



Original Research Article

PSMA-11-PET/CT versus choline-PET/CT to guide stereotactic ablative radiotherapy for androgen deprivation therapy deferral in patients with oligometastatic prostate cancer

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ARTICLE INFO

Keywords:

Prostate cancer

SABR

Oligometastases

Androgen deprivation therapy

PSMA-11-PET

ABSTRACT

Background: In patients with oligometastatic recurrent prostate cancer, standard treatment is androgen deprivation therapy (ADT). However, ADT has many potential side effects that may result in impaired quality of life. Early identification to select patients suitable for stereotactic ablative radiotherapy (SABR) is of utmost importance to prevent or delay start of ADT and its side effects. Because Prostate-Specific Membrane Antigen-11-Positron Emission Tomography (PSMA-11-PET) has a higher sensitivity than choline-PET, we hypothesise that PSMA-11-PET based SABR results in longer response duration and subsequent longer delay in starting ADT than choline-PET.

Methods: Patients with oligometastatic (≤ 4 metastases) recurrent prostate cancer (with no local recurrence) based on PSMA-11-PET or choline-PET treated with SABR from January 2012 until December 2017 were included. Primary endpoint was ADT-free survival. Secondary endpoints were Prostate Specific Antigen (PSA) response after SABR and time to PSA rise after SABR.

Results: Fifty patients ($n = 40$ PSMA-11-PET and $n = 10$ choline-PET) with in total 72 lesions were included. Median follow-up was 24.3 months. PSMA-11-PET enabled eligibility of patients with lower PSA levels than choline-PET (median 1.8 versus 4.2 ng/mL, $p = 0.03$). The PSMA-11-PET group had a significant longer PSA response duration (median 34.0 months (95% confidence interval (CI), 16.0–52.0) versus 14.7 months (95% CI 4.7–24.7), $p = 0.004$) with a subsequent longer ADT-free survival (median 32.7 months (95% CI, 20.8–44.5) versus 14.9 months (95% CI, 5.7–24.1), $p = 0.01$).

Conclusions: With PSMA-11-PET we are able to select patients with oligometastatic recurrent prostate cancer suitable for SABR in an earlier disease stage at lower PSA levels. PSMA-11-PET guided SABR resulted in a significant longer response duration and ADT-free survival compared with choline-PET and can therefore prevent or delay ADT related side effects.

Introduction

In patients with oligometastatic recurrence from hormone-sensitive prostate cancer (without local recurrence), standard treatment is deferred androgen deprivation therapy (ADT) [1,2]. Unfortunately, ADT has many side effects and impact on quality of life, e.g. hot flushes, fatigue, decrease of libido, erectile dysfunction, loss of muscle and bone

mass and depression [3].

Stereotactic ablative radiotherapy (SABR) is a non-invasive treatment that provides good local control of localised tumour locations with minimal reported toxicity [4–6]. Another advantage is that it takes relatively little time as it is generally given in 3 to 5 high dose fractions. In other tumour types, e.g. lung cancer, colorectal cancer and breast cancer, metastasis directed therapy is often performed to achieve

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<https://doi.org/10.1016/j.ctro.2021.06.004>

Received 26 April 2021; Received in revised form 16 June 2021; Accepted 23 June 2021

Available online 29 June 2021

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prolonged disease-free interval or even to improve survival [7]. For patients with prostate cancer, SABR is usually performed to decrease the Prostate Specific Antigen (PSA) level and thereby to improve progression-free survival and postpone ADT [4]. The effect of SABR on progression-free survival is currently investigated in the ORIOLE trial, which randomises patients with oligometastatic disease between observation and SABR [8].

Positron Emission Tomography (PET) imaging initiated the practice of SABR for oligometastatic prostate cancer recurrences. Radiolabeled choline analogues (choline-PET) resulted in a better identification of metastatic lesions in prostate cancer patients compared to fluorine-18-fluorodeoxyglucose (18F-FDG)-PET that is mostly used for malignant tumours. With the subsequent introduction of radioactive labeled Prostate Specific Membrane Antigen (PSMA) ligands (which bind to the PSMA expressed on the surface of prostate cancer cells, often PSMA-11), the sensitivity to detect recurrent localisations was further increased [9].

However, PSMA-11-PET is still not the standard imaging modality for this group of patients in many countries and therefore comparing the treatment outcomes between choline-PET and PSMA-11-PET is of high clinical interest.

In this study we evaluated the clinical outcomes of patients treated by PSMA-11-PET and choline-PET based SABR. Primary endpoint was ADT-free survival. Secondary endpoints were initial PSA response after SABR and the time to PSA rise after SABR. Because of the earlier identification of suitable patients, we hypothesise that PSMA-11-PET based SABR results in longer response duration and delay in starting ADT compared to choline-PET.

Materials and methods

Patients and data

This retrospective evaluation of clinical data has been approved by the local institutional review board and considered not to be subject to the Medical Research Involving Human Subjects Act. Informed consent was obtained and patient data was retrieved via the local Datadesk. Data management by the researchers was carried out in accordance with the Dutch Personal Data Protection Act.

All patients treated with SABR between January 2012 and December 2017 at The Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital (NKI-AVL) for oligometastatic recurrence without local recurrence of previously treated prostate cancer were reviewed. Patients were referred by discretion of the treating urologist based on increased PSA levels.

Oligometastatic disease was defined as a maximum of 4 lesions (lymph node, bone or visceral) as detected by PET. We pragmatically choose 4 as cutoff for inclusion for our study, based on a recent consensus meeting [10]. Patients on hormonal treatment at start of SABR were excluded.

Choice for SABR was always discussed and decided in a multidisciplinary board and based on shared decision making. Other options were salvage lymph node dissection, tracer guided node picking in context of a clinical trial, hormonal treatment and wait and see policy. However, since the introduction of SABR in our hospital it has become a substantial part of the preferred treatment, because of the low morbidity and high local control rate. Considerations not to treat oligometastatic disease with SABR were for example location of the lesions, rate of PSA level rise and overlap with previous radiotherapy fields.

Registered patient and tumour characteristics were age, PSA levels (at primary diagnosis, at start SABR and all levels after SABR), TNM-stage, Gleason-score, primary treatment (radical prostatectomy, external beam radiation or brachytherapy) and duration of ADT adjunct to primary treatment. Furthermore, we registered radiotherapy treatment planning information (treatment date, dose, fractionation scheme, location, clinical and planning treatment volume (CTV/PTV), SABR related toxicity (scored by CTCAE-criteria v4) and start and date

of ADT. Follow-up was performed with maximum of 5 years after SABR.

Primary endpoint was ADT-free survival, defined as the interval between start of SABR and start of ADT. Initiation of ADT was based upon the physician's discretion and based on clinical and imaging factors and PSA results. Secondary endpoints were PSA response and PSA rise after SABR. PSA-response was defined as decrease in PSA level of $\geq 25\%$ compared with the last measured PSA level before start of SABR (since a national or international definition for PSA response is lacking, we choose this percentage according to a previous PSA evaluating study [4]). PSA rise was defined as 2 consecutive PSA rises > 0.2 ng/mL after prostatectomy and rising PSA level > 2 ng/mL above the nadir in patients treated with radiotherapy (according to the European Association of Urology guidelines at that time [11]).

Imaging procedures

All images were acquired using an integrated PET/Computed Tomography(CT)-scanner (Gemini II-TF or Gemini Big Bore TF, Philips Healthcare, Cleveland, OH, USA). PET images were acquired from mid-thigh to the base of the skull with 3 min per bed position, and with attenuation correction based on low-dose CT without intravenous contrast. Choline-PET was generally performed in case of PSA levels > 5 ng/mL or when PSA > 1 ng/mL and PSA doubling time < 3 months or Gleason score ≥ 8 , and images were acquired at 60 min after administration of 190 MBq [18F]methylcholine. PSMA-11-PET was generally performed in case of PSA levels > 0.2 ng/mL after prostatectomy and PSA levels > 2 ng/mL above the nadir in patients previously treated with radiotherapy, and images were acquired at 45 min after 100 MBq [68 Ga]PSMA-11. Choline-PET scans were performed until July 2016 and well balanced with PSMA-11-PET. In the last period of inclusion, all scans performed were PSMA-11-PET, due to the availability of the tracers and the hospital's policy.

Statistics

IBM SPSS statistics version 25.0 was used for statistical analysis. For PSA response and PSA rise chi square tests were performed, to analyse response duration and ADT-free survival Kaplan-Meier estimates were used. To compare baseline characteristics and analyse predictive factors for PSA response and ADT-free survival, chi square tests, Fisher's exact tests and T-tests were used, Pearson or Spearman correlations were calculated and linear regression analysis was performed. All p-values were two-tailed, and $p < 0.05$ was deemed statistically significant.

Treatment

Before start of SABR, all patients underwent a CT-scan of the tumour and surrounding tissues, and in patients with bone metastasis a Magnetic Resonance Imaging (MRI)-scan was also performed, for target definition of the detected lesions. A vacuum mattress was used for immobilization purposes during treatment preparation and radiation therapy.

The gross tumour volume (GTV) was considered as the CTV. For bone lesions the GTV was expanded with 2 mm to 6 mm to obtain the PTV depending on the location (and thereby the variability due to movement) of the metastasis. For lymph node metastases a margin from GTV to PTV of 3 mm or 5 mm was used (depending on the expected mobility of the lesion).

The SABR dose and fractionation scheme for lymph nodes was 5×10 Gy (biological equivalent dose (BED) 235 Gy, $\alpha/\beta = 2.7$ [11]) and for bone metastases 3×14 Gy (BED 260 Gy) (in case of costal lesions 5×10 Gy, BED 235 Gy). However, protocol exceptions were made upon the physician's discretion for 5 patients (proximity of an adjacent bowel loop ($n = 1$), location at narrow part of os ischium ($n = 1$), overlap with previous radiotherapy field ($n = 1$), favourable location ($n = 1$), unknown ($n = 1$)).

Radiation therapy was performed using external beam radiation with

Table 1
Patient and tumour characteristics.

	PSMA-11-PET (n = 40)	choline-PET (n = 10)	p
Age, years (mean, range)	68 (55–84)	68.5 (56–80)	0.84
Gleason score primary tumour (%)			0.75
6	7 (17.5%)	1 (10%)	
7	20 (50%)	5 (50%)	
8	6 (15%)	1 (10%)	
9	7 (17.5%)	2 (20%)	
Missing	0 (0%)	1 (10%)	
Primary treatment (%)			0.75
Brachytherapy	4 (10%)	0 (0%)	
External beam radiation	9 (22.5%)	3 (30%)	
Prostatectomy	27 (67.5%)	7 (70%)	
Number of metastases (%)			0.88
1	25 (62.5%)	8 (80%)	
2	11 (27.5%)	2 (20%)	
3	3 (7.5%)	0 (0%)	
4	1 (2.5%)	0 (0%)	
Type of metastasis (%)			0.48
Lymph node	21 (52.5%)	6 (60%)	
Bone	15 (37.5%)	3 (30%)	
Lymph node + bone	3 (7.5%)	1 (10%)	
Bone + liver	1 (2.5%)	0 (0%)	
PTV, mL (mean, range)	19.6 (2.7–55.7)	17.2 (3.1–36)	0.54
PSA at start SABR, ng/mL (median, range)	1.8 (0.23–8.4)	4.2 (1.1–17.8)	0.03
ADT after SABR (%)	20 (50%)	9 (90%)	0.03

PTV = planning treatment volume, mL = millilitre, ng = nanogram, PSA = prostate specific antigen, ADT = androgen deprivation therapy, SABR = stereotactic ablative radiotherapy.

a linear accelerator (Elekta, Sweden). The technique used was volumetric modulated arc therapy (VMAT).

Results

Fifty patients with in total 72 metastatic prostate cancer lesions treated with SABR were included from January 2012 until December 2017. Median follow-up was 24.3 months (interquartile range (IQR), 14.7–34.6). Overall survival at 3 years was 96% (median overall survival not reached). In 40 patients metastases were visualised by PSMA-11-PET, choline-PET was used in 10 patients. Patient and tumour characteristics are depicted in Table 1. There was no difference in

baseline characteristics, except for PSA at start of SABR, which was as expected to be lower in the PSMA-11-PET group (median 1.8 versus 4.2 ng/mL, $p = 0.03$). The type and number of metastases are listed in Table 1.

The majority of patients (56%, $n = 28/50$) had a PSA response after SABR whereby no difference was observed between the PSMA-11-PET and choline-PET group (57.5%, $n = 23/40$ patients versus 50%, $n = 5/10$ patients, respectively, $p = 0.47$). However, PSMA-11-PET imaged patients experienced a significant longer response compared with patients imaged by choline-PET (median 34.0 months (95% confidence interval (CI), 16.0–52.0) versus 14.7 months (95% CI 4.7–24.7), $p = 0.004$) (Fig. 1). Of all patients with PSA response, 39.3% ($n = 11/28$)

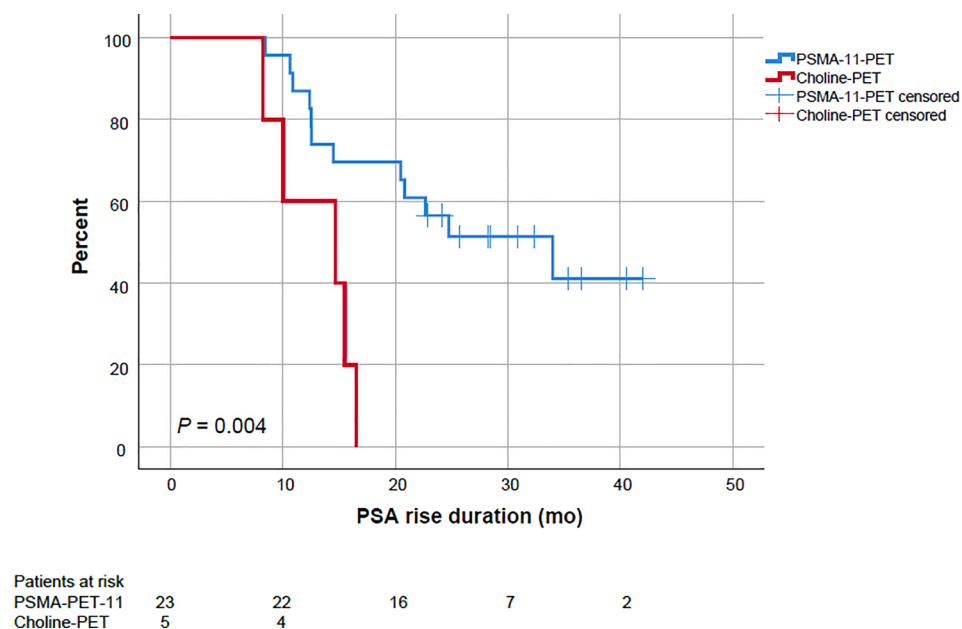


Fig. 1. Duration PSA response (responders).

had no PSA rise at the time of this evaluation (median 30.9 months, IQR 25.7–36.5). The other 17/28 patients (60.7%) experienced a PSA rise after a median of 14.5 months (IQR, 10.8–20.7). In 6 of these patients, re-treatment was performed to postpone ADT again, for the other patients ADT was started (Fig. 2).

In patients with a PSA response, the median ADT-free survival was 36.1 months (95% CI, 29.9–42.3), for patients without response this was 14.9 months (95% CI, 11.4–18.4) ($p = 0.004$) (Fig. 3). Patients imaged by PSMA-11-PET experienced a significant longer ADT-free survival than patients imaged by choline-PET (32.7 months (95% CI, 20.8–44.5) versus 14.9 months (95% CI, 5.7–24.1), respectively, $p = 0.01$) (Fig. 4). For the whole group median interval between start of SABR and start of ADT was 27.3 months (95% CI, 16.1–38.5).

In 20% ($n = 10/50$) only mild side-effects of SABR were reported ($n = 5$ patients diarrhea, $n = 1$ nausea, $n = 1$ rectal discomfort and $n = 1$ pain flare). In $n = 1$ patient moderate nausea and in $n = 1$ patient severe fatigue was reported after SABR.

We analysed independent predictive factors related to ADT-free survival after SABR. There was a significant correlation between PSA at start of SABR and ADT-free survival; patients with lower PSA levels experienced improved ADT-free survival compared with patients with higher PSA levels ($r_s = -0.418$, $p = 0.001$). The Gleason score of the primary tumour, treated volume of the metastases and type (lymph node vs. bone) and number of metastases were not of independent predictive value for ADT-free survival. In multivariate linear regression analyses including diagnostic modality and the PSA at start of SABR, only PSA appeared to be predictive for ADT-free survival ($B = -1.234$, $\beta = -0.335$, $p = 0.025$), while type of diagnostic modality was not predictive ($B = -2.332$, $\beta = -0.083$, $p = 0.57$).

Discussion

This study shows that PSMA-11-PET improves selection of patients with oligometastatic prostate cancer suitable for SABR by detection of metastases in an earlier stage at lower PSA levels compared with choline-PET. Subsequently, PSMA-11-PET guided SABR resulted in a significant longer response duration and ADT-free survival than in patients whereby the metastases were localised by choline-PET.

As prostate cancer is one of the most common malignancies

worldwide, it afflicts thousands of men every year with 1.414.259 new cases in 2020 [12]. Many of these patients will experience metastatic disease, initially or at a later stage [13]. In case of metastatic disease in hormone-sensitive prostate cancer, first choice of treatment is deferred ADT [14]. Unfortunately, ADT has many side effects like hot flushes, fatigue, decrease of libido, erectile dysfunction, loss of muscle and bone mass, depression and many more. It is reported that ADT related side effects result in reduced quality of life [3]. Further postponing ADT by successful SABR is therefore an important treatment strategy to ensure a better quality of life.

Several other studies report on ADT-free survival after SABR with use of choline-PET [3,5]. However, data for PSMA-11-PET are scarce and this is the first study to our knowledge to compare PSMA-11-PET and choline-PET for clinical outcome in terms of ADT-free survival in representative cohorts. Although the choline-PET group in our study is small, the ADT-free survival of 14.9 months is in line with the 15.6 months of a larger retrospective study ($n = 43$ patients) comparing choline-PET based SABR with observation in patients with oligometastatic prostate cancer [4]. Another clinical trial randomised 62 patients (with 1–3 metastases based on choline-PET) between surveillance and local treatment (surgery or SABR). After 3 years a difference in ADT-free survival was found in favour of the treatment group (median ADT-free survival 13 months versus 21 months) [6]. One study investigated the PSA response after PSMA-11-PET based SABR [15]. The PSA declined in 16/19 patients (84%) after SABR, however, seven patients were concomitantly treated with ADT.

Predictive factors for the outcome of SABR on ADT-free survival would help to select patients benefitting from this treatment. It is not surprising that patients with lower PSA levels at start of SABR experienced improved ADT-free survival compared with patients with higher PSA levels. Unfortunately, no predictive cut-off value was found to robustly exclude patients that will not benefit from this treatment strategy. Also, no differences were found in outcome regarding Gleason score of the primary tumour, treated volume of metastases, type of metastases (lymph node vs. bone) and number of treated metastases, nor the type of diagnostic modality used (PSMA-11-PET vs. choline-PET). However, PSA levels at start of SABR were higher in the choline-PET group and therefore can explain the better outcome in ADT-free survival of the PSMA-11-PET group. Based on our results, SABR should be

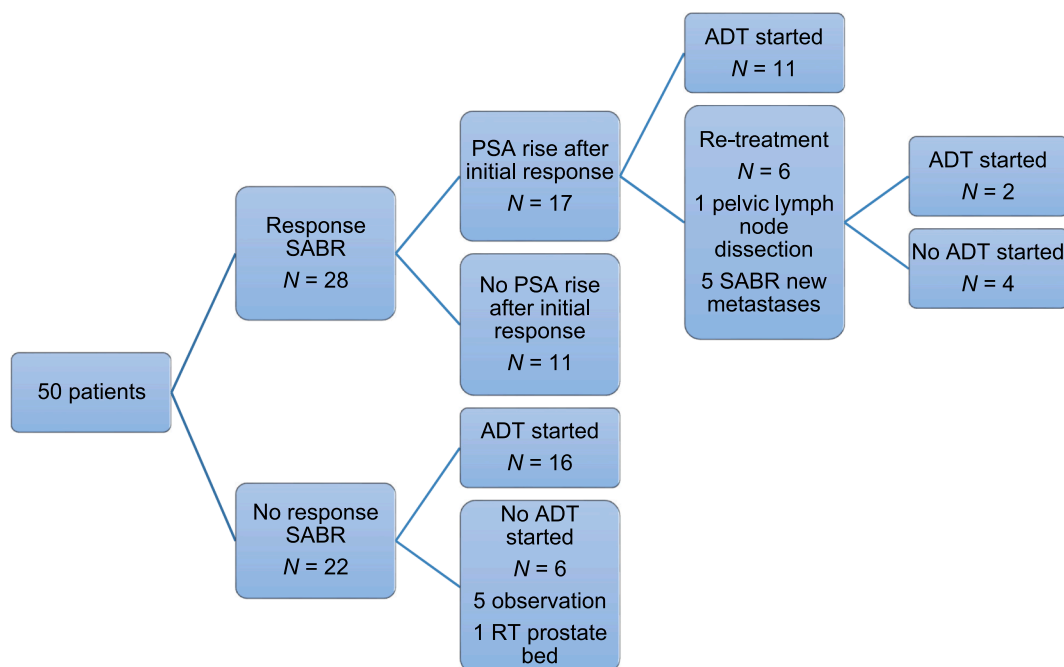


Fig. 2. Flowchart of treatment.

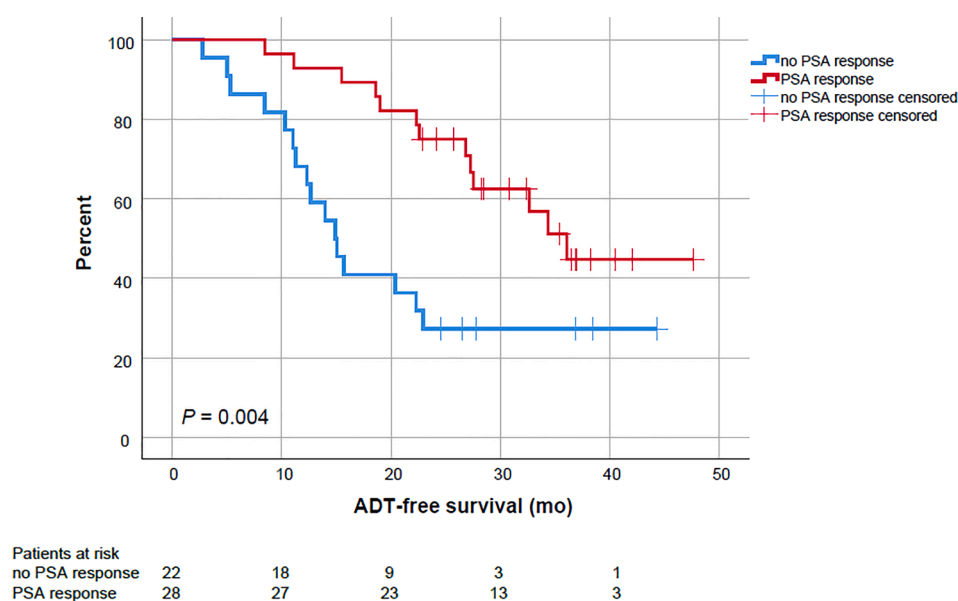


Fig. 3. ADT-free survival responders versus non-responders.

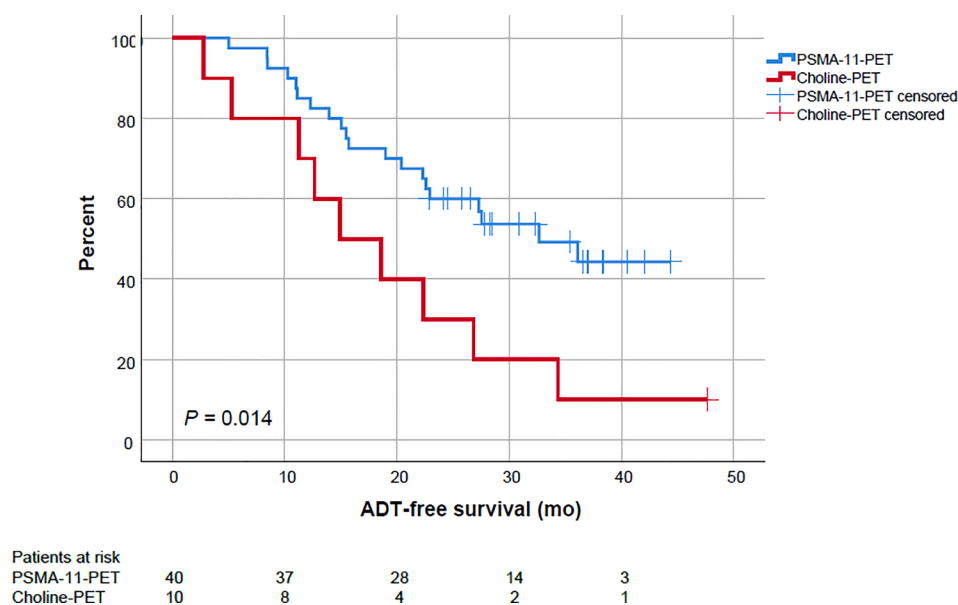


Fig. 4. ADT-free survival PSMA-11-PET versus choline-PET.

considered in all oligometastasised patients. Although in a recent consensus meeting fair to good agreement was reached on the maximum number of metastases in oligometastatic prostate cancer ranging between 3 and 5, patients with more lesions may also expect benefit from this treatment strategy [10]. The feasibility and value of (PSMA-11-PET guided) SABR for patients with more than 5 lesions to achieve a longer ADT-free survival (and better quality of life) should be subject of future studies.

Patients with a high PSA doubling time may not benefit from SABR to postpone the ADT as the number of (microscopic) disease locations is beyond local treatment [16,17]. However, it is not known whether the PSA doubling time is determined by the number of locations (including microscopic lesions) or the aggressiveness of the tumour (e.g. proliferation rate). In the latter case, a subset of patients with a high PSA doubling time may still benefit from SABR. To answer this question a robust pre-SABR PSA doubling time analysis in relation to a homogeneous PSMA-11-PET guided follow-up scheme is needed, which was out

of the scope of this study.

In this study patients with bone, lymph node and visceral metastases were included. In a recent Dutch consensus meeting a fair agreement was reached regarding exclusion of patients with visceral metastases for SABR because of the worse prognosis [10]. When eligible patients for inclusion in our study were reviewed, only one patient with a visceral metastasis was identified. This patient was treated with SABR for a bone and liver metastasis and was later treated (with fractionated radiotherapy) for recurrence of the prostate bed. Up to the moment of analyses, this patient was still ADT-free (37 months after the initial disease progression and start of SABR). The recent SEER (Surveillance, Epidemiology, and End Results) database analysis of 1358 patients showed that the impact of visceral metastasis on the prognosis may depend on the type of metastasis (as patients who developed isolated lung metastases had improved survival compared to those with isolated brain or liver metastases [18]). This aspect should be considered in selecting patients for SABR and future analysis.

Analyses of the treatment outcome after the introduction of better (e.g. more sensitive or specific) image modalities is often retrospectively performed due to ethical reasons. The PSMA-11-PET has not been compared with choline-PET in a prospective manner with a clinically relevant endpoint (like ADT-free survival). Our study compared the two modalities in a retrospective manner since choline-PET is still a commonly used image modality. This retrospective aspect incorporates a bias in both patient selection and time of treatment, although the treatment techniques and devices used for SABR did not change during the inclusion period and in the earlier years of the inclusion period, use of choline-PET and PSMA-11-PET was equally divided.

The aim of this study was to show that with a more sensitive modality a longer ADT-free survival can be achieved. Indeed, lower PSA level was an independent prognostic factor for improved ADT-free survival (in contrast to the imaging modality) reflecting that patients with lower PSA level could be identified with PSMA-11-PET. This supports the hypothesis that higher sensitivity imaging PSMA-11-PET improves triaging patients benefitting from SABR, resulting in longer response duration and improved ADT-free survival. However, the indication for choline-PET was less favourable than for PSMA-11-PET and it can be hypothesised that if the cutoff for a choline-PET would have been lower, a longer ADT-free survival could have been reached. Subsequently, a subset of these patients would still be prone to have undetected (and untreatable) lesions [9,14] and therefore not benefit from SABR. This also afflicts patients diagnosed with PSMA-11-PET. As still 44% of the PSMA-11-PET patients had no PSA response, there is still a high need for novel generation imaging further improving SABR outcomes. However, in this regard earlier detection with more sensitive imaging modalities can result in lead time bias, meaning that survival is not actually improved, but diagnosis is made earlier and therefore survival is prolonged.

In our study there is no predefined cutoff PSA level for start of ADT as there are no standardised criteria [2,4]. Initiation of ADT was based upon the physician's discretion and patient's preference and/or symptomatic progression (based on clinical and imaging factors and PSA results). With the strong evidence that ADT treatment impairs the quality of life it is again complicated to retrieve this outcome in a prospective manner. This however underlines the importance that in future intervention trials (e.g. studying the efficacy of novel treatment strategies) state of the art imaging techniques and quality of life assessments are included.

Conclusion

With PSMA-11-PET we are able to select patients with oligometastatic recurrent prostate cancer suitable for SABR in an earlier stage. PSMA-11-PET to guide SABR resulted in a significant longer response duration and ADT-free survival compared with choline-PET. As choline-PET is still widely used for detection of prostate cancer recurrence, much can be gained with the use of PSMA-11-PET.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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