Original Study

Salvage Stereotactic Body Radiotherapy for Patients With Limited Prostate Cancer Metastases: Deferring Androgen Deprivation Therapy

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Abstract

Patients with metastatic prostate cancer are uniformly treated with castration (surgically or medically), which is associated with numerous side effects such as sexual dysfunction, fatigue, osteoporosis, metabolic syndrome, and others. This single-arm study including 24 patients with limited bone or lymph node prostate cancer (PCa) metastases shows that repeated salvage stereotactic body radiotherapy is well tolerated and defers the necessity to start castration treatment.

Background: We investigated whether repeated stereotactic body radiotherapy (SBRT) of oligometastatic disease is able to defer the initiation of palliative androgen deprivation therapy (ADT) in patients with low-volume bone and lymph node metastases. **Patients and Methods:** Patients with up to 3 synchronous metastases (bone and/or lymph nodes) diagnosed on positron emission tomography, following biochemical recurrence after local curative treatment, were treated with (repeated) SBRT to a dose of 50 Gy in 10 fractions. Androgen deprivation therapy-free survival (ADT-FS) defined as the time interval between the first day of SBRT and the initiation of ADT was the primary end point. ADT was initiated if more than 3 metastases were detected during follow-up even when patients were still asymptomatic or in case of a prostate specific antigen elevation above 50 ng/mL in the absence of metastases. Secondary end points were local control, clinical progression-free survival, and toxicity. Toxicity was scored using the Common Terminology Criteria for Adverse Events. **Results:** We treated 24 patients with a median follow-up of 24 months. Ten patients started with ADT resulting in a median ADT-FS of 38 months. The 2-year local control and clinical progression-free survival was 100% and 42%, respectively. Eleven and 3 patients, respectively, required a second and third salvage treatment for metachronous low-volume metastatic disease. No grade 3 toxicity was observed. **Conclusion:** Repeated salvage SBRT is feasible, well tolerated and defers palliative ADT with a median of 38 months in patients with limited bone or lymph node PCa metastases.

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Introduction

Patients with metastasized prostate cancer (PCa) are generally considered palliative. The first line treatment is androgen deprivation therapy (ADT) attempting to defer progression in asymptomatic patients or to palliate symptoms in symptomatic patients.[1]

In 1995, it was suggested that the evolution of metastatic disease has intermediate states in which metastases might be present in limited numbers, termed oligometastases.[2] This state implies that local control of oligometastases may yield improved systemic control. In PCa, this concept might also be valid as the overall survival of patients with metastatic disease varies as a function of the number of metastatic lesions.[3]

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As a result, early detection and eradication of a small number of metastatic lesions with surgery or radiotherapy might also delay systemic treatment and even improve survival[4] in PCa.

Two valid options are available for eradication of oligometastases: surgery[5] or high-dose extracranial stereotactic body radiotherapy (SBRT).[6] SBRT is a noninvasive procedure allowing the delivery of ablative doses to, in the situation presented here, metastasis while sparing the surrounding normal tissue to a maximal extent.[7]

We hypothesized, by performing high-dose SBRT that disease progression could be slowed down. The primary end point was androgen deprivation therapy-free survival (ADT-FS) when performing SBRT to oligometastases from PCa, confined to the bone and/or lymph nodes. Secondary end points included local control, clinical failure, and toxicity.

Patients and Methods

Between May 2005 and August 2011, 24 patients with a biochemical recurrence[1] after treatment with curative intent (radical prostatectomy, primary radiotherapy, or a combination of both) were diagnosed with ≤3 synchronous asymptomatic metastases and were eligible for this study. At biochemical recurrence, patients were staged with bone scan and [18F]-fluorodeoxyglucose (FDG) (n = 20) or [11C]-choline positron emission tomography (PET) (n = 4) with coregistered computed tomography (CT).[8] All scans were interpreted by the radiologist and nuclear medicine physician in consensus reading with knowledge of the clinical history of the patients and of the results of other diagnostic techniques. Every focal tracer accumulation deviating from the physiological distribution of the tracer was regarded as suggestive of disease. Diffuse, bilateral tracer uptake in inguinal lymph nodes was considered as being inflammatory.[9] A biopsy of the suspected lesions was not performed before inclusion and treatment. In case of equivocal findings on bone scan and PET-CT, an additional magnetic resonance imaging (MRI) scan of the suspected region was performed. Local recurrence was excluded with multiparametric MRI.[10,11] All patients had normal testosterone levels at inclusion (normal laboratory range: 180-740 ng/mL). All cases were presented to and approved by the multidisciplinary uro-oncology team and the local ethics committee (EC UZG2011/495).

All patients underwent a PET/CT-based treatment planning with 3 mm slice thickness in supine position with an ankle and knee fix (Sinmed, Cablon Medical, Leiden, The Netherlands). Gross tumor volume (GTV) was delineated using all available clinical, iconographic, and metabolic information. A planning target volume (PTV) was created by adding a 0.3 to 0.5 cm margin around the GTV depending on target location. Organs at risk were delineated, depending on the site of the GTV. A median dose of 50 Gy in 10 fractions of 5 Gy was prescribed to the PTV, which corresponds to an equivalent 2-Gy dose of 80 and 92 Gy, when considering an α/β ratio of 3 and 1.5, respectively. The number of fractions was stepwise reduced in case of violation of maximal tolerated dose of organs at risk. Treatment was delivered 3 times a week using 6- to 18-MV photons from a linear accelerator equipped with a multileaf collimator and cone-beam CT (CBCT) (Varian CLINAC, Varian, Palo Alto, CA or Elekta Synergy, Elekta, Crawley, UK).

At each fraction, a CBCT was used for patients' set-up and target verification. In case of multiple (1-3) synchronous lesions, all lesions were treated in the same session and the positioning protocol was repeated per lesion.

To increase radiosensitivity, a single injection of a short-acting (1-month depot) luteinizing hormone releasing hormone (LHRH) analogue was given within 1 month before the start of radiation therapy.[12] An antiandrogen treatment was initiated 6 days before this injection and continued during 4 weeks to prevent flare-up. No premedication with steroids was used before SBRT.

During treatment, patients were clinically evaluated weekly and at 1 and 3 months thereafter. Follow-up visits with prostate specific antigen (PSA) measurement were scheduled every 3 months during the first year and every 6 months thereafter.

The primary end point was ADT-FS, defined as the time interval between the first day of SBRT and the initiation of palliative ADT. Cases were censored at last follow-up visit if no ADT was started. ADT was initiated if more than 3 metastases were detected during follow-up even when patients were still asymptomatic[1] or in case of a PSA elevation above 50 ng/mL or more in the absence of metastasis on morphologic and functional imaging.[13] Secondary end points were clinical failure and toxicity. Reassessments with bone scan and PET/CT imaging was performed in case of 3 rising PSA values elevated after initial response, in case of PSA elevation above the pre-SBRT PSA that was confirmed at least once or if clinically indicated to rule out local or distant metastatic progression. Clinical progression was defined as the detection of local progression or distant disease at reassessment. In case of an oligometastatic recurrence outside the previous SBRT field, a re-treatment with SBRT was performed. The length of follow-up was calculated from the first day of SBRT to the last PSA measurement or death. Survival probabilities were estimated by the Kaplan–Meier method. Univariate (log-rank) analysis was used to examine the predictive value of tumor-related variables such as Gleason score of primary disease, localization of metastases (lymph node or bone), PSA before SBRT, number of metastases at SBRT, and time from diagnosis to SBRT. All *P* values were set at 0.05. Statistical analysis was performed with SPSS v.15.0 (IBM Corp, Somers, NY).

Results

Patient Characteristics

On initial inclusion, 29 lesions (lymph node/bone metastases ratio: 13/16 patients) were treated in 24 patients (lymph nodes/bone metastases ratio: 11/13 patients). Fourteen bone metastases were detected on both bone scan and PET imaging. One PET positive bone lesion was confirmed positive on MRI, but negative on bone scan. One bone scan positive lesion was confirmed positive on MRI, but negative on PET. The median time interval from PCa diagnosis to the detection of oligometastatic disease was 4.5 years (range, 2-14 years). Basic patient characteristics at initial diagnosis and at time of first SBRT are presented in Table 1.[14] One patient had a surgical resection of a unique rib metastasis before inclusion in this study at time of an isolated lymph node relapse. All patients completed the SBRT protocol with a median dose of 50 Gy (range, 40-50 Gy) delivered in 10 fractions (range, 8-10). In 6 patients the number of fractions was reduced because the maximal tolerated dose to an organs at risk was violated. An example of a typical dose distribution of

Table 1 Baseline Patient Characteristics (N = 24 Patients)

Characteristic	Value
At Primary Diagnosis	
Serum PSA (ng/mL)	
Median	36.5
Range	7-54
Gleason score	
Median	7
Range	5-10
Risk groups,[14] n (%)	
Low	1 (4)
Intermediate	7 (29)
High	16 (67)
Treatment modality, n (%)	
Primary RT	3 (12)
Primary RP	4 (17)
RP and RT	16 (67)
RT and RP	1 (4)
TTP from initial diagnosis to SBRT (mo)	
Median	40
Range	23-168
At SBRT	
PSA (ng/mL)	
Median	6.59
Range	0.34-72.9
Age (years)	
Median	67
Range	54-78
Location of lesions, n (%)	
Bones	
Axial	18 (37)
Nonaxial	9 (18)
Lymph nodes	
Pelvic	15 (31)
Extrapelvic	7 (14)

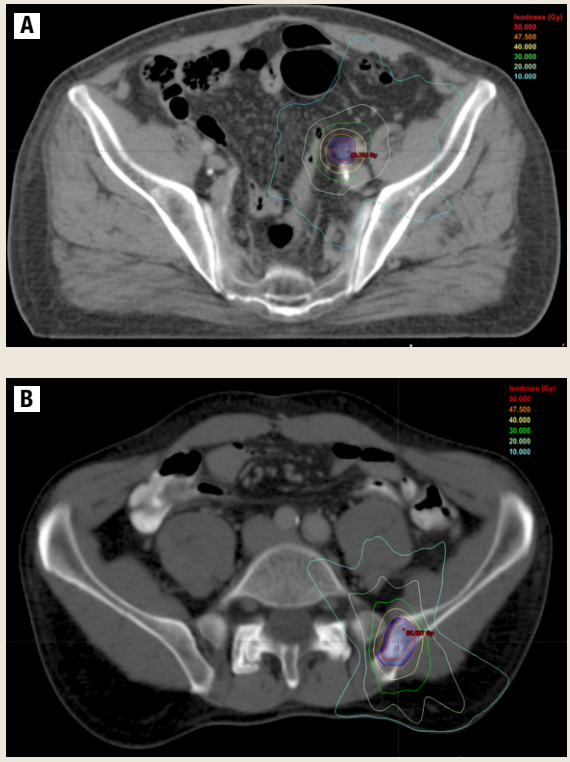
Abbreviations: PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy; SBRT = stereotactic body radiotherapy; TTP = time to progression.

an SBRT plan for a lymph node and bone metastasis is given in Figure 1.

Outcome After First SBRT Course

There were no in-field recurrences, resulting in a local control of 100%. After the first SBRT course the pattern of recurrence was as follows: oligometastatic relapse in 11 patients, multiple metastatic relapse in 6 patients, and a biochemical failure without clinical evidence of disease in 3 patients. Four patients had no evidence of disease (Figure 2). The 1- and 2-year clinical progression-free survival was 72% and 42% with a median time to clinical progression of 18 months (95% confidence interval [CI], 6-23 months). On univariate analysis, neither Gleason score ($P = .34$), time from diagnosis to SBRT ($P = .75$), PSA level before SBRT ($P = .65$), or number of lesions ($P = .76$) resulted in a significantly worse progression-free survival. The median time to clinical progression was 15 months (95% CI, 5-25) for bone metastases compared with 22 months (95% CI, 7-37) for lymph node metastasis ($P = .13$).

Figure 1 Transverse Views of a Dose Distribution of a Single Lymph Node Metastasis (A) and Single Bone Metastasis (B) Treated with 50 Gy in 10 Fractions



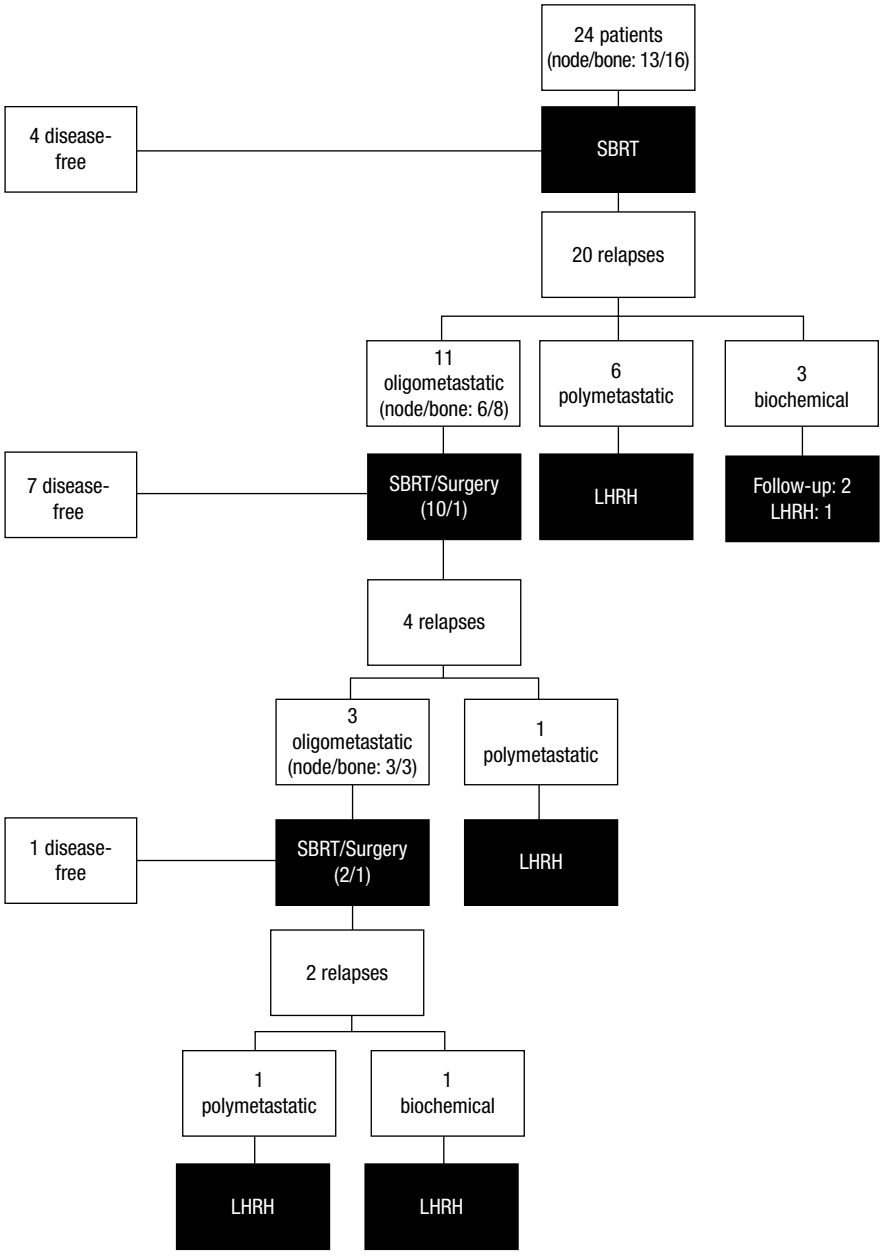
Treatment at Recurrence

A detailed overview of the treatment at recurrence and the results are depicted in Figure 2. Combining the initial and retreatment SBRT sessions, 49 metastatic lesions (lymph node/bone metastases ratio: 22/27) were treated in 38 treatment sessions. Again, no in-field recurrences were observed. At last follow-up, 12 patients were alive without evidence of disease (Figure 2).

Androgen-Free and Overall Survival

After a median follow-up of 24 months (range, 1-72 months), 8 patients started with ADT because of polymetastatic disease and 2 because of a PSA elevation above 50 ng/mL (13 and 46 months after SBRT), resulting in an ADT-FS of 82% at 1 year and 54% at 2 years (Figure 3). The median time ADT could be deferred was 38 months (95% CI, 18-58 months). On univariate analysis, only Gleason score at initial diagnosis was a significant predictor for the start of ADT (hazard ratio: 4.3 with 95% CI, 1.01-18.46; $P = .048$). None of the other variables were significant: localization of metastases ($P = .44$),

Figure 2 Overview of Initial Treatment Strategy and Relapse Pattern with Subsequent Therapy



Abbreviations: biochemical = biochemical failure of treatment without clinical progression; LHRH = luteinizing hormone releasing hormone; oligometastatic = defined as 1 to 3 metastases confined to lymph nodes or bone; polymetastatic = defined as >3 metastases.

PSA before SBRT ($P = .90$), number of metastases at SBRT ($P = .70$), and time from diagnosis to SBRT ($P = .53$). Three patients died of PCa at 4 (n = 1) and 5.8 years (n = 2) from the time of SBRT.

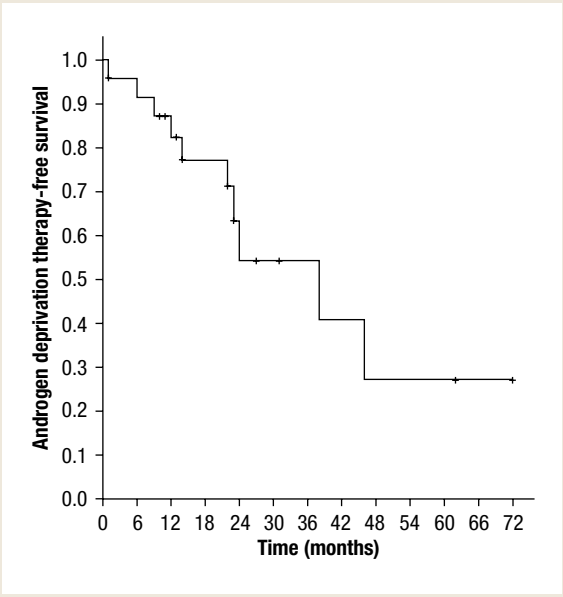
Toxicity

The SBRT treatment was well tolerated with an absolute rate of acute grade 2 genitourinary (GU) and gastrointestinal (GI) toxicity of 8% and 6%, respectively without any grade 3 toxicity. Late GU and GI grade 2 toxicity was reported only after 6% and 3% of the treatments, respectively. Neither late grade 3 toxicity nor toxicity of other system organ classes was observed.

Discussion

The current standard for patients diagnosed with metastatic PCa or node positive disease is immediate ADT.[1] This approach is not

Figure 3 Kaplan-Meier Curve Representing Androgen Deprivation Therapy-Free Survival



disputed in symptomatic patients but is less straightforward for asymptomatic patients, certainly when the metastatic load is low. The recent evidence of the potential toxic nature of ADT and its impact on quality of life has resulted in the advice that, as an alternative to immediate ADT, clinical surveillance can be suggested in patients with metastases who strongly wish to avoid treatment-related side effects.[1] Consequently, it is clear that therapeutic approaches meant to defer ADT-induced morbidity should be considered in patients with low-volume metastatic disease.

Although the concept of aggressive treatment of low-volume metastatic disease is well established in several types of cancer,[15] this is not the case in PCa.[1] Nevertheless, the hypothesis that an aggressive treatment could be beneficial for low-volume metastatic prostate cancer was generated several years ago. Singh et al observed that patients with ≤5 bone metastases had a superior survival compared with those with >5 lesions.[3] Others demonstrated that survival after initiation of ADT is dependent on the extent of lymph node and bone involvement.[16-18] Moreover, patients with initial low-volume metastatic disease were more likely to progress locally instead of distant, while the opposite was true for patients with high-volume metastatic disease.[16] This heterogeneity in outcome raises the hypothesis that there might be a benefit of considering these patients as 2 different entities that might benefit from different treatment approaches: systemic treatment for high-volume metastatic cancer and aggressive local treatment for low-volume metastatic disease.

More specific and sensitive imaging modalities such as [11C] choline PET/CT have been recently introduced in the setting of biochemical recurrence,[19] detecting lymphatic and/or hematogenous metastases at lower PSA values compared with anatomic imaging modalities such as CT and MRI and consequently often in a low-volume.

Recently, the first studies addressing salvage SBRT for low-volume metastatic disease were published.[20-22] The tolerability of salvage SBRT is excellent without grade 3 toxicity[20-22] as confirmed in the current study. Reported local control rates are 100% for nodal metastases[20,21] and >95% for bone metastases.[22] Both biochemical and clinical progression can be, at least temporarily, slowed down with a median time to clinical progression of 1.5 year in our series. More interestingly, the pattern of recurrence appeared to be oligometastatic in 50% of the patients, allowing retreatment with SBRT. There are several unique aspects in our study. This is a homogeneous patient group in a well-defined disease state of noncastrate metastatic prostate cancer without previous palliative systemic or radiation therapy. As both asymptomatic low-volume lymph node and bone metastases were eligible for inclusion, this is only the second study reporting the results on oligometastases to the bone of PCa. This is the first study reporting on the interesting end point of deferring systemic treatment, with a median deferment of palliative ADT of 3 years. These results might serve as a base to initiate phase 2 randomized trials and to create a paradigm shift in the treatment of low-volume lymph node and bone metastatic disease.

Limitations of the current study include the small number of patients and the lack of a control group undergoing active clinical surveillance monitoring the natural progression of oligometastatic PCa. A randomized phase II trial comparing eradication of oligometastatic disease with SBRT or surgery versus active surveillance with the start of ADT at time of progression has recently started recruiting patients (http://clinicaltrials.gov: NCT01558427). The primary end point is ADT-free survival. Second, all patients received a single injection of a 1-month preparation of an LHRH-analogue shortly before the initiation of SBRT in order to increase radiosensitivity.[12] As the added value of LHRH in combination with dose-escalation remains undefined,[23] it is recommended to continue the addition of ADT to dose-escalated radiotherapy. Moreover, the influence of this strategy on PSA response and distant clinical progression-free survival is probably limited as the duration of testosterone suppression by a single injection of a 1-month depot of an LHRH-analogue is only between 2 and 4 months depending on the definition of testosterone recovery.[24] Finally, there is no standard imaging protocol to restage patients with a PSA-relapse after maximal local therapy. However, PET-CT is a promising tool in this setting. Initially, [18F]-FDG-PET-CT was used in the first 20 patients, with reported sensitivity and specificity of 80% and 73%, respectively for PSA levels greater than 2.4 ng/mL.[8] In view of the emerging data showing an improved sensitivity and specificity at even lower PSA values with choline,[19] we decided to switch to the latter tracer. Consequently, it is possible that a proportion of patients screened with [18F]-FDG-PET-CT were not truly oligometastatic at inclusion because of a possible underestimation of the extent of disease with this tracer.

Conclusion

Salvage hypofractionated stereotactic body radiotherapy is well tolerated and defers the initiation of palliative ADT in patients with low-volume bone or lymph node PCa metastases.

Clinical Practice Points

- The management of patients with asymptomatic PCa metastases is controversial.

- We hypothesized that early detection and eradication with stereotactic body radiotherapy of oligometastases might delay the start of ADT.
- This safe approach allowed a median deferment of ADT of approximately 3 years.
- The results of this hypothesis-generating study should be confirmed in a randomized trial.

Disclosure

All authors have no conflicts of interest.

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