy is applied by a number of other groups as part of the treatment for oligometastatic prostate nodal recurrences [3, 4], although only a minority have made it their standard treatment regimen [19, 20]. A drawback of this approach is the potential increase in gastro-intestinal toxicity [21]. The OLIGOPELVIS trial [22] will assess the two year outcome in oligometastatic prostate cancer patients (1-5 pelvic oligometastases) treated concomitantly with high-dose IMRT (54 Gy, 30 fractions to the pelvis and 66 Gy, 30 fractions to the lymph nodes) and ADT for six months.

The results might also be improved with the addition of adjuvant ADT. This is also in agreement with the excellent 5-yr DPFS of 64% as reported by Suardi et al. [15], who added 2 yrs of ADT in patients without biochemical response following SLND.

It might be expected that the results of a lesion-based approach will also improve with more sensitive imaging techniques. In the current series, the majority of patients were restaged with choline PET-CT. However, recent literature data shows that the sensitivity drops significantly from a patient to a regional or lesion based level [5], which explains the relapse pattern following a lesion-based approach. ^{68}Ga-labelled ligand for prostate-specific

membrane antigen (PSMA), outperforms choline PET/CT in a patient as well as lesion based comparative study, with PSMA capable of detecting very small metastatic LN at very low PSA levels [23]. This study achieved a detection rate of 50% even in patients with PSA levels as low as 0.2 ng/ml. Although currently not commercially available, magnetic resonance lymphography (MRL), using ferumoxtran-10 ultrasmall superparamagnetic particles of iron oxide, remains one of the most promising imaging modalities for detection of metastases of normal-sized LN in PCa and has shown high sensitivity (65–92%) and excellent specificity (93–98 %) [24, 25]. These imaging modalities may, after further clinical studies, obviate the need for including prophylactic nodal volumes in the radiotherapy field.

An interesting finding of this study is the potential of SBRT to delay the start of palliative ADT with more than 2 years. In the majority of cases, palliative ADT was started at time of progression to a polymetastatic state no longer amenable for metastasis-directed therapy. Considering the quite long life expectancy of patients with oligometastatic PCa recurrence [26, 27], postponing the start of palliative ADT might be an interesting endpoint in view of the preservation of quality of life in these patients. In the current setting, SBRT was used to postpone progression with very low toxicity and might present an interesting alternative to immediate ADT. Currently, one randomized phase II trial is comparing metastasis-directed therapy with deferred ADT in the oligometastatic PCa setting with time to palliative ADT as the primary endpoint (NCT01558427). The UK-led CORE trial will randomise patients with oligometastatic prostate, breast or non-small cell lung cancer to standard therapy with or without SBRT to all lesions. It is anticipated that this trial will open to recruitment in 2016.

Although the current study tries to limit potential bias with pre-specified inclusion and exclusion criteria, there are several limitations that should be mentioned. This is a retrospective analysis of data from different centres with differing radiotherapy schedules. The absence of a comparative arm and a relatively short median follow-up makes it difficult to estimate the true impact of SBRT. However, this study represents the largest and only multi-institutional series to date reporting the safety and efficacy of SBRT for nodal PCa recurrences. As such, it provides interesting benchmark results to help inform future trials.

Conclusion

SBRT for oligometastatic PCa nodal recurrences is safe without grade III toxicity. The majority of subsequent relapses are nodal and oligometastatic.

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Figure legends:

Table 1: Patient characteristics

Table 2: Univariate Cox proportional hazards model predicting distant clinical progression-free survival.

Appendix A supplementary table: radiotherapy and follow-up schedules according to centre.

Figure 1: Kaplan-Meier analysis depicting time to distant progression.

Figure 2: a. Schematical overview of the distribution of nodal (pelvic, retroperitoneal or a combination of both) recurrences treated with stereotactic body radiotherapy. b. Schematical overview of the distribution of relapses following stereotactic body radiotherapy. Numbers in the coloured circles correspond to the unique patient ID in the database and his leading metastatic lesion. Pie chart distributions below panel A and B show the overall distribution of metastases.

Characteristics	All patients ($n = 72$)
Age at PCa diagnosis (years)	
Median (IQR)	60 (56–65)
Follow-up from PCa diagnosis (years)	
Median (IQR)	8.5 (5.8–9.9)
Primary therapy	
Radical prostatectomy alone	10 (13.9%)
Radical prostatectomy with postoperative radiotherapy	23 (33.0%)
Radical prostatectomy with postoperative radiotherapy + ADT	19 (26.4%)
Radiotherapy + ADT	14 (19.4%)
Radiotherapy alone	6 (8.3%)
PSA at initial diagnosis (ng/ml)	
Mean (range)	19.4 (1.3–180)
Median (IQR)	9.3 (6.8–20.6)
Unknown	4
EAU prognostic grouping at initial diagnosis	
Intermediate	25 (35%)
High	33 (46%)
Very high	14 (19%)
Interval from diagnosis to metastases (year)	
Mean (range)	5.2 (1.8–20.8)
Median (IQR)	3.7 (3.0–7.4)
PSA level at first documented metastases (ng/ml)	
Mean (range)	10.7 (0.3–116.7)
Median (IQR)	3.4 (1.6–7.7)
PSA-DT at first documented metastases (months)	
Mean (range)	6.0 (1.0–30.0)
Median (IQR)	(2.9–6.9)
Unknown	27
Number of lesions at diagnosis of oligorecurrence	
1 metastasis	51 (76%)
2 metastases	10 (15%)
3 metastases	6 (9%)
Treated sites with SBRT	
Pelvic	53 (73%)
Obturator	12 (10%)
Internal iliac	9 (8%)
External iliac	17 (14%)
Presacral	2 (2%)
Common iliac	6 (5%)
Combination of nodal sites	7 (6%)
Extrapelvic	12 (10%)
Both	7 (6%)
Imaging modality prior to SBRT	
Choline PET-CT	54 (75%)
FDG PET-CT	17 (24%)
MRI	1 (1%)
Adjuvant ADT	
No	41 (57%)
Yes	31 (43%)
Median duration of ADT	1 month (1–6 months)

Table 1: Patient characteristics

Covariate	DPFS	
	Hazard ratio (95% confidence interval)	*P* value
EAU prognostic group at diagnosis		
Low–intermediate	1	
High	1.54 (0.73–3.24)	0.25
Very high	1.46 (0.58–3.66)	0.42
Interval from diagnosis to metastases (year)	1.00 (0.99–1.01)	0.64
PSA level at time of metastases (ng/ml)		
≤ 4	1	
> 4	1.44 (0.75–2.72)	0.27
Number of lesions at diagnosis of metastases		
1	1	
> 1	0.74 (0.32–1.69)	0.47
Adjuvant ADT		
No	1	
Yes	0.76 (0.38–1.49)	0.43
Biological effective dose		
≤ 100 Gy	1	
> 100 Gy	1.34 (0.61–2.9)	0.47

Table 2: Univariate Cox proportional hazards model predicting distant clinical progression-free survival.

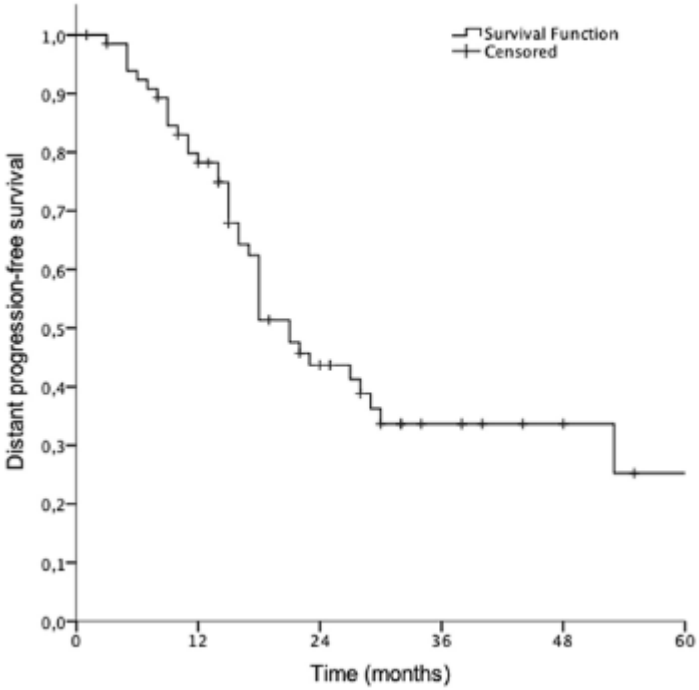
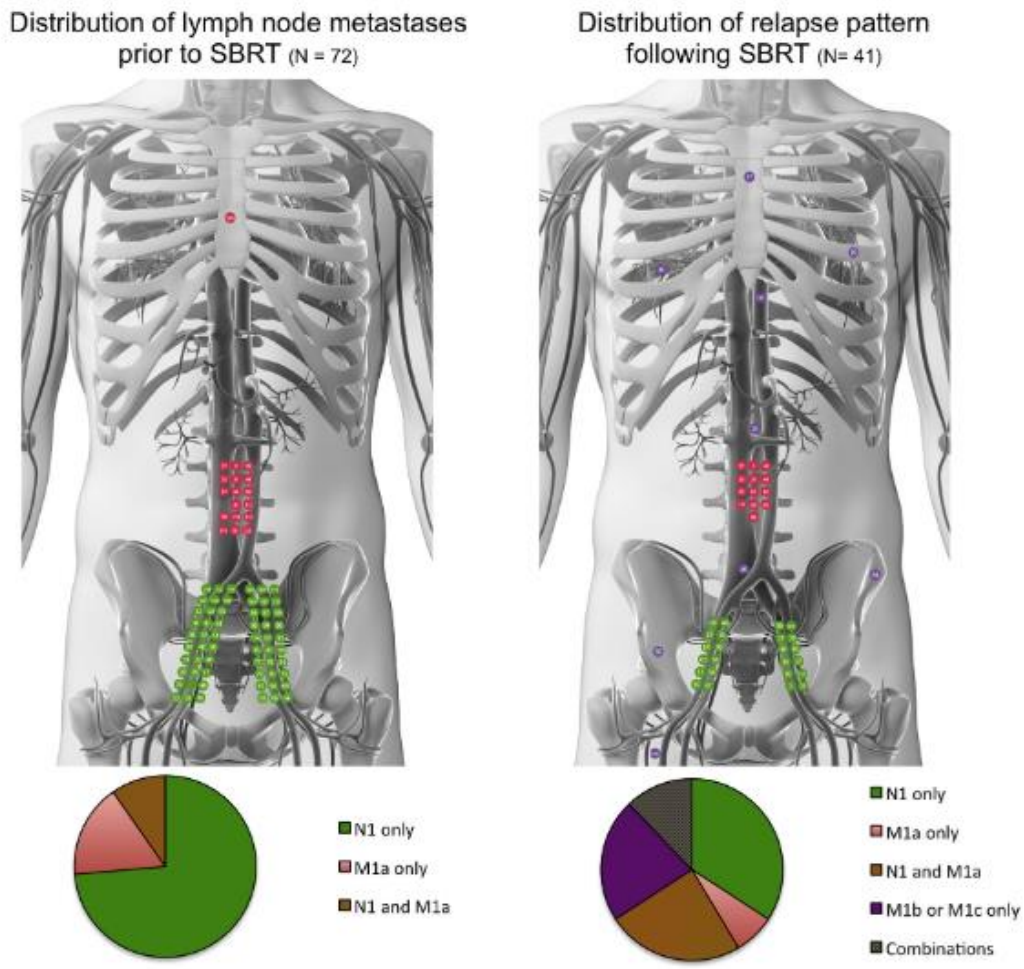


Figure 1: Kaplan-Meier analysis depicting time to distant progression.



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