

# Multimodal Primary Treatment of Metastatic Prostate Cancer with Androgen Deprivation and Radiation

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**Abstract.** *Aim: We combined anti-androgen therapy with radiotherapy in a first-line setting for metastatic prostate cancer aiming to cause maximal cancer-cell death to delay the emergence of castration-resistant disease. Materials and Methods: In this non-randomized retrospective series of 46 patients, the initial median prostate-specific antigen (PSA) was 98.5 µg/l (range=6.7-15,500), median Gleason score 9 and most men had at least T<sub>3</sub>N<sub>1</sub>M<sub>1</sub> disease. All patients received luteinizing hormone releasing hormone analog or degarelix with bicalutamide. If PSA remained above 1 µg/l, docetaxel was initiated. At PSA nadir, all patients received radical radiotherapy of the prostate. Results: The median follow-up time was 4.38 years (range=0.36-11.24). Most radiotherapy-related adverse events were grade 1 and transient. There were no grade 4 events. Overall survival (OS) at 5 years was 81.3%. Conclusion: The feasibility and safety of aggressive multimodality treatment were good resulting in an excellent median OS of 8.35 years.*

Androgen deprivation therapy is the only treatment recommended by the U.S. National Comprehensive Cancer Network and Finnish National Current Care Guidelines for primarily metastatic prostate cancer (PCa) (1, 2). In 2016, the European Association of Urology added a recommendation of docetaxel in combination with hormonal therapy as primary treatment of metastatic PCa for patients who are fit enough for chemotherapy (3). Radiotherapy and radiopharmaceuticals, such as samarium-153 (<sup>153</sup>Sm-EDTMP) or radium-223 (<sup>223</sup>Ra), are typically reserved only for palliation, when bone metastases are widespread.

Hormonal therapies are well-established and initially effective in most patients but the problem is that castration-resistant disease eventually emerges. Approximately 91-93% of patients with metastatic castration-resistant prostate cancer (CRPC) have bone metastases (4, 5). The expected survival has been increasing over the past few years to the current estimate of 3.5 years (6).

Docetaxel was approved for CRPC in 2004 and cabazitaxel for docetaxel-resistant disease in 2010 (4, 7). When metastatic CRPC progresses, and if the prostate has not been treated, the main non-skeletal threat is urinary retention. This situation may require catheterization or, even, renal pyelostomies, leading to poor prognosis and quality of life (8). Other risks include intensive- and poorly-manageable pain, fractures, spinal-cord compression and paraplegia, infections, fatigue, and death.

Prostate radiotherapy can significantly improve the quality of life and prevent obstructive urinary symptoms, even in the metastatic setting (9). The use of radical doses results in excellent prophylactic and palliative results. The additional combination of irradiation with hormone therapy

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can further prolong the survival of PCa patients with lymph node metastases (10).

Intensity-modulated radiotherapy (IMRT) became available in the late 1990s and volumetric-modulated arc therapy (VMAT) radiotherapy technique in the late 2000s, enabling optimized dose distributions and, especially, reducing normal tissue doses. High-dose radiotherapy combined with effective systemic therapy might minimize the number of PCa cells in the prostate and in pelvic lymph nodes, despite the disease being metastatic. Moreover, the VMAT technique makes it possible to irradiate pelvic-bone metastases, lymph nodes and prostate in tandem and with different doses for each target. The active lesions can be targeted even more precisely when dose planning computer tomography (CT) is registered with magnetic resonance imaging (MRI),  $^{18}\text{F}$ -sodium fluoride - ( $\text{Na}^{18}\text{F}$ ),  $^{18}\text{F}$ -fluoromethylcholine - ( $^{18}\text{F}$ -FCH) and/or  $^{68}\text{Ga}$ - and prostate-specific membrane antigen - labeled positron emission tomography - CT ( $^{68}\text{Ga}$ -PSMA-PET-CT).

Our objective was to use adaptive multimodal treatment in order to kill as many tumor cells as possible, on a body-wide level, in the setting of primarily metastatic PCa. Prostate-specific antigen (PSA) was used as a practical surrogate for good systemic control and for establishing the ideal timing for starting radiotherapy. In addition to radical local/locoregional radiotherapy, we used radiopharmaceuticals on a patient-by-patient basis to achieve systemic irradiation of skeletal metastases.

This is a non-randomized, retrospective register study based on patient records at Docrates Cancer Center, Helsinki, Finland. All patients had newly-diagnosed and previously-untreated PCa that was metastasized, at least, into the skeleton.

## Materials and Methods

Analysis of this patient series was authorized by the Finnish National Institute for Health and Welfare, Data Protection Ombudsman, as well as Population Register Centre, and conducted according to the principles of the Declaration of Helsinki. It included 46 consecutive patients who had histologically-confirmed prostate adenocarcinoma with bone metastases (Table I). Another unifying factor for all patients was the same oncologist who gave the primary treatment and provided the contouring and specifications of targets and organs at risk regarding radiotherapy.

**Screening.** Screening (Table I) was performed with whole body CT, bone scintigraphy and MRI or (from 2010 onwards) PET-CT (Siemens Biograph 6; Siemens Magnetom Espree, Erlangen, Germany) using  $^{18}\text{F}$ -choline,  $^{18}\text{F}$ -Fluoride or, most recently (from October 2015),  $^{68}\text{Ga}$ -PSMA. Most of the patients underwent endorectal multiparametric MRI (1.5T; Siemens Magnetom Espree) before diagnostic biopsies.

**Systemic therapies.** The treatment strategy was the same for every patient in this fairly homogenous patient group: instead of using androgen deprivation alone we strived to use several different

treatments to reduce the number of cancer cells in the body as low as possible, prior to initiation of radiation therapy.

All patients underwent castration with luteinizing hormone-releasing hormone (LHRH) analogs or LHRH antagonist as primary treatment. In addition, anti-androgen bicalutamide commenced with a daily dose of 150 mg following a single fraction breast irradiation of 12 Gy (6-9 MeV) for reduction or prevention of mastodynia and gynecomastia.

Patients underwent PSA measurements once a month and if PSA decrease stopped, they received docetaxel 75 mg/m<sup>2</sup> every three weeks or 50 mg/m<sup>2</sup> every two weeks (4, 11). In Finland, abiraterone (orally 1 g daily together with 10 mg of prednisolone) became available in 2011 and enzalutamide (orally 160 mg daily) in 2014 (12, 13).

Prior to 2010, docetaxel was the only chemotherapy shown to yield a survival benefit in metastatic CRPC. Therefore, the experimental combination of gemcitabine and oxaliplatin was used in selected patients (14, 15). Our practice was to administer gemcitabine 1,000 mg/m<sup>2</sup> together with oxaliplatin 85 mg/m<sup>2</sup> every two weeks. Following approval, cabazitaxel 25 mg/m<sup>2</sup> every 3 weeks was used as second-line chemotherapy (7). All other therapies the patients received are listed in Table II.

**Radiation therapy.** When PSA nadir was reached, every patient received external beam radiation with radical doses (78 or 80 Gy in 2 Gy fractions) to the prostate. Dose planning CT was registered with MRI,  $^{18}\text{F}$ -Choline-,  $^{18}\text{F}$ -Fluoride- or  $^{68}\text{Ga}$ -PSMA-PET-CT in order to contour the target and borders of normal anatomical structures (organs at risk) as precisely as possible. In addition to the prostate, radiotherapy covered bone metastases without significantly increasing the dose of rectum as seen in Figure 1a.

The mean radiation dose to the prostate was 78.2 Gy in 44 men. Two patients received a combination of 50 Gy VMAT and 2x10 Gy high-dose-rate (HDR) brachytherapy. All patients received at least 50 Gy in 2 Gy fractions (mean=51) into seminal vesicles; in two patients, the dose was increased up to 79.5 Gy.

Regional, as well as retroperitoneal or para-aortic, lymph nodes were treated with 45-50 Gy, which was escalated to 59.4-76 Gy to PET-CT active metastases (Figure 1b-d). The treatment of bone metastases was tailored: single fractions ranged from 1.8 to 3.5 and total doses from 38.6 to 76.5 Gy depending on the location and number of bone metastases. The total radiation dose of pelvic lymph nodes was at least 45 Gy given in 25 fractions.

The radiation technique used before 2009 was IMRT, after which the VMAT RapidArc replaced it. The radiation therapy technique used in the treatment of concomitant bone metastases has been presented in detail by Kiljunen *et al.* (16).

**Radiopharmaceuticals.** Radiopharmaceuticals were used to treat 32 patients who had relatively large and diffuse bone metastases Table III, in order to decrease the tumor burden and consequently to achieve better disease control. It was noteworthy that bone metastases were active in  $\text{Na}^{18}\text{F}$ -PET-CT, despite immeasurable PSA, providing the rationale for early  $^{223}\text{Ra}$  therapy (Figure 1e). We switched from  $^{153}\text{Sm}$  (1 mCi/kg) to  $^{223}\text{Ra}$  (55 kBq/kg) in February 2013.

**Follow-up.** Blood parameters were monitored monthly and later once every three or six months. If PSA increase occurred or patients had any possibly cancer-related symptoms, we attempted to localize the relapse by scanning with PET-CT, after which we

Table I. Baseline characteristics and TNM dissemination. Three patients had urinary retention at baseline.

Age at diagnosis (years)		
Median		63
Range		39-86
Initial prostate-specific antigen (PSA) (µg/l)		
Median		98.5
Range		6.7-15 500
Mean		658
Gleason Score		n
7		7
8		14
9		20
10		5
Staging		n
T	1	1
	2	4
	3	21
	3b	6
	4	14
N	0	18
	1	28
M	0	0
	1	46
Metastatic sites		n
Bones		46
Pelvic lymph nodes		24
Other lymph nodes		17
Lung		1

considered if there was a need for new irradiation with VMAT RapidArc. One of our patients received 3x9 Gy salvage HDR brachytherapy for local relapse.

## Results

All patients presented with aggressive, high-risk, high-volume disease. Initial median PSA was 98.5 µg/l (range=6.7-15,500), mean PSA 658 µg/l, median Gleason score 9 and most men had at least T<sub>3</sub>N<sub>1</sub>M<sub>1</sub> disease (Table I). One patient had T<sub>1</sub> classification but his initial PSA was still 1,000 µg/l reflecting very high-volume disease. Altogether, 24 patients had metastases in obturator, parailiac or in presacral lymph nodes, while 17 had metastases disseminated in inguinal, retroperitoneal, mediastinal or supraclavicular lymph nodes. Of 46 patients, 22 achieved PSA 1 µg/l or lower before prostate radiotherapy.

Table II. All given therapies excluding castration, bicalutamide, volumetric-modulated arc therapy (VMAT) radiotherapy and radiopharmaceuticals to 46 patients.

Therapy	n
Zoledronate, ibandronate or denosumab	41
Docetaxel	30
Cabazitaxel	11
Abiraterone	24
Enzalutamide	19
Gemcitabine + oxaliplatin	8
Syklofosfamide	2
Doxorubicin	2
Carboplatin + etoposide	2
Cetuximab	1
Vinblastine + estramustine	1
Vinorelbine	1
Pembrolizumab in trial	1
Other: Salvage HDR brachytherapy	1

HDR, High-density rate. Before VMAT, 13 patients received docetaxel and two patients received abiraterone.

Table III. Description of all 43 radiopharmaceutical treatments given to 32 patients.

Radiopharmaceutical ± chemotherapy	n
<sup>153</sup> Sm alone	14
<sup>153</sup> Sm + mitoxantrone	1
<sup>153</sup> Sm + mitoxantrone and <sup>153</sup> Sm alone	1
<sup>153</sup> Sm + mitoxantrone and <sup>153</sup> Sm + docetaxel	2
<sup>153</sup> Sm + mitoxantrone and <sup>223</sup> Ra	2
<sup>153</sup> Sm + docetaxel and <sup>223</sup> Ra	1
<sup>153</sup> Sm and <sup>223</sup> Ra	5
<sup>223</sup> Ra alone	5
<sup>177</sup> Lu-PSMA	1

<sup>153</sup>Sm, Samarium-153; <sup>223</sup>Ra, Radium-223; <sup>177</sup>Lu, Lutetium-177; PSMA, prostate-specific membrane antigen. Two patients received <sup>153</sup>Sm before VMAT radiotherapy. Mitoxantrone was given 4 mg/m<sup>2</sup>/week x6 and docetaxel 30 mg/m<sup>2</sup>/week x4. One 90-year-old, WHO 0 patient received <sup>177</sup>Lu-PSMA at Universitätsklinik für Nuklearmedizin, Innsbruck, Austria.

**Radiation therapy.** All patients received radical radiation doses to the prostate (Table IV). Altogether, 11 patients received irradiation up to the retroperitoneal lymph node region and 24 received additional planning target volumes for their metastases (1-8 metastases per patient) (Table IV, Figure 1b-d). Generally, we followed the recommendations of QUANTEC and RTOG as described recently (16).

**Tolerability.** Adverse events that occurred during radiotherapy or were present one year after definitive VMAT are presented in Table V (17). Events related to the treatment

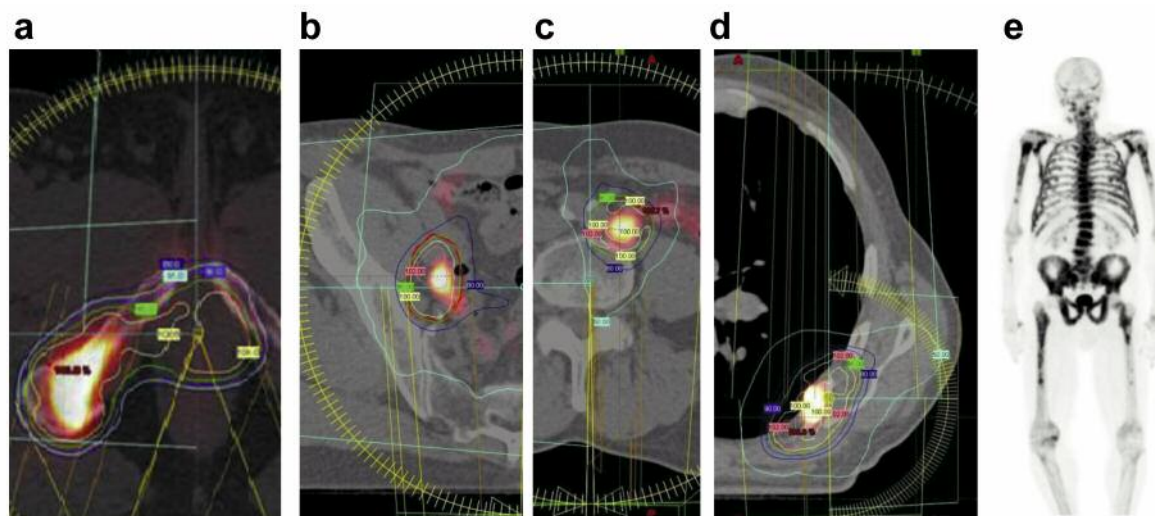


Figure 1. Multimodal treatments for three patients. (a) Dose distribution of VMAT radiotherapy on the level of prostate and ischial tuberosity of a 71-year-old patient with initial PSA 6.78  $\mu\text{g/l}$  while receiving finasteride, Gleason score 8,  $\text{T}_3\text{N}_1\text{M}_1$ . Bone metastasis in right ischial tuberosity treated up to 60/2 Gy (targeted by  $\text{Na}^{18}\text{F}$ -PET-CT), prostate 78/2 Gy, seminal vesicles 50/2 Gy and pelvic lymph nodes 45/1.8 Gy. (b-d) 79-year-old, initial PSA 26.7  $\mu\text{g/l}$  while receiving finasteride, Gleason score 9,  $\text{T}_3\text{N}_1\text{M}_1$ . Radiation doses: prostate 78/2 Gy, seminal vesicles 50/2 Gy, pelvic and retroperitoneal lymph nodes 45/1.8 Gy.  $^{18}\text{F}$ -FCH-PET positive lymph nodes in Figure 1b and 1c treated up to 45/1.8 Gy + 26/2 Gy respectively. The rib in Figure 1d targeted by  $\text{Na}^{18}\text{F}$ -PET-CT treated up to 52.5/3.5 Gy. (e) 74-year-old, initial PSA 236  $\mu\text{g/l}$ , alkaline phosphatase 2,498 U/l, Gleason score 9,  $\text{T}_3\text{N}_1\text{M}_1$ .  $\text{Na}^{18}\text{F}$ -PET-CT showed active uptake, despite earlier castration chemotherapy and radical radiotherapy to the prostate with VMAT radiotherapy and HDR brachytherapy. Therefore, the patient received  $^{223}\text{Ra}$  for 6 cycles, despite PSA <0.05  $\mu\text{g/l}$ .

of metastases did not exceed grade 1. One patient experienced grade 2-3 pollakisuria and nocturia, one had weak urinary stream, three required catheterization for urinary retention and one experienced incontinence. However, the latter patient used high-dose diuretics due to heart problems, which may have contributed. With the benefit of hindsight, we think that radiotherapy could have been better optimized with this patient by using a more complicated dose plan with 4 arcs instead of 2. One patient experienced transient grade 3 diarrhea, which occurred at the beginning of radiotherapy and resolved before its completion. The main result was that one year after radiation therapy, none of our patients had worse than grade 1 gastrointestinal events and only one patient experienced a grade 2 genitourinary event.

**Survival.** Eleven patients died from PCa, of whom eight had PSA higher than 1  $\mu\text{g/l}$  (median=3.2  $\mu\text{g/l}$ , range=1.07-104  $\mu\text{g/l}$ ) just before radical radiotherapy began. One patient died at the age of 90 due to pneumonia, which was related to a traumatic hip fracture. He had immeasurable PSA at the time of his death.

The median follow-up time reached 4.38 years (mean=4.63, range=0.36-11.24). At 5 years, progression-free survival (PFS) was 21.6%. Median PFS was 3.03 years

(Figure 2). Overall survival (OS) was an impressive 81.3% at 5 years. Median OS was 8.35 years (Figure 3).

## Discussion

Patients with metastatic PCa can live up to 15 years, despite large skeletal metastases, if the disease is treated using all different modalities of hormone manipulations, chemotherapies, radiotherapy, radiopharmaceuticals and experimental approaches (18). It is also known that total urinary obstruction, usually caused by locally-progressing CRPC, can be treated with radical doses of radiotherapy (9). Radiotherapy, however, is not generally used when PCa is diagnosed in the metastatic phase.

We hypothesized that it would be useful to prevent urinary retention by using radiotherapy in earlier phases of the disease. Given that the prostate is the source of metastases, we anticipated that local treatment could significantly reduce further seeding and dissemination of the disease. The best timing for radiation therapy might be immediately during the remission, which will be achieved in most cases by castration alone.

Men can live over 10 years when treated with castration alone, although this does not occur in the majority of patients (19). This is unachievable for the most aggressive tumor

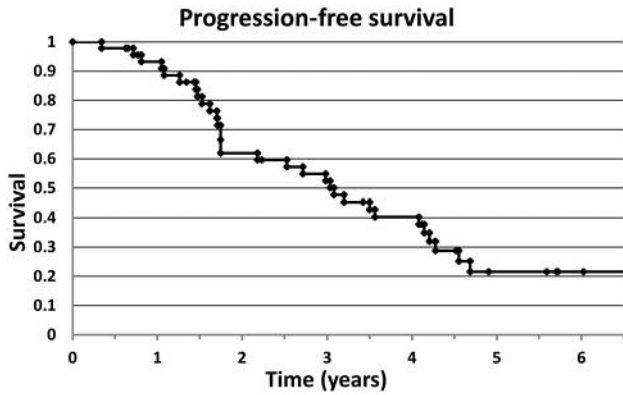


Figure 2. Progression-free survival.

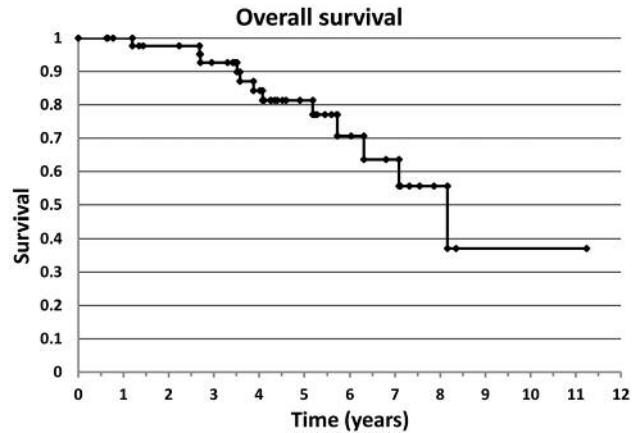


Figure 3. Overall survival. Data collected from the Population Register Centre of Finland.

Table IV. The number of patients (n) with different planning target volume dose prescriptions for primary pelvic radiation therapy.

Dose range	Prostate cancer radiotherapy prescription			Metastatic prostate cancer radiotherapy prescription		
	Prostate	Seminal vesicles	Regional lymph nodes	Bone metastases**	Lymph node metastases	Retroperitoneal/para-aortic lymph nodes
	n (mean dose [Gy])	n (mean dose [Gy])	n (mean dose [Gy])	n (mean dose [Gy])	n (mean dose [Gy])	n (mean dose [Gy])
76-80 Gy	44 (78.2)	2 (79.5)		3 (76.5)	1 (76.0)	
60-75 Gy				9 (66.0)	2 (66.7)	
50-59 Gy	2 (50.0*)	44 (51.0)	7 (50.4)	2 (50.1)	1 (59.4)	6 (50.3)
40-49 Gy			39 (45.0)	8 (43.0)		5 (45.0)
30-39 Gy				1 (38.6)		

\*High-density-rate (HDR) brachytherapy booster 2x10 Gy after the external beam radiation therapy. 2 Gy/fr equivalent total dose >116 Gy ( $\alpha/\beta=1.5\text{Gy}$ ). \*\*Fraction sizes range between 1.8 Gy and 3.5 Gy. Total dose calculated as 2 Gy/fr equivalent dose ( $\alpha/\beta=1.5\text{Gy}$ ).

types and in patients with high tumor volume, in particular. The response to castration may be lost within a couple of months, as seen in 13 patients in our practice (28.2%). In these cases, we immediately started docetaxel. The criterion for docetaxel initiation was that either PSA started increasing or it stopped decreasing.

In maximal androgen blockade studies, bicalutamide has been typically used at 50 mg, with the rationale being that patients' testosterone levels are low due to castration. Bicalutamide, however, prevents the effects of testosterone, not by binding to testosterone but by blocking its effect on androgen receptors that are numerous, despite low testosterone levels, suggesting that low dose may be suboptimal.

Japanese researchers showed that a higher dose of bicalutamide (80 mg), in combination with castration, significantly improved the survival of metastatic PCa without

impairing quality of life (20, 21). Recent studies of abiraterone and enzalutamide showed efficacy even in the castration-resistant phase, confirming that total eradication of the testosterone effect is worthwhile (12, 13). Therefore, we combined bicalutamide 150 mg and LHRH analogs or degarelix as first-line therapy.

VMAT enables concomitant radiotherapy of PCa and pelvic-bone metastases (16). This technique can be optimized by contouring targets with PET-CT. In the pelvis, the rationale for treatment of individual metastases at an early phase, together with the prostate, relates to the feasibility of covering of all lesions simultaneously. If radiotherapy is given just to the prostate and pelvic lymph nodes, it is more dose-limiting to treat other pelvic metastases later. Our experience suggests that long-term remission of pelvic lesions can be achieved with this

Table V. Adverse events recorded during volumetric-modulated arc therapy (VMAT) radiotherapy or one year after graded by common terminology criteria for adverse events (17).

	During radiotherapy					One year after radiotherapy				
	Grade									
	0	1	2	3	4	0	1	2	3	4
Adverse events related to urination	5	35	2	4	0	26	14	1	1	0
Adverse events related to bowel function	14	31	0	1	0	37	5	0	0	0
Other*	0	3	0	0	0	0	0	0	0	0

\*Esophagitis related to radiotherapy of mediastinal lymph nodes. Follow-up was less than one year for four patients. Erectile function was not recorded since all men were castrated.

approach. Further rationale for the treatment of individual PET-active metastases is provided by Gundem *et al.* who suggested that metastases can seed new metastases (22). If oligometastases could be controlled, dissemination might decrease.

To assess the feasibility of combining radiotherapy with castration, we assessed its tolerability. Some of our patients (28.2%) received docetaxel before VMAT radiotherapy, potentially increasing overall toxicity. No grade 4 or 5 adverse events were seen, however. The number of grade 3 events was low and all were reversible. All patients had recovered from adverse events by one year. Good tolerability of the combination of castration and irradiation was not surprising, since this is a routine approach in local high-risk PCa (23); however, here, we confirmed its safety in the metastatic setting also.

In 2004, docetaxel was demonstrated to provide a survival benefit in CRPC (4). In the STAMPEDE trial, docetaxel-treated patients had 50% survival at 5 years compared to 39% in the control group receiving the standard of care (androgen deprivation therapy) alone (6). In CHARTEED, the median OS was 57.6 months with androgen deprivation therapy combined to six cycles of docetaxel compared to 44 months with androgen deprivation therapy alone (24).

All PCa patients are not alike. Hinting at the presence of relevant subgroups, PSA decreased rapidly in half of the men reported here, while the other half needed chemotherapy to reach PSA nadir. Of note, Tarish *et al.* reported that castration mediates radiosensitization by impairing DNA-double-strand repair (25).

In 2005, Loberg *et al.* reported that radiopharmaceuticals can improve survival and be integrated within chemotherapy regimens, which Fizazi *et al.* confirmed with <sup>153</sup>Sm and docetaxel (26, 27). The seminal trial in this area was ALSYMPCA, featuring <sup>223</sup>Ra, which showed a clear survival benefit (28). Our practice is to give <sup>153</sup>Sm or <sup>223</sup>Ra as early as possible with the assumption that treatment benefits are greater when tumor load is low.

The main concern related to early treatment with marrow toxic agents, such as radiopharmaceuticals and chemotherapies, is the damage they can cause to hematopoiesis, thus potentially limiting the usability of subsequent regimens. Approximately 65% of our patients received docetaxel and 24% received cabazitaxel. In addition, we used several less routine chemotherapies. At the time of diagnosis of metastatic disease, 28% of our patients were 70 years or older, which forced us to be cautious with each therapy option available. Two patients were cytopenic when they died. It is possible that protracted treatment caused grade 3 leucocytopenia for one and grade 4 leucocytopenia and thrombocytopenia in the other. However, both patients had massive PCa progression in the bone marrow prior to death, which was probably the main cause of cytopenia. These patients survived 7.1 and 8.1 years, respectively.

The OS in this patient series was 81% at 5 years and median survival was 8.1 years. Both figures compare favorably to concurrent series reported for the same group of high-risk patients with poor prognosis. In both CHARTEED and STAMPEDE studies, the OS of patients with metastatic PCa was about 50% at 5 years (6, 24). Most recently, Rusthoven *et al.* retrospectively analyzed the impact of radiation combined to androgen deprivation in previously-untreated metastatic PCa compared to androgen deprivation alone (29). Median OS was 4.6 years and 5-year OS 49%. The main difference compared to our approach appeared to be that we also irradiated bone oligometastases and patients received radiopharmaceuticals if they had widely disseminated bone metastases. In general, the practice of irradiation of oligometastases seems to be increasing in popularity (30).

A common criticism of retrospective series relates to selection bias. To avoid this caveat, the patients reported here are consecutive patients. All of them had stage 4 disease. The initial PSA distribution was quite typical: 19.6% had initial PSA ≤20 µg/l; 32.6% had PSA >20 µg/l but ≤100 µg/l; 28.3% had PSA >100 µg/l but ≤500 µg/l; and 19.6% had PSA >500 µg/l. Even the age distribution was representative

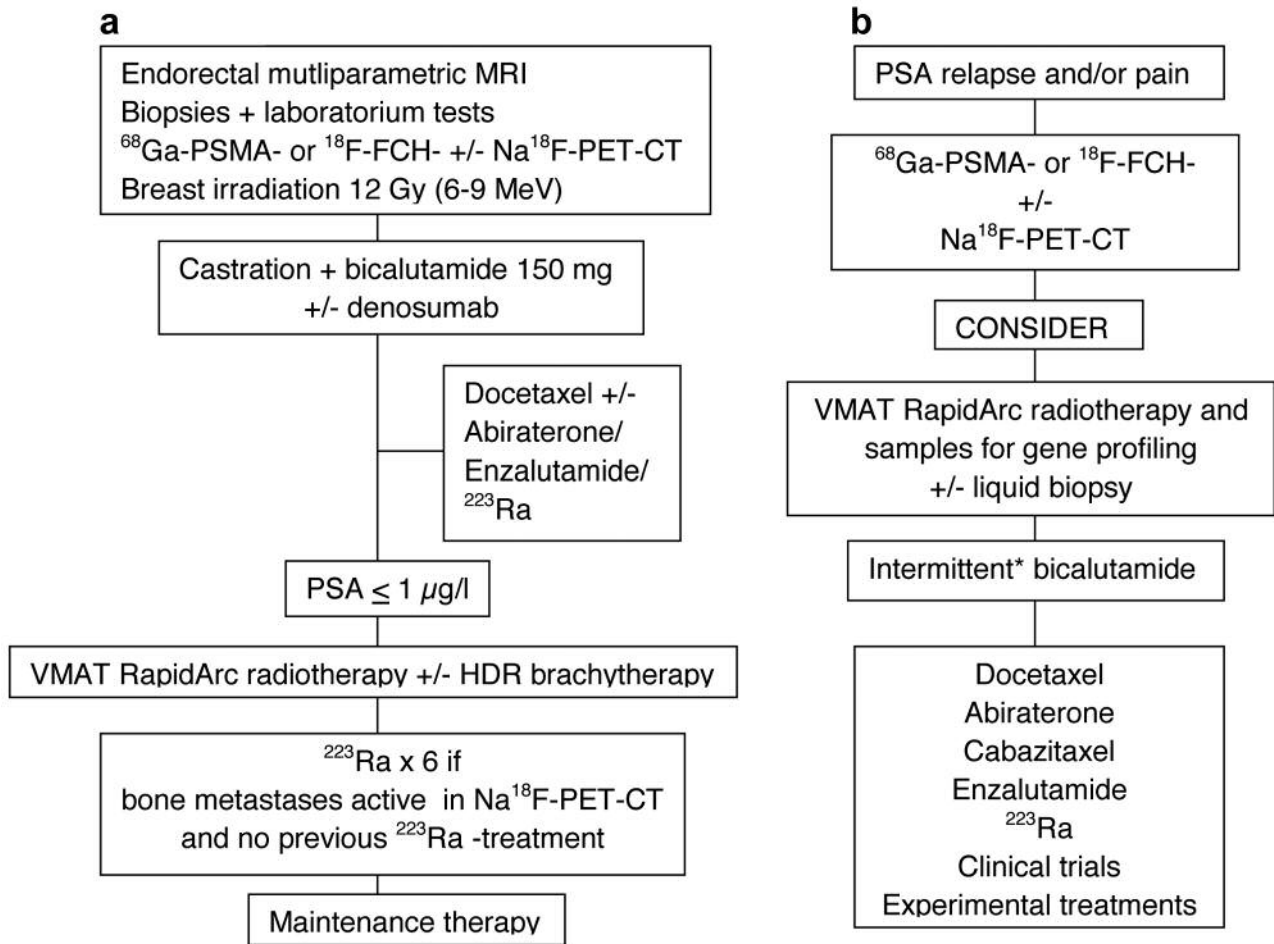


Figure 4. Algorithms for primarily metastatic prostate cancer. (a) Algorithm for diagnostic and treatment procedures in primarily metastatic prostate cancer. (b) Algorithm for follow-up and therapy options in possible relapse of primarily metastatic prostate cancer. \*Intermittent: 6 months on therapy, 6 months on pause; only if PSA level is low and active cancer cells are not visible in PET-CT or in other studies. MRI, Magnetic resonance imaging; <sup>68</sup>Ga-PSMA, Gallium-68-prostate-specific membrane antigen; <sup>18</sup>F-FCH, <sup>18</sup>F-fluoromethylcholine; Na<sup>18</sup>F, <sup>18</sup>F-sodium fluoride; PET, positron emission tomography; CT, computer tomography; <sup>223</sup>Ra, Radium-223; VMAT, volumetric-modulated arc therapy; HDR, high-density rate.

of PCa patients. All patients were treated according to the same principles, although scheduling and many details were adjusted individually in an adaptive manner.

The obvious weakness of any retrospective analysis is the fact that it is not prospective and randomized. However, many treatment innovations are first used in small patient series, prior to rigorous analysis in controlled trials. We feel our results are promising enough to take the approach forward into randomized trials (Figure 4a, b).

In conclusion, multimodal primary treatment of metastatic prostate cancer with both androgen deprivation and radiation is demonstrated to be potentially feasible in the patient series reported here. Impressive OS data encourages extension of this approach into clinical trials.

### Conflicts of Interest

T.J. is a founder of and shareholder in Docrates Cancer Center. T.H. has received travel support from MSD Finland, Sanofi, Eli Lilly, Janssen and Merck. T.H. has received lecture fee from Bayer. A.H. is shareholder in Targovax ASA. A.H. is employee and shareholder in TILT Biotherapeutics Ltd. and Aeruginosa Oy. A.H. has received travel support from BMS and LeoPharma. A.H. acts as consultant for Amgen Inc. A.K. is shareholder in Docrates Cancer Center.

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