Multidisciplinary treatment of metastatic prostate cancer

Bouman, E.W.

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Benefits of using stereotactic body radiotherapy in patients with metachronous oligometastases of hormone-sensitive prostate cancer detected by [18F]fluoromethylcholine PET/CT

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Abstract

Background

For patients with oligometastatic recurrence of prostate cancer (PC), stereotactic body radiation therapy (SBRT) represents an attractive treatment option as it is safe without major side effects. The aim of this study is to investigate the impact of SBRT in delaying the start of androgen deprivation therapy (ADT).

Patients and methods

Forty-three patients treated with SBRT for oligometastatic recurrence (<5 metastases) of hormone sensitive PC, defined with [^{18}F]fluoromethylcholine PET/CT were included. As a control group, 20 patients with oligometastatic disease not treated with SBRT were identified from another hospital. Data were collected retrospectively.

Results

A post-SBRT PSA response was seen in 29/43 patients (67.4%). Median ADT free survival (ADT-FS) was 15.6 months (95% CI 11.7-19.5) for the whole group, and 25.7 months (95% CI 9.0-42.4) for patients with a PSA response. Seven patients were treated with a second course of SBRT because of oligometastatic disease recurrence; the ADT-FS in this group was 32.1 months (95% CI 7.8-56.5). Compared to the control group, the ADT-FS from first diagnosis of metastasis was significantly longer with 17.3 (95% CI 13.7-20.9) months versus 4.19 months (95% CI 0.0-9.0), p<0.001. Also, time between diagnosis of the metastasis until progression of disease during ADT use (castration resistance) was longer for the SBRT treated patients (mean 66.6 (95%CI 53.5-79.8) versus 36.41 (95% CI 26.0-46.8) months, p=0.020. There were no grade III or IV adverse events reported.

Conclusion

SBRT can safely and effectively be used to postpone ADT in appropriately selected patients with oligometastatic recurrence of PC.

Introduction

Prostate cancer (PC) is the most common malignancy in European men[1]. For patients with hormone sensitive metastatic PC after curative-intent treatment of the primary tumor, androgen deprivation therapy (ADT) is the standard first-line therapy[2]. A recent systematic review of randomized controlled trials suggests that the addition of docetaxel to ADT should be considered the new standard of care in patients with high volume disease. The addition of docetaxel improved survival, with an absolute improvement in 4-year survival of 9% (HR 0.77, 95% CI 0.68-0.87, P<0.0001)[3]. However, ADT has numerous side effects, including fatigue, reduced/absent libido, sexual dysfunction, depression and hot-flushes as well as insulin resistance and bone mass loss[4, 5].

The introduction of hybrid imaging modalities such as [18F]fluoromethylcholine ([18F]FCH) PET/CT offers the possibility to detect metabolically active lesions at relatively low prostate specific antigen (PSA) levels, early in the development of metastatic disease, when just one or a few metastases may be present[6, 7]. For the subgroup of patients with oligometastatic disease, typically defined as less than 4 or 5 metastases in bone and/or lymph nodes[8, 9], local therapy might represent an attractive treatment paradigm. Stereotactic body radiation therapy (SBRT), defined as high-dose external beam radiotherapy typically delivered in only a few fractions using advanced techniques that allow for relative sparing of nearby normal tissues, is a non-invasive ambulatory local therapy[10]. Emerging evidence suggests that treatment of single metastases with SBRT might prolong progression free survival (PFS) and allows deferred start of ADT[11-15], thereby avoiding the related side effects. SBRT has been associated with low levels of toxicity in prostate cancer patients irradiated for bone or lymph node metastases[16, 17].

Available evidence of the benefit of SBRT originates from small single arm, mostly retrospective, studies in heterogeneous patient groups. In the present study, we retrospectively reviewed data from patients with hormone sensitive oligometastatic prostate cancer recurrence as defined with [18F]FCH PET/CT, who subsequently underwent SBRT. We compared the primary outcome, ADT- free survival (ADT-FS), of these patients with a cohort of patients (with oligometastatic disease defined with [18F]FCH PET/CT) who did not receive SBRT. The latter patients were treated in another hospital which did not offer SBRT as standard treatment according to their guidelines. Due to this approach, we were able to compare the ADT-FS as well as the time on ADT till

castration resistance between these groups that were well matched for baseline clinical and pathological characteristics. To our knowledge, this has not been described in the literature yet.
Secondary endpoints were PFS, SBRT-related toxicity, pattern of recurrence and progression of the disease.

Patients and Methods

Patient population

Formal ethical approval for performing this retrospective study was obtained from the Medical Ethics Committee of the VU University Medical Center, Amsterdam, The Netherlands. This approval states that the study does not fall within the scope of the Medical Research Involving Human Subjects Act (section 16.2 WMO, 26th February 1998). All patients with PC who underwent [18F]FCH PET/CT, for restaging purposes, between January 2009 and December 2015 at the VU University Medical Center (VUmc), Amsterdam, the Netherlands were reviewed (n=241). Patients referred from other hospitals who underwent SBRT at VUmc, but had the imaging at their own centers were also screened for eligibility. Patients with hormone sensitive oligometastatic disease, defined as ≤4 [18F]FCH PET/CT positive metastatic lesions, were identified for further analysis[9].

Patients were included in the analysis if they had a histologically proven diagnosis of prostate cancer, were initially treated with curative intent, had biochemical PSA relapse, had metabolically active oligometastatic disease on [18F]FCH PET/CT and received SBRT to all lesions as initial oligometastatic treatment. Patients who received ADT and/or chemotherapy initiated for metastatic disease prior to the SBRT were excluded, as well as patients with one or more other types of carcinoma apart from the prostate cancer. A biochemical PSA relapse was defined as two consecutive PSA rises above 0.2 ng/ml after radical prostatectomy and a rising PSA level > 2 ng/ml above the nadir value in patients previously treated by means of External Beam Radiation Therapy (EBRT) in accordance with the EAU guidelines[2].

Data were collected on the following parameters: the date of initial diagnosis, Gleason and tumor staging, PSA (at the time of initial diagnosis, at the time of diagnosis of the metastasis, prior to SBRT, nadir after SBRT and follow up after SBRT), date and type of previous therapy, SBRT characteristics, date of [[18F]FCH PET/CT, date of progression (PSA or on imaging), start of systemic therapy after SBRT and, if applicable, follow up after start of ADT. We also reviewed the medical records for data on acute and late side effects of SBRT.

A cohort of patients with oligometastatic PC not treated with SBRT, the control group, was identified by screening patients, and their results of a [18F]FCH PET/CT, from the Academic Medical Center (AMC), Amsterdam, the Netherlands. Patients who were referred to the VUmc only for imaging, but were treated at the referring hospital were eligible as well. Both in the AMC as in the referring community hospitals, SBRT was not common practice, so these patients were treated by active surveillance followed by start of ADT in case of progressive disease.

[18F]fluoromethylcholine PET/CT

[18F]FCH was synthesized according to the methods proposed by DeGrado et al. with minor modifications, as previously described by Oprea-Lager *et al.*[18, 19]. Patient preparation was similar to that required for [18F]fluorodeoxyglucose ([18F]FDG) PET[20]. The standard activity of [18F]FCH was 4 MBq per kg body weight[21], resulting in an average (±SD) administered activity of 352.4 ± 57.3 MBq [18F]FCH, with a maximum administered amount of 485 MBq [18F]FCH. The studies were performed in both the VUmc and the AMC on a Gemini/Ingenuity PET-CT scanner (Philips Healthcare, The Netherlands, 39 and 20 patients) or a Biograph PET/CT (Siemens, 4 patients) with an axial field per view of 18 cm.

All patients underwent the same [18F]FCH PET/CT image acquisition protocol, including a low-dose CT (LD/CT) for anatomical localization and attenuation correction (AC), using a beam current of 30 to 50 mAs at 120 keV. Following the LD/CT, 'early' PET image acquisition started 2 min after intravenous injection of the radiolabeled choline, using a 35 cm scan trajectory over the pelvic region (2 min/bed position). After a micturition break, at 30 min post injection, a 'late' whole body PET sequence was started, from mid-thigh to the skull vertex, with arms up. The acquisition time was again 2 min per bed position with

a standard number of 9 bed positions. The total acquisition time for the WB PET/CT was, on average, 30 minutes.

Time of flight (TOF) information was used during reconstruction. Reconstructed images had an image matrix size of 144×144, a voxel size of 4×4 mm and a slice thickness of 5 mm. PET/CT images were analysed by an experienced nuclear medicine specialist. Metastatic lesions were defined as enhanced [18F]FCH uptake versus the direct background, incompatible with physiological uptake[22].

Radiation therapy

For radiotherapy planning, a CT scan was acquired with the patient in supine position. For lymph node, bone and spine metastases at or below the fourth thoracic vertebra, patients were positioned using a simple upper torso support (Posires; CIVCO Medical Solutions) and foam knee support (CIVCO), while lying on a thin mattress. Their arms were above the head or alongside the body, depending on tumor location and what position was most reproducible. For more cranial spine targets, patients were immobilized in a thermoplastic head and neck mask. Contrast was not routinely used and typical slice thickness was 1.25 mm. If necessary, a 4-dimensional CT scan was acquired (e.g. to assess mobile organ motion). The gross tumor volume (GTV) and organs at risk (OAR) were delineated using all available clinical and radiological information. For lymph node metastases the [18F]FCH PET/CT was typically rigidly registered to the planning CT scan. For patients with bone lesions and MRI of the involved region, for example the pelvis or spine, was obtained to confirm the PET findings[23]. For lymph nodes, a 3 or 5 mm planning target volume (PTV) margin was added to the GTV. The clinical target volume (CTV) for spine metastases that had not previously been irradiated was defined using an approach consistent with Cox *et al.*[24] with an additional 2 or 3 mm PTV margin outside the spinal canal. For non-spine bone metastases and for lymph node or bone metastases in a previously irradiated region, the dose, target volume and margins were individualized. Maximum dose constraints to OARs or to a planning organ at risk volume (PRV) expansion around the OAR, were based on AAPM recommendations[25]. The most commonly used dose-fractionation schedules were 30 Gray (Gy) in 3 fractions or 35 Gy in 5 fractions over 1.5-2 weeks. The dose was prescribed to the PTV and heterogeneous dose was permitted (with the maximum PTV point dose up to 150% of the prescribed dose, located in the GTV, in patients not previously irradiated). The minimum PTV dose and the volume of PTV receiving the prescribed dose was determined by dose-limiting OARs. Treatment is currently delivered

using flattening-filter free (FFF) volumetric modulated arc therapy (VMAT, RapidArc® on the TrueBeam™ platform, Varian Medical Systems Inc., USA), with the treatment plan usually consisting of 2 arcs (full arcs ± avoidance sectors, or partial arcs). All patients were treated with on-line cone-beam CT (CBCT) image-guidance with 4 or 6 degrees of freedom positional correction prior to irradiation ± between arcs (standard for spine treatments)[26, 27].

Outcome

ADT-FS, the primary outcome, was defined as the time between the first day of SBRT and start of ADT[12, 14, 15, 17]. For the comparison of the ADT-FS between SBRT and non-SBRT treated patient, we used the time since the first diagnosis of oligometastatic disease till start of ADT. Start of ADT was decided by the treating physician based on clinical, laboratory and/or imaging arguments.

Disease progression was defined as two consecutive PSA rises (≥25% or an absolute increase of 2ng/mL) or new metastases on follow-up imaging such as [18F]FCH PET/CT, CT, MRI and/or bone scan. PSA response after SBRT was defined as a decrease of at least 25% compared to the last measured PSA before the SBRT. Follow up was defined as the first day of SBRT, until the last known PSA level, visit or death. In both cohorts, patients who did not start with systemic therapy during the follow up period were censored at the day of the last visit.

Statistical analysis

Statistical analysis was performed using SPSS Statistics, version 22.0 (IBM). Values are expressed as median and range, unless otherwise specified. A $P < 0.05$ was considered significant. The Kaplan Meier analysis was used to estimate the ADT free survival and PFS.

Results

We identified 43 patients with [18F]FCH PET/CT positive oligometastatic PC who received SBRT to a total of 54 metastases. Twenty patients could be included in the control cohort. Based on retrospective analysis, no important clinical or diagnostic reasons including pathology reports could be defined that determined the choice for SBRT versus no SBRT other than center specific guideline.

Patients in both cohorts are comparable in terms of time since initial diagnosis (7.3 year in SBRT group vs. 7.2 year in control cohort), PSA at diagnosis of oligometastatic disease (4.5 ng/mL versus 4.2 ng/mL), Gleason score (median 7), primary treatment and PSA at start of ADT (11.3ng/mL versus 12.1 ng/mL). The incidence of patients with more than one metastasis was higher in the control cohort than in the SBRT group (19.6% versus 55% p=0.003).

In the SBRT cohort, in 41/43 patients the PSA was measured every 3 months at least; 1 patient had an interval of 3.7 months and 1 patient had an interval of 4.5 months (without a rise in PSA during this interval). In the control group, PSA was measured at least every 3 months in 19 patients; 1 patient had an interval of 3.4 months.

Patient and disease characteristics of both cohorts are summarized in Table 1, the selection and inclusion of patients are shown in Figure 1.

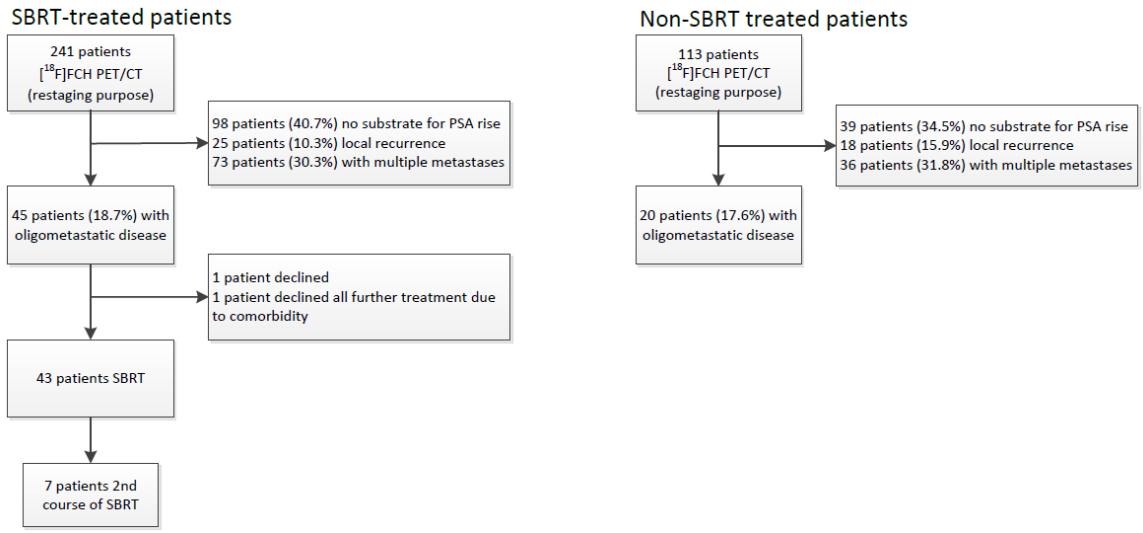

Figure 1 Selection and inclusion of patients

Table 1 Patient characteristics

Characteristics	**SBRT-treated patients (n=43)**	**Non SBRT patients (n=20)**	***P***
Age at inclusion (year)	68.0 (52.6-81.1)	69.6 (53.8-85.5)	.37
Follow up PC diagnosis (year) mean (IQR)	7.3 (4.7-9.9)	7.2 (5.0-14.6)	.91
Follow up from SBRT (year) mean (IQR)	2.6 (1.15-3.9)	NA	NA
Time between PC diagnosis and SBRT (year) mean (IQR)	4.7 (0.9-8.2)	NA	NA
PSA at PC diagnosis median (range) ng/mL	12.4 (4.2-94.9)	8.5 (2.7-27.4)	.015
PSA at start SBRT median (range) ng/mL	4.5 (1.0-42.9)	4.2 (0.9-14.0)*	.84
PSA nadir after SBRT median (range) ng/mL	2.0 (<0.1-48.7)	NA	NA
PSA at start ADT median (range) ng/mL	11.3 (2.2-71.9)	12.1 (3.2-24.7)	.76
Gleason score (median)	7	7	NS
9	4 (9.3%)	0	
8	8 (18.6%)	4 (21%)	
7	19 (44.2%)	11 (58%)	
6	12 (27.8%)	4 (21%)	
Primary treatment, number of patients (% of patients)			NS
Prostatectomy	24 (55.8%)	7 (35%)	
Prostatectomy+RT	5 (11.6%)	2 (10%)	
EBRT (+HT)	5 (+3) (18.6%)	4(+3) (35%)	
Brachytherapy (+HT)	4 (+2) (14.0%)	4 (20%)	
Number of metastases pp, number of patients (% of patients)			
1	35 (81.4%)	9 (45%)	.003
2	6 (14.0%)	8 (40%)	
3	1 (2.3%)	3 (15%)	
4	1 (2.3%)	0	
Type of metastases, number of patients (% of patients)			NS
Lymph node	33 (76.6%)	13 (65%)	
Bone	9 (20.9%)	7 (35%)	
Bone+lymph node	1 (2.3%)	0	
SBRT schedule (n patients) Gy			
3x10	29	NA	
3x15	4	NA	
5x7	10	NA	

Abbreviations: PC = prostate cancer, IQR = inter quartile range, SBRT = stereotactic body radiation therapy, PSA = prostate specific antigen, RT = radiotherapy, EBRT = external beam radiotherapy, HT = hormone therapy, pp = per patient, Gy=Gray

**PSA at date of diagnosis of oligometastatic disease by [18F]FCH PET/CT*

SBRT treated patients

Thirty-three patients had lymph node metastases (n=41 lymph nodes), 9 patients had bone metastases (n=10 lesions) and 1 patient had both bone (n=2) and lymph node (n=1) metastases. The median FU was 2.6 year (IQR 1.15-3.9). Eight patients were referred from other hospitals for [18F]FCH PET/CT and subsequent SBRT; 7 patients underwent imaging in another hospital and were referred for SBRT only.

A post-SBRT PSA response was seen in 29 patients (67.4%, with an undetectable PSA in 6 patients), in 1 patient the PSA remained stable for 8.3 months, and the other 13 patients showed PSA progression in the months after the SBRT.

Median time between the start of SBRT and the start of ADT, was 15.6 months (95% CI 11.7-19.5) for the SBRT-treated group. The ADT-FS for patients with an initial PSA response was 25.7 months (95% CI 9.0-42.4). Patients without an initial PSA response had a median ADT-FS of 10.4 months (95% CI 10.2-10.5, p=0.02; Figure 2). The median PSA at the start of ADT was 11.3 ng/mL (range 2.2-71.9).

Of the 29 patients with an initial PSA response, 18 patients had progressive disease (documented PSA progression) during follow-up (after a median of 11.1 months, 95% CI 6.9-15.4), of whom 14 started ADT. Median FU from start of SBRT for the 11 patients without disease progression was 13.3 months (95% CI 7.1-19.4). Seven patients underwent a second course of SBRT for oligo-progressive disease, with a median time between the first and second course of SBRT of 19.8 months (95% CI 0.0-46.8). Median ADT-FS from start of the first SBRT was 32.1 months (95% CI 7.8-56.5).

Nine patients had progressive disease during ADT-use (development of castration resistant PC (CRPC)), with a median time on ADT of 17.5 months, and a time between diagnosis of the metastases and CRPC of 25 months.

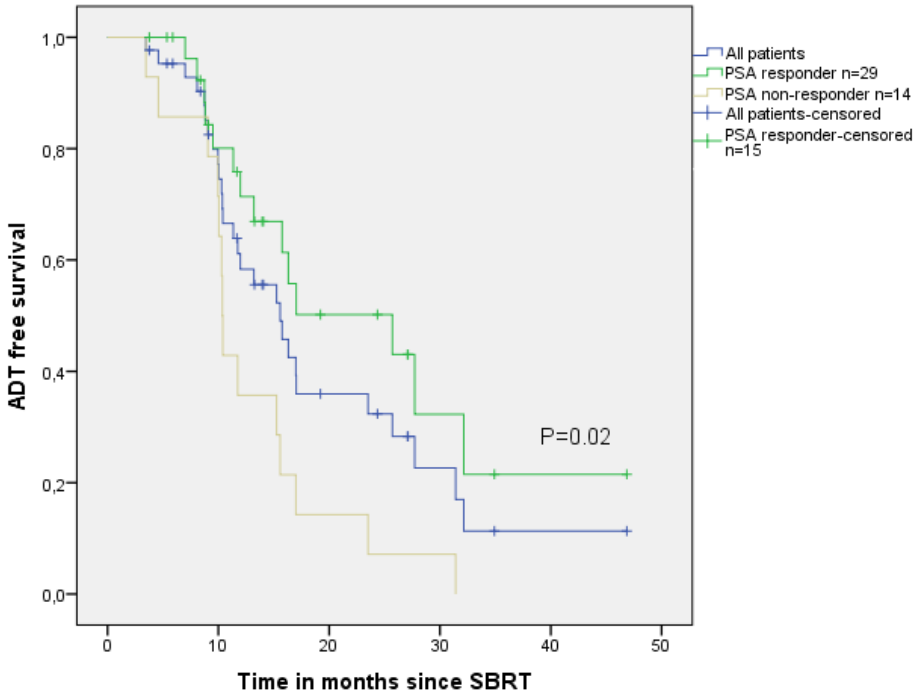

Figure 2 Androgen Deprivation Therapy (ADT)- Free Survival; Time Between Start of Stereotactic Body Radiotherapy and Start of ADT

Pattern of disease progression (SBRT treated patients)

Seventeen patients had a second [18F]FCH PET/CT because of a rising PSA after the first course of SBRT. The median time interval between the pre-SBRT [18F]FCH PET/CT and the scan at progression after SBRT was 12.6 months (IQR 10.3-26.3). Eight of these 17 patients did not have a PSA response after SBRT. Two patients had no visible lesions and in the other 15 patients the rise in PSA could be attributed to lesions outside the initial high dose radiation volume. In 1 patient with progression in a lymph node, this was, in retrospect, seen on the pre-SBRT CT scan (it had a 3-mm diameter and was PET negative, thus not being considered suspicious and therefore not included in the high dose radiation volume). The scan of another patient showed disease in a node located adjacent to the treated node, that had not been included in the high dose volume.

In 15 of 17 patients, the treated metastases showed no [18F]FCH uptake on the second [18F]FCH PET/CT post-SBRT. In the 2 remaining patients, the uptake in the treated metastases had strongly diminished to the extent that they were not suspected of malignancy. The findings on the second [18F]FCH PET/CT (the sites of recurrence) are shown in Supplemental table 1.

Of the 13 patients with lymph node metastases, recurrence was observed in new lymph node(s) in 12 patients (of whom 2 had new bone metastases as well) and only in bone in the remaining patient. Of the 4 patients initially treated with SBRT for bone metastases, 2 progressed elsewhere with multiple bone lesions, and 2 patients had a single positive lymph node. In 4 patients, a [18F]FCH PET/CT was performed after a second course of SBRT. In 1 of these patients, a lymph node treated during the second course of SBRT showed persisting but lower than baseline 18F-FCH uptake (time between the scans 12.6 months, time between SBRT and scan 11.6 months).
In 21 patients who underwent a [18F]FCH PET/CT after the first or second cycle of SBRT, 25 lesions were treated. Of these 25 lesions, all but one were considered metabolically responsive, resulting in a metabolic cure rate of 24 of 25.
An overview of the locations of recurrence is provided in Supplemental table 1.

Toxicity

Medical records revealed some form of short term SBRT related toxicity in 4 patients (9.3%): 1 of the patients with bone metastases reported a pain flare (grade I), 3 patients reported gastro-intestinal side effects (grade I in 1 patient, grade II in 2 patients). We did not find any case of long term or late toxicity.

Control group

As the patients in the control cohort did not have had SBRT, the ADT-FS was calculated from the date of diagnosis of oligometastatic disease till start of ADT (this definition was also used for the SBRT-treated patients in the comparison of these cohorts).
The time from the diagnosis of oligometastatic disease to the start of ADT was significantly longer for the patients treated with SBRT than for patients in the control cohort (median of 17.3 (95% CI 13.7-20.9) vs. 4.19 (95% CI 0.0-9.0) months), P<0.001, (Figure 3). The PSA at start of ADT was comparable between both groups (11.3ng/mL versus 12.1).
Once ADT had been started the subsequent PFS (time to castration resistance) was comparable between the 2 groups, with a median of 31.5 months for patients treated with SBRT versus 26.9 months for patients with active surveillance, P=0.54. As shown in Figure 4, this results in a longer time between diagnosis of the oligometastatic disease and castration resistant prostate cancer (CRPC) for patients treated with SBRT, P=0.020.

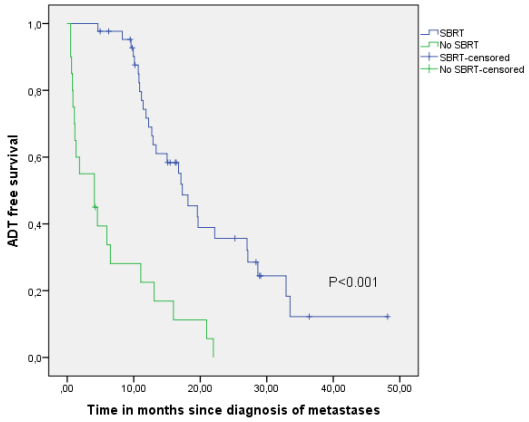

Figure 3 Androgen Deprivation Therapy (ADT)-Free Survival for Patients Treated With Stereotactic Body Radiotherapy (SBRT) Versus Non-SBRT

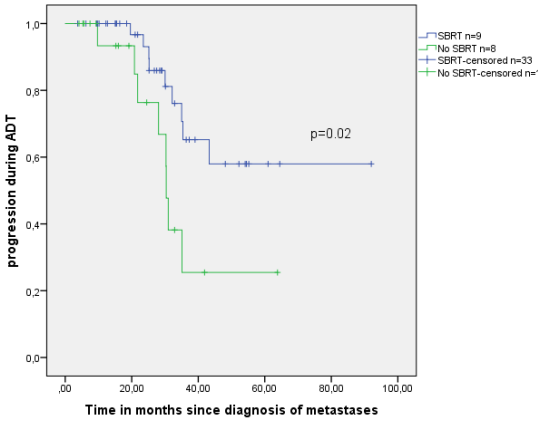

Figure 4 Time in Months Between Diagnosis of Oligometastatic Disease and Castration-Resistant Prostate Cancer (Patients Not Yet Using Androgen Deprivation Therapy (ADT) Included in the Censored Group)

[18F]FCH PET/CT versus CT-scan or MRI

Seven patients with 8 lymph node metastases and 1 bone metastasis underwent a diagnostic CT-scan prior to the [18F]FCH PET/CT. One lymph node and the bone metastasis were not seen on this conventional CT-scan. All other patients underwent a low-dose CT-scan for attenuation correction and anatomical correlation, as a part of the hybrid [18F]FCH PET/CT; 4 choline accumulating lymph nodes were considered radiologically not suspicious (all <6 mm in diameter) on this CT-scan, and were detected by the uptake of [18F]FCH.

Two patients with bone metastases underwent an additional MRI scan, which revealed the same metastases as the [18F]FCH PET/CT. None of the patients underwent a bone scan prior to the [18F]FCH PET/CT.

Discussion

The results of this study suggest that the initiation of ADT, and its side effects, is significantly delayed by salvage SBRT in patients with [18F]FCH PET/CT detected hormone sensitive oligometastatic PC. In addition, when progression occurs after SBRT, the PFS during ADT is comparable to patients who were not treated with SBRT. This may result in a delay in the development of CRPC which might suggest the potential for a positive effect on overall survival as well. However, this remains unproven and the impact on long term survival of delaying ADT in this patient population is currently uncertain.

This study differs from previous publications in that it includes a control cohort comprising patients with [18F]FCH PET/CT detected oligometastatic cancer not treated with SBRT. The homogenous cohort of patients, all treated with SBRT for [18F]FCH PET/CT detected oligometastatic progression, represents one of the largest series reported in literature.

Our results are broadly in line with other recently published studies (using both [18F]FCH PET/CT and [18F]FDG PET/CT to identify oligometastatic disease), despite some differences in study design and patient population. Although oligometastatic disease has generally been defined as ≤5 lesions[9, 28], in practice the majority of patients who receive local therapy, have only 1 or 2 lesions (95% in this study) and patients with fewer lesions may have a better prognosis[9]. We therefore selected a more conservative definition of oligometastatic disease for this analysis, of ≤4 lesions.

Pasqualetti *et al.* treated 23 patients (≤3 lesions detected by [18F]FCH PET/CT), with repeated SBRT until patients developed> 3 lesions. They reported an ADT-FS of 39.7 months (95% CI 17.2-62.1 months), which is comparable to our subgroup of 7 patients who received a second course of SBRT (median ADT-FS of 32.1 months[12]).

Decaestecker *et al.* performed a prospective study of repeated SBRT in 50 patients (70 bone/lymph node lesions) with ≤3 metachronous metastases treated between 2005-2013[14]. Sixteen patients had a second course of SBRT, 4 patients a third and one a fourth. Eighteen patients had a [18F]FCH PET/CT, and 32 [18F]FDG PET/CT. They found an ADT-FS of 25 months (95% CI 20-30 months).

Ost *et al.*, reported pooled patient data representing 7 institutes (n=119 patients, 163 lesions)[13]. Most patients were diagnosed with oligometastatic disease using [18F]FCH PET/CT (71%). Fifty-nine of the included patients did not receive adjuvant ADT; the median PFS (instead of our endpoint ADT-FS) of this subgroup was 18 months, versus 25 months for patients who did receive adjuvant ADT (p=0.09).

Consistent with these studies, we found a very high rate of local control (no definite local failures). We also observed persisting [18F]FCH PET activity, lower than pre-SBRT baseline, in some lesions. This correlates with [18F]FCH PET findings after SBRT at other locations and highlights that persisting low level activity should not always be interpreted as indicative for recurrence[29, 30].

An [18F]FCH PET/CT was performed in 8 patients without a PSA response after SBRT, and none of these patients showed uptake in the SBRT treated lesions. This suggests that patients without a response already had more advanced disease than initially established (i.e. false negative [18F]FCH PET/CT). With new, more sensitive imaging methods, such

as prostate specific membrane antigen (PSMA) PET/CT, this problem might be reduced, facilitating better selection of patients[31].

We acknowledge several limitations. The promising initial results for SBRT are based on retrospective or observational single arm studies, in heterogeneous patient groups. This hinders definite conclusions. Also in this study, due to the retrospective design with the associated limitations, we were not able to randomize the patients. Although no patients with ≤4 metastases were excluded for SBRT (as shown in Figure 1), the percentage of patients with more than 1 metastasis was higher in the control cohort, and may have influenced the outcome of this analysis. Still, we are convinced that this influence is minimal and that the results implicate a true clinical benefit of SBRT in this group of patients.

Start of ADT was determined by the treating physician. Despite the fact that we did not notice important differences in criteria for start of ADT between both centers (and the PSA at start of ADT was comparable between both cohorts), individual reasoning might have influenced the moment of ADT start.

In none of the previous studies, metastatic disease was proven by histopathological evidence nor was this the case in our analysis. However, the lesions are all very suspicious on imaging and in combination with a rise in PSA, histopathological evidence seems to be unnecessary.

Interestingly, the first prospective randomized phase II trial in patients with oligometastatic recurrence of prostate cancer (the STOMP trial, NCT01558427) is running and aims to randomize 62 patients between active surveillance and metastases directed therapy (surgery or SBRT) and is estimated to complete in 2017[32]. The primary endpoint of this study is ADT-FS.

Conclusion

This study provides evidence that stereotactic body radiation therapy for the first recurrence of metabolically active oligometastatic disease on [18F]FCH PET/CT in patients with hormone sensitive prostate cancer can safely postpone ADT.

Supplemental table 1 - Locations of Initial Oligometastatic Disease, and Location of Metastases Post-SBRT

Patient	Localisation first metastases	Metastases post-SBRT	Recurrent metastases in high dose SBRT volume	Time between scans (months)
1	Distal left para-iliac lymph node	Lymph node para-vertebral (L5) left Dorsal of left m. psoas major Ventral of right m. iliacus	no	13.1
2*	Distal left para-iliac lymph node	Rib 5, vertebra Th 7, para-aortal, para-iliac and pre-sacral lymph nodes	no	10.1
3	Lymph node medial of left iliac bones	2 para-rectal lymph nodes	no	10.5
4	Lymph node medial of right acetabulum	Lymph node para-iliac right	no	20.1
5	Lymph node medial of right acetabulum, lymph node pre-sacral right	Aorto-caval lymph node	no	21.2
6*	lymph node para-iliac right	No metastases, local recurrence?	no	9.9
7	Iliac lymph node left	Lymph node pelvis right	no	20
8*	Prevertebral lymph node, (promontorium, caudal of aortic bifurcation)	Lymph node cranial of aorta bifurcation, vertebra Th10	no	12.0
9	Pre-sacral lymph node	Lymph node para-vertebral (L5)	no	28.4
10	Lymph node para-iliac right	Para-iliacal right, para-aortal and aorto-caval lymph nodes	no	35.6
11	Lymph node cranial-medial of fobturator foramen right	Pre-sacral left and right, para-iliacl left lymph nodes	no	10.1
12*	Lymph node obturator right (2 lymph nodes)	Vertebra Th 9, iliac bone	no	5.18
13*	Lymph node peri-rectal left	Pelvis left	no	20.0
14*	Vetera Th 9, iliac bone	Lymph node para-iliac	no	6.0
15	Vertebra L3	Iliac bone right, vertebrae C3, L2, L4	no	16.8
16*	Left iliac bone	Iliac bone left, ischium, acetabulum right, rib 1+5 right and 2+7 left, vertebrae Th3, Th7, Th8, L2, L3	no	11.2
17*	Vertebra L5	Para-iliac lymph node right	no	15.9
				Median 13.1 Mean 15.7

**Patient without a PSA response after SBRT*

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