Journal of Nuclear Medicine, published on January 8, 2021 as doi:10.2967/jnumed.120.256602

QUANTIFICATION OF METASTATIC PROSTATE CANCER WHOLE-BODY TUMOR BURDEN WITH FDG PET PARAMETERS AND ASSOCIATIONS WITH OVERALL SURVIVAL AFTER FIRST LINE ABIRATERONE OR ENZALUTAMIDE: A SINGLE-CENTER RETROSPECTIVE COHORT STUDY

Running Title:
Metastatic prostate cancer tumor burden by FDG-PET

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Disclosures:

Hedvig Hricak has been a member of the Board of Directors of Ion Beam Applications (IBA), a medical technology company, since May 2017 and receives annual compensation for this role.

Howard I. Scher is a consultant/advisory board member for Ambry Genetics Corporation, Amgen, Bayer, ESSA Pharma, Janssen Biotech, Janssen Research & Development, OncLive Insights, Menarini Silicon Biosystems, Physicians Education Resource, Pfizer, Sanofi Aventis, and WCG Oncology; Intellectual Property Rights BioNTech, Elucida Oncology, MaBVAX, Y-mAbs Therapeutics, Inc and institutional research funding from Epic Sciences, Illumina, Janssen Diagnostics, Menarini Silicon Biosystems, and ThermoFisher.

ABSTRACT

RATIONALE: New biomarkers for metastatic prostate cancer are needed. The aim of this study was to evaluate the prognostic value of FDG-PET whole body tumor burden parameters in patients with metastatic prostate cancer who received first line abiraterone or enzalutamide therapy.

METHODS: Retrospective study of patients with metastatic castration-sensitive (mCSPC, n=25) and metastatic castration-resistant prostate cancer (mCRPC, n=71) who underwent ^{18}F-FDG-PET/CT within 90 days before first-line treatment with abiraterone or enzalutamide at a tertiary care academic cancer center. Whole-body tumor burden on PET/CT was quantified as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) and correlated with overall survival (OS) probabilities using Kaplan-Meier curves and Cox models.

RESULTS: The median follow-up in survivors was 56.3 months (IQR: 37.7, 66.8); the median OS for patients with mCRPC and mCSPC was 27.8 and 76.1 months (p<.001). On univariate analysis, the OS probability of mCRPC patients was significantly associated with plasma levels of alkaline phosphatase (HR: 1.90, p<.001) and lactate dehydrogenase (HR: 1.01, p<.001), hemoglobin levels (HR: 0.80, p=.013), whole body SUVmax (HR: 1.14, p<0.001), the number of FDG-avid metastases (HR: 1.08, p<0.001), whole body MTV (HR: 1.86, p<.001) and TLG (HR: 1.84, p<.001). In multivariable analysis with stepwise variable selection, hemoglobin levels (HR: 0.81, p=0.013) and whole-body TLG (HR: 1.88, p<.001) were independently associated with OS. In mCSPC patients, no significant association was observed between these variables and OS.

CONCLUSION: In patients with mCRPC receiving first-line treatment with abiraterone or enzalutamide, FDG PET WB TLG is independently associated with OS and might be used as quantitative prognostic imaging biomarker.

KEY WORDS: metastatic prostate cancer; ^{18}F-fluoro-desoxy-glucose positron-emission tomography computed tomography; whole-body tumor burden; overall survival; abiraterone; enzalutamide;

INTRODUCTION

The availability of multiple life-prolonging therapeutic options for patients with metastatic prostate cancer (mPC) has increased the demand for biomarkers to deploy these agents for optimal patient benefit. The clinical course of patients with mPC is highly variable and identifying individuals in need for treatment, selection of the appropriate management strategy, and treatment response assessment remain challenging even for the most experienced oncologists. Patients' symptoms, dynamics of prostate specific antigen levels, and radiographic disease progression are probably the most important decision drivers at present, but clearly more quantitative descriptors of tumor burden are needed in clinical practice as well as for clinical trials.

Conventional planar bone scintigraphy ('bone scan') remains the mainstay for osseous tumor burden quantification in mPC in the United States. However, radiotracer accumulation in bone scans is not specific to metastases and may be seen in any type of bone-remodeling process, including benign entities such as degenerative joint disease. The Response Evaluation Criteria in Solid Tumors (RECIST) provide guidelines for size measurement of non-osseous tumors on computed tomography (CT) and magnetic resonance imaging (MRI) (*1*) but do not address bone metastases without extraosseous components. The frequent bone tropism of prostate cancer thus limits their applicability in this population. Qualitative descriptors of bone metastases on CT or MRI by radiologists are subjective, poorly reproducible, and do not qualify as quantitative biomarkers. Although MRI offers a range of quantitative metrics beyond tumor size which could theoretically be used as biomarkers (*2*), these measurements are susceptible to technical variations and the lack of standardization challenge their practical utility (*3*). Another problem in CT and MR imaging is the differentiation between metabolically active tumor and reactive peritumoral changes, e.g. osseous sclerosis. Because of all these shortcomings, Prostate Cancer Working Groups 2 and 3 advise assessing sites of disease independently and encourage the development of potential new biomarkers for mPC, including imaging-derived metrics (*4*).

^{18}F-fluoro-desoxy-glucose positron-emission tomography combined with CT (FDG-PET/CT) is a well-established, safe, and thoroughly studied imaging tool for a variety of malignancies. This tracer is FDA-approved for all types of malignancies and reimbursable under the current policy of the Centers for Medicare & Medicaid Services for a broad range of diseases which includes the "guidance of subsequent anti-tumor treatment strategy" for patients with metastatic prostate cancer (*5*). While FDG-PET/CT has

very limited clinical utility for staging of newly diagnosed prostate cancer (*6*) and for the detection of biochemically recurrent disease (*7*), it's potential in mPC patients is understudied. Based on prior observations that a considerable proportion of castration-resistant mPC lesions demonstrate FDG uptake and that the number of FDG-avid metastases and more intense tracer uptake are associated with poorer outcome in this population (*8-10*), we hypothesized that FDG-PET/CT could be used as a quantitative measure of tumor burden in mPC on a whole-body scale. Therefore, we conducted retrospective survival analyses of mPC patients undergoing FDG-PET/CT before first line treatment with second generation anti-androgens (i.e. abiraterone or enzalutamide).

MATERIALS AND METHODS

STUDY COHORT

This was retrospective single-center cohort study of patients referred for evaluation of metastatic castration-resistant (mCRPC) and castration-sensitive (mCSPC) prostate cancer with FDG-PET/CT by their treating sub-specialized genitourinary oncologist at a tertiary care academic cancer hospital between June 2009 and December 2016. The institutional review board approved this retrospective study and the requirement to obtain informed consent was waived. Patients who underwent FDG-PET/CT within 60 days prior to the initiation of first-line systemic therapy with either enzalutamide (XTANDI®) or abiraterone acetate plus prednisone (ZYTIGA®) and no intervention between the PET scan and therapy start were considered eligible (n=104). The clinical decision to treat with abiraterone or enzalutamide was made by the treating oncologist. Individuals who received abiraterone or enzalutamide in combination with taxane-chemotherapy or an experimental drug as well as those with diffuse intense FDG uptake in the skeletal muscles due to insulin injection prior to the PET scan were excluded. The final study population consisted of 96 patients. A flow chart of the study cohort selection is provided in Figure 1.

IMAGING PROTOCOL AND ANALYSIS

FDG-PET/CT examinations were performed with a hybrid PET/CT scanner (Discovery; GE Healthcare, Milwaukee, Wis) about 60 minutes after intravenous injection of approximately 370 MBq of ^{18}F-FDG (obtained from IBA Molecular North America Inc and calibrated by our in-house radiopharmacy). The radiotracer was administered after a minimum 4-6 hours fasting interval and only if the patient's blood glucose level was <200 mg/dL. The field of view extended from the mid skull to the upper thighs. Low-dose CT was performed for anatomic correlation and attenuation correction (tube voltage: 120–140 kV, tube current: 80 mA, section thickness: 5 mm, reconstruction interval: 5 mm, pitch: 0.75–1.5). Oral but no intravenous contrast material was administered. Quantitative image analysis was performed by a board-certified oncologic and molecular imaging fellowship-trained radiologist on a dedicated workstation (PET Volume Computer Assisted Reading-VCAR, GE Healthcare). Volumes of interest (VOIs) were semi-automatically drawn for each metastatic lesion, defined as non-physiologic tracer accumulation above mediastinal blood pool avidity. Areas of physiologic accumulation or excreted tracer (e.g. kidneys, urinary bladder, ureters, urethra) were excluded from the VOIs. The following quantitative PET-derived metrics (*11*) were recorded separately for every cancer lesion:

- Maximum Standardized Uptake Value (SUVmax, [g/mL]), defined as the ratio of a lesion's highest radioactivity concentration measured by PET [kBq/mL] and the decay-corrected and body-weight adjusted injected radiotracer activity [kBq/g].
- Metabolic Tumor Volume (MTV, [mL]), defined as the volume of tissue with an SUV of at least 41% of a lesion's SUVmax (i.e. relative threshold), according to guidelines of the European Association of Nuclear Medicine (EANM) (*12*).
- Total Lesion Glycolysis (TLG, [g]), defined as the mass of FDG taken up within a MTV, calculated as the product of the MTV and its average SUV, according to EANM guidelines (*12*).

The MTV and TLG for all metastatic lesions were summated to generate the MTV and TLG for the whole body. Inter-reader reproducibility for these metrics were previously reported to be very high with intraclass correlation coefficients consistently ranging above 0.9 (*13-15*), and relative measurement error of repeated measurements ranging between 14.5% and 20.4% (*16*). However, these numbers might be less favorable for small tumors and depend on the applied segmentation method (*17*). A representative imaging example of our imaging analysis methodology is given in Figure 2.

ENDPOINT

The endpoint of this study was overall survival (OS), defined as the time interval from initiation of systemic treatment with enzalutamide or abiraterone to death from any cause. Observations from patients alive at the last follow-up were right censored.

STATISTICAL METHODS

Cox proportional hazard regression was used to examine associations between clinical variables (i.e. age, therapy agent), laboratory parameters (i.e. prostate specific antigen, alkaline phosphatase, lactate dehydrogenase, and hemoglobin), and FDG-PET/CT derived metrics (i.e. SUVmax, number of FDG-avid metastases, whole body MTV, whole body TLG) with OS from the start of the treatment, in univariable and multivariable analyses. Started with univariably important variables ($p<0.05$), the multivariable model in the mCRPC group was build using stepwise variable selection approach based on Wald test statistics. No multivariable analysis was performed for mCSPC group considering the small sample size. The logarithmic transformation was applied to alkaline phosphatase, prostate specific antigen, MTV, and TLG. The Kaplan-Meier method was used to estimate OS in patient groups dichotomized at the median of whole-body TLG. Clinical characteristics, laboratory and imaging

parameters were compared using the Fisher's exact test and the Wilcoxon rank-sum test between patients with mCRPC and mCSPC. All statistical analyses were performed in R 4.0.2 (R Foundation for Statistical Computing).

RESULTS

Of the 96 included individuals, seventy-one had mCRPC (71/96, 74.0%), and 25/96 (26.0%) had mCSPC. Fifty-seven patients (59.4%) received abiraterone plus prednisone treatment and 39 (40.6%) received enzalutamide; these frequencies did not differ significantly between mCRPC and mCSPC patients, as detailed in Table 1. At the time of treatment start, patients with mCRPC were significantly older than mCSPC patients (p=0.002), had higher levels of prostate specific antigen (p=0.016) and lactate dehydrogenase (LDH, p=0.003), and lower levels of albumin (p=0.019) and hemoglobin (p<0.001). On PET/CT, mCRPC patients had significantly more FDG-avid metastases compared to mCSPC patients (p=0.018), but there was no significant difference of the SUVmax between the two groups. Quantitative metrics of tumor burden on PET/CT were significantly higher in mCRPC patients, including whole-body MTV (p=0.005) and whole-body TLG (p=0.004). The median OS after treatment start was 39.8 months (95% CL: 29.7, 55.8), significantly shorter in mCRPC patients compared to individuals with mCSPC (p<0.001). At the last follow up, 56 mCRPC and 8 mCSPC patients were deceased. The median follow-up in survivors after treatment start was 56.3 months (IQR: 37.7, 66.8), with no significant differences between mCRPC and mCSPC patients. These and additional descriptive statistics are detailed in Table 1. We did not observe significant differences in laboratory values, PET-derived metrics, or OS probabilities between patients treated with abiraterone vs. enzalutamide in the mCSPC or mCRPC cohort, respectively.

SURVIVAL ANALYSES

CASTRATION RESISTANT DISEASE. In patients with mCRPC, the median OS was 27.8 months [95% CL: 22.1, 39.7] and the 5-year OS probability was 17.6% (SE: 5.2%). On the univariate Cox-regression analyses of this subgroup, we observed significant associations of OS with laboratory parameters (i.e. alkaline phosphatase [HR: 1.90, p<0.001], hemoglobin [HR: 0.80, p=0.013], and lactate dehydrogenase [HR: 1.005, p<0.001]); and with all of the FDG-PET/CT derived metrics, i.e. SUVmax (HR: 1.14), number of FDG avid metastases (HR: 1.08), whole-body MTV (HR: 1.86) and whole-body TLG (HR: 1.84) (p<0.001 for all), as detailed in Table 2. Kaplan-Meier curves of OS stratified by the median whole-body TLG are shown in Figure 3. In a multivariate Cox regression model, whole-body TLG (HR: 1.88, p<0.001) and hemoglobin levels (HR: 0.81, p=0.013) were significantly associated with OS in mCRPC patients (Table 2).

CASTRATION SENSITIVE DISEASE. In patients with mCSPC, the median OS was 76.1 months [95% CL: 50.3, -] and the 5-year survival probability was 72.8% (SE: 8.7%). In this subgroup, we observed an association of hemoglobin levels and OS but this did not reach statistical significance (p=0.065). None of the PET/CT-derived metrics were associated with OS in this subgroup on univariate analysis.

DISCUSSION

In this retrospective cohort study, we investigated the potential of ^{18}F-FDG-PET/CT for measuring the whole-body tumor burden of metabolically active metastatic prostate cancer. In patients with mCRPC, we found significant associations of PET/CT-derived metrics (i.e. SUVmax, number of FDG-avid metastases, whole-body MTV and TLG) with the OS probability. We applied stepwise variable selection to account for collinearity and found that among the analyzed laboratory and PET-derived metrics, whole-body TLG and hemoglobin levels were independently associated with the OS probability. Whole-body TLG was more closely related to OS probability than established laboratory biomarkers, including LDH, which had been found to be the strongest predictor of OS probability in multiple previous studies, e.g. in a pooled analysis from four phase 3 clinical trials in first-line mCRPC (i.e. the ASCENT2, MAINSAIL, VENICE, and ENTHUSE 33 trials) (*18*). This indicates that FDG-PET/CT derived quantitative metrics are worthy of continued development as biomarkers for mCRPC patients. In patients with mCSPC, in contrast, we did not observe significant associations between tumor burden on FDG-PET/CT and OS; however, the small number of patients with mCSPC in our study limits its statistical power and raises concerns about a possible type-2 error. This assumption is supported by the fact that we were not able to confirm previously proposed prognostic biomarkers in this population, including alkaline phosphatase and LDH (*19*). Future studies with larger mCSPC cohorts are warranted to further explore potential roles of FDG-PET/CT in this population.

Our study corroborates previous reports that indicated a potential utility of FDG-PET/CT in patients with metastatic prostate cancer. Jadvar and colleagues, for example, found that in patients with mCSPC, more numerous and more intensely FDG-avid metastases were associated with a shorter interval to failure of hormonal treatment (*20*). The same group also published prospective data on a cohort of mCRPC patients where the intensity of FDG uptake (i.e. the SUVmax) was associated with poorer OS (*21*). Our group made similar observations in mCRPC patients, where the number of FDG-avid metastases (*9*) and the SUVmax (*10*) were associated with shorter survival. In all these studies, tumor burden was estimated semi-quantitatively by lesion count and metabolic cancer activity was quantified solely by the maximum lesional FDG uptake (i.e. SUVmax). Our current methodology gives a truly quantitative and more comprehensive measure of metabolically active tumor burden on a whole-body scale by integrating the tumor volume (i.e. MTV) and intensity of FDG uptake (i.e. average SUV) in a single metric (i.e. TLG). Another methodologic difference between our and those previous studies lies in the cohort selection. We aimed to minimize potential confounders of patients' survival and therefore

restricted our analyses to individuals before the start of their first-line treatment with abiraterone or enzalutamide. In contrast to one of the above cited studies (*21*), we excluded patients receiving first-line cytotoxic chemotherapy as this treatment is nowadays primarily given to patients with visceral metastases and a relatively poor prognosis. Including such patients would have made our study cohort more diverse, would have probably confounded our survival analyses, and would have limited the applicability of our results in contemporary patient cohorts. Secondly, we excluded patients with previous life-prolonging systemic cancer therapy due to potential effects of prior treatments on cancer biology, which includes lesional FDG avidity and possible downstream confounding of OS probability. In our opinion, this rigorous patient selection has minimized potential confounders for this proof-of-concept study and substantiates a direct association of tumor burden on FDG-PET/CT and survival probability in mCRPC patients. This quantitative imaging biomarker could be used clinically to estimate a patient's prognosis and help to define the best timepoint for the initiation of systemic therapy. The association of whole-body TLG with OS probability also suggests that this metric might be useful for the assessment of treatment response, which would need to be studied in prospective trials with pre-defined post-therapy scan intervals.

The major limitation of this study is its retrospective design including the possibility of selection bias on multiple levels. Most importantly, this cohort of patients undergoing FDG-PET/CT represents only a subgroup of patients from our institution undergoing first-line abiraterone or enzalutamide treatment for metastatic prostate cancer. The decision to order the PET/CT scan was made by the treating oncologist and was based on medical as well as non-medical considerations, including costs and insurance coverage. In addition to patient selection, some technical and methodological factors deserve consideration when interpreting these results. First, we used the ≥41% of the SUVmax as a cut-off to calculate MTV and TLG in accordance with current guidelines (12). To the best of our knowledge, this cut-off has not been validated specifically in patients with metastatic prostate cancer. We did not analyze SUVmean as a separate variable as this is included in the calculation of TLG. Second, only one reader measured PET metrics and we did not assess for inter-observer reproducibility. Previously published reports found that for MTV and TLG, intraclass correlation coefficients range above 0.9 (*13-15*), and that relative measurement errors are expected to range between 15% and 20% (*16*). However, the variability for whole-body assessment of multiple lesions might be higher than for single-lesion measurements. Also, the manual lesion segmentation in this proof-of-concept study can be time consuming and impractical during clinical routine, particularly in patients with multiple lesions.

Automated segmentation algorithms based on artificial intelligence are already under development and clinical evaluation (*22,23*), and might help to minimize manual input and inter-observer variability. Next, our study lacks modern benchmark prognostication tools, e.g. bone scan index and circulating tumor cells or nucleic acid. Adding the availability of such tests to our inclusion criteria would have further decreased the number of eligible patients and prohibited meaningful statistical analyses. The sample size of our study was not large enough to derive a reliable cutoff whole-body TLG, or for exploring potential prognostic differences between nodal, osseous, and visceral tumor burden. Larger studies are needed to address these questions. The current study does, however, provide a strong justification for future studies to refine and evaluate FDG-PET/CT derived metrics and compare them to modern prognosticators. As our study focused on individuals receiving first-line second generation anti-androgens to minimize potential confounders of OS, our results cannot be directly translated to other treatments modalities, e.g. cytotoxic chemotherapy or targeted radioactive agents. Lastly, the reported outcomes are based on first line therapy and we did not account for subsequent anti-cancer therapies which could have changed prognosis independent of FDG-PET/CT metrics at baseline.

CONCLUSION

We observed strong associations between FDG-PET/CT-derived metrics of whole-body tumor burden and the OS probability of patients with mCRPC receiving first-line abiraterone or enzalutamide therapy. Whole-body Total Lesion Glycolysis (TLG) was independently associated with OS probability and is worthy of continued development as a biomarker in mCRPC patients.

ACKNOWLEDGMENTS

This work was supported in part through the NIH/NCI Cancer Center Support Grant P30 CA008748, and through the Peter Michael Foundation

KEY POINT

QUESTION: In patients with metastatic prostate cancer, can ^{18}F-FDG-PET/CT provide functional quantitative measures of whole-body tumor burden?

PERTINENT FINDINGS: In a cohort study of 71 patients undergoing first-line treatment of metastatic castration-resistant prostate cancer (mCRPC) with second generation anti-androgens, a PET/CT derived whole-body imaging biomarker that integrates tumor volume and the cancer's metabolic activity (i.e. Total Lesion Glycolysis, TLG) was strongly associated with overall survival. Such associations were not observed in a cohort of 25 patients with castration-sensitive disease.

IMPLICATIONS FOR PATIENT CARE: With this quantitative and functional imaging metric, physicians can measure the burden of metabolically active mCRPC on a whole-body scale and estimate an individual patient's prognosis.

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TABLE 1. Descriptive statistics for the entire study cohort and separately for mCRPC and mCSPC patients, respectively. Numbers are presented as absolute counts (percentages) or medians (interquartile range), unless otherwise indicated.

Parameter	**Overall (n=96)**	**mCRPC (n=71)**	**mCSPC (n=25)**	**p-value***
Age at initial prostate cancer diagnosis (years)	66.2 (59.7, 71.6)	67.4 (59.7, 72.9)	64.2 (59.7, 65.9)	0.012
Gleason grade group at initial diagnosis				
1	5 (5.2)	4 (5.6)	1 (4.0)	
2	7 (7.3)	7 (9.9)	0	0.439
3	19 (19.8)	12 (16.9)	7 (28.0)	
4	22 (22.9)	16 (22.5)	6 (24.0)	
5	36 (37.5)	27 (38.0)	9 (36.0)	
Not available	7 (7.3)	5 (7.0)	2 (8.0)	
Initial prostate cancer treatment (%)				
Prostatectomy ± hormonal therapy	40 (41.7)	24 (33.8)	16 (64.0)	0.022
Radiation ± hormonal therapy	27 (28.1)	24 (33.8)	3 (12.0)	
Hormonal therapy	29 (30.2)	23 (32.4)	6 (24.0)	
Initial cancer diagnosis to castration resistance (months)	-	50.5 (13.9, 125.3)	-	-
Initial cancer diagnosis to treatment# start (months)	42.5 (11.9, 116.0)	57.9 (15.4-127.1)	8.4 (6.2-74.5)	0.002
Castration resistance to treatment# start (months)	-	1.2 (0.3, 5.5)	-	-
Age at start of treatment# (years)	71.0 (65.8, 79.6)	73.8 (67.1, 82.1)	67.9 (63.7, 70.7)	0.002
Treatment Type				
Abiraterone plus prednisone	57 (59.4)	39 (54.9)	18 (72.0)	0.161
Enzalutamide	39 (40.6)	32 (45.1)	7 (28.0)	
Laboratory parameters at treatment# start				
Prostate Specific Antigen (ng/mL)	13.3 (3.1, 32.4)	15.1 (4.4, 37.7)	3.5 (1.0, 23.4)	0.016
Albumin (g/dL)	4.2 (4.1, 4.4)	4.2 (4.0, 4.4)	4.4 (4.1, 4.7)	0.019
Alkaline phosphatase (U/L)	88 (70, 141)	94 (70, 150)	75.5 (62, 96.5)	0.079
Hemoglobin (g/dL)	12.7 (11.8, 13.6)	12.3 (11.3, 13.1)	13.8 (12.6, 14.8)	<0.001
Lactate dehydrogenase (U/L)	201 (173, 251)	218 (182, 260)	187 (155, 204)	0.003
^{18}F-FDG-PET/CT data				
Time from PET/CT to treatment# start (days)	22.5 (11.5, 40)	22 (12, 36)	23 (8, 43)	0.708
Injected ^{18}F-FDG activity (MBq)	459 (437, 459)	463 (433, 488)	451 (440, 463)	0.269
Time from tracer injection to scan start (min)	67 (61, 79.5)	70 (63, 80)	62 (60, 73)	0.052
SUVmax (g/ml)	7.1 (5.3, 10.9)	7.2 (5.5, 11.7)	5.9 (4.8, 9.0)	0.188
Number of FDG-avid metastases	4 (2, 14)	5 (3, 15)	2 (0, 8)	0.018
Whole-Body Metabolic Tumor Volume (mL)	45.7 (13.0, 120.8)	57.0 (20.9, 145.3)	15.5 (0, 62.9)	0.005
Whole-Body Total Lesion Glycolysis (g)	123.3 (38.5, 568.1)	167.0 (48.7, 583.7)	59.5 (0, 194.1)	0.004
Follow-up after treatment# start in survivors (months)	56.3 (37.7, 66.8)	45.3 (32.9, 65.7)	60.1 (29.7, 67.8)	0.334

Median survival after treatment[#] start (months) [95% CI]	39.7 [28.6, 53.5]	27.8 [22.1, 39.7]	76.1 [50.3, -]	<0.001

***** for comparison of mCRPC and mCSPC patients; **#** treatment with abiraterone plus prednisone, or enzalutamide; **CI**: confidence intervals, **FDG**: fluoro-desoxy-glucose, **mCRPC**: metastatic castration-resistant prostate cancer; **mCSPC**: metastatic castration-sensitive prostate cancer; **PET/CT**: positron emission tomography computed tomography; **SUV:** standardized uptake value

TABLE 2. Results of Cox proportional hazard regression analyses of overall survival probability after initiation of abiraterone/enzalutamide therapy. Results are shown separately for mCRPC and mCSPC patients, respectively.

Metastatic Castration Resistant Patients (n=71)				
	Univariate		**Multivariate**	
Parameter	**Hazard Ratio [95% CI]**	**p-value**	**Hazard Ratio [95% CI]**	**p-value**
Age at start of treatment[#]	1.03 [0.99, 1.06]	0.11		
Treatment agent				
Enzalutamide (n=32)	Reference	0.48		
Abiraterone (n=39)	1.21 [0.71, 2.08]			
Laboratory parameters at treatment[#] start				
Prostate Specific Antigen (log)	1.13 [0.95, 1.35]	0.17		
Albumin	0.55 [0.23, 1.31]	0.18		
Alkaline phosphatase (log)	1.90 [1.34, 2.70]	<0.001	Not selected*	
Hemoglobin	0.80 [0.67, 0.95]	0.013	0.81 [0.69, 0.96]	0.013
Lactate Dehydrogenase	1.005 [1.003, 1.008]	<0.001	Not selected*	
^{18}F-FDG-PET/CT metrics				
SUVmax (g/ml)	1.14 [1.08, 1.21]	<0.001	Not selected*	
Number of FDG-avid metastases	1.08 [1.05, 1.11]	<0.001	Not selected*	
Whole-Body MTV (log)	1.86 [1.49, 2.33]	<0.001	Not selected*	
Whole-Body TLG (log)	1.84 [1.51, 2.26]	<0.001	1.88 [1.53, 2.32]	<0.001
Metastatic Castration Sensitive Patients (n=25)				
Age at start of treatment	1.02 [0.9, 1.15]	0.76		
Treatment agent				
Enzalutamide (n=7)	Reference	0.72		
Abiraterone (n=18)	0.73 [0.13, 3.98]			
Laboratory parameters at treatment[#] start				
Prostate Specific Antigen (log)	1.07 [0.72, 1.58]	0.74		
Albumin	1.29 [0.9, 17.2]	0.85		
Alkaline phosphatase (log)	1.55 [0.59, 4.05]	0.37		
Hemoglobin	0.66 [0.43, 1.03]	0.065		
Lactate Dehydrogenase	1.00 [0.98, 1.02]	0.89		
^{18}F-FDG-PET/CT metrics				
SUVmax (g/ml)	0.99 [0.90, 1.09]	0.80		
Number of FDG-avid metastases	1.03 [0.96, 1.11]	0.43		
Whole-Body MTV (log)	1.21 [0.83, 1.76]	0.33		
Whole-Body TLG (log)	1.18 [0.86, 1.61]	0.31		

treatment with abiraterone plus prednisone, or enzalutamide; ***** not selected during stepwise selection; **(log)**: logarithmic transformation; **CI**: confidence interval, **FDG**: fluoro-desoxy-glucose, **MTV**: metabolic tumor volume, **PET/CT**: positron emission tomography computed tomography, **SUV**: standardized uptake value; **TLG**: total lesion glycolysis

FIGURES

FIGURE 1: Flow chart of study cohort selection.

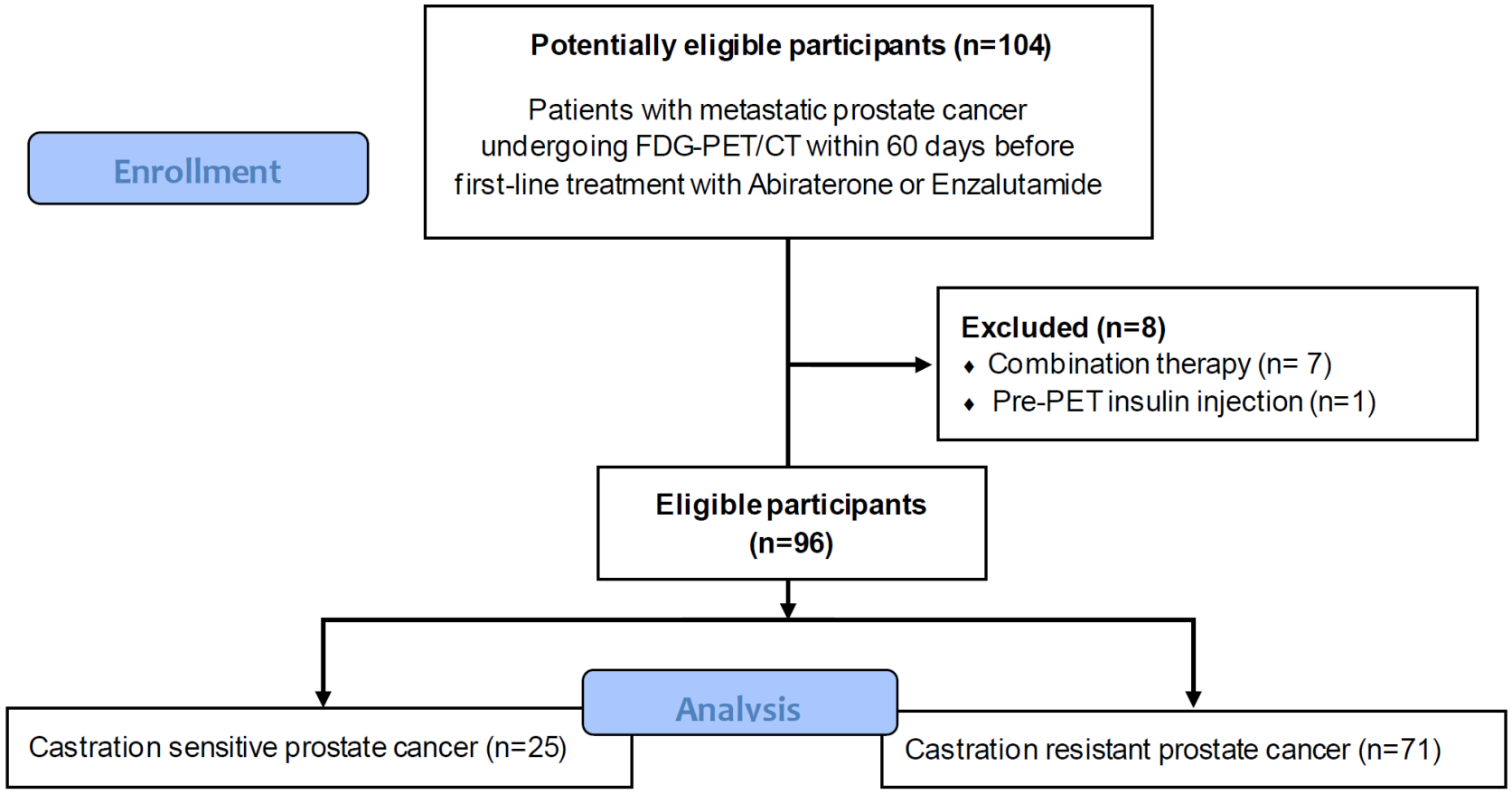
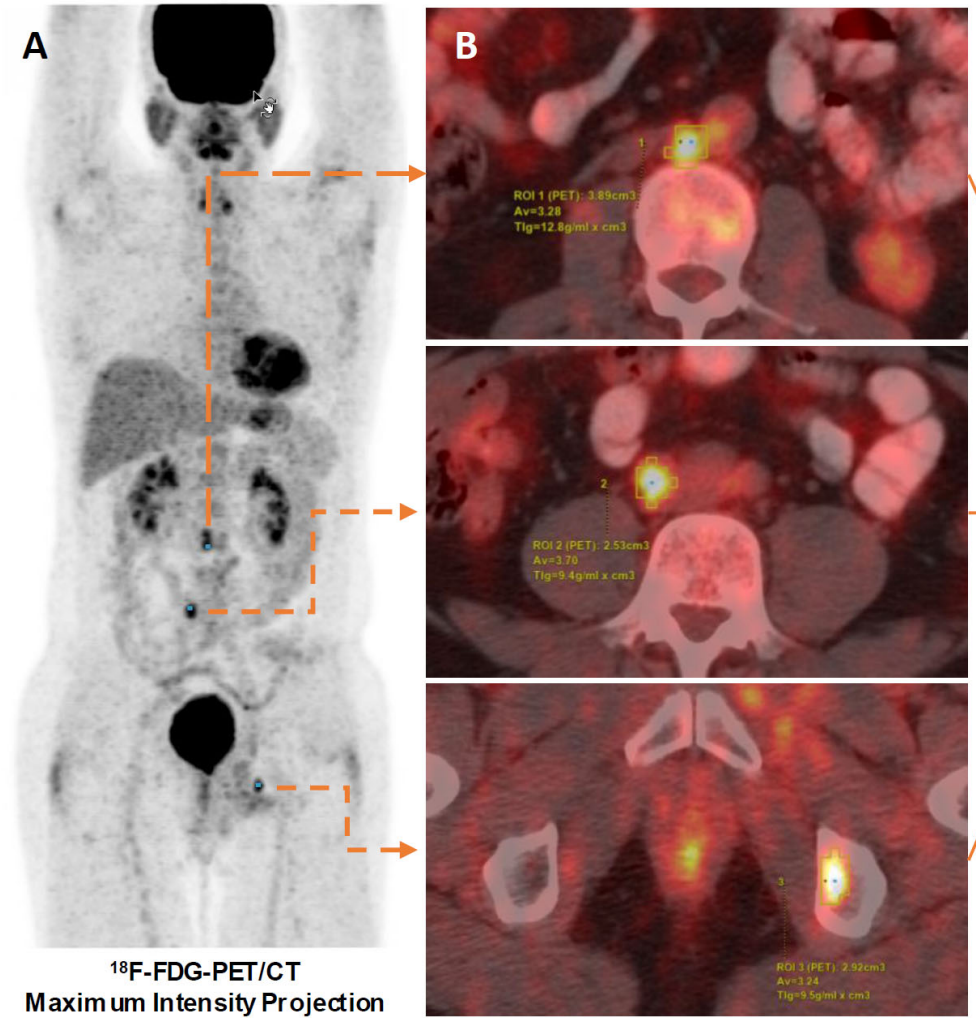
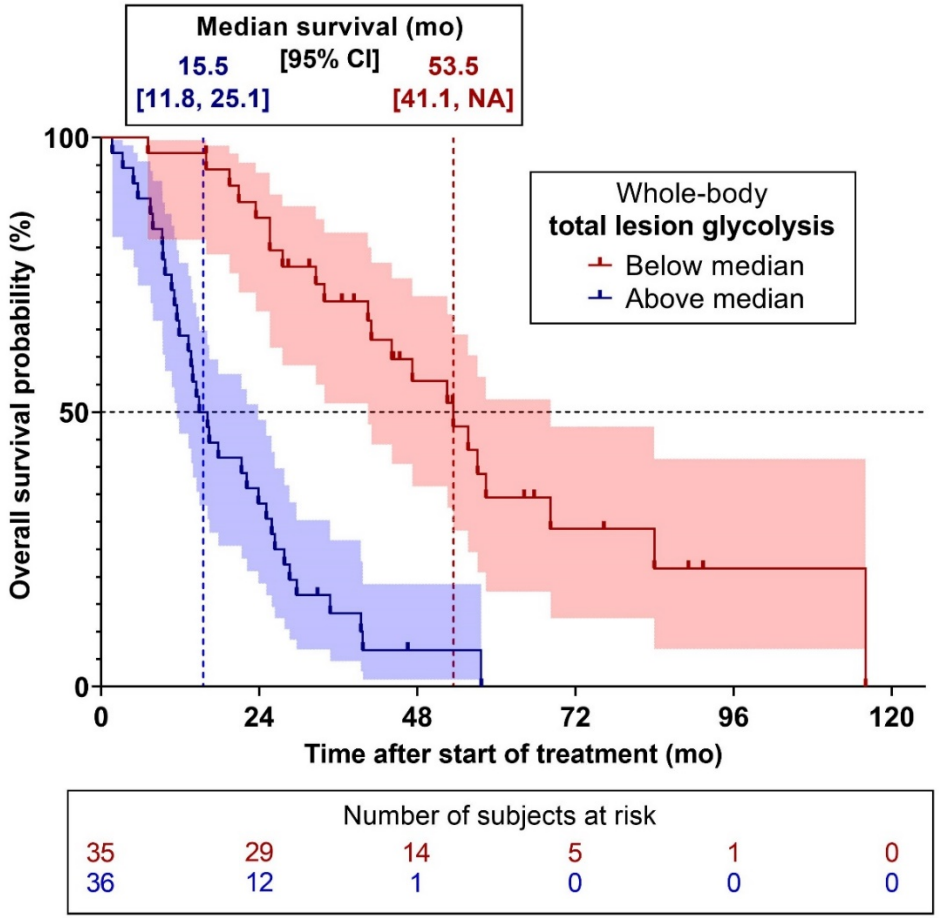


FIGURE 2: FDG-PET/CT of a patient with metastatic prostate cancer illustrating the image analysis methodology of this study. Maximum Intensity Projection (A) shows FDG-avid metastases in an aortocaval lymph node (B, top), a common iliac lymph node (B, middle), and ischial bone (B, bottom). For every FDG-avid metastasis, PET-derived metrics (i.e. MTV, TLG) were extracted and then summarized on a whole-body scale for statistical analyses.



Site of disease	Average SUV (g/mL)	MTV (mL)	TLG (g)
Aortocaval lymph node	3.28	3.89	12.8
Common iliac lymph node	3.70	2.53	9.4
Ischial bone	3.24	2.92	9.5
Whole body	**-**	**9.34**	**31.7**

FIGURE 3: Overall survival probabilities of patients with metastatic castration-resistant prostate cancer (mCRPC) following first-line treatment with abiraterone or enzalutamide, stratified by median whole-body total lesion glycolysis (TLG) measured on FDG-PET/CT. Sample size was too small for deriving a reliable optimal cutoff TLG and no statistical test was applied. Median overall survival times with 95% confidence interval (CI) are provided.



GRAPHICAL ABSTRACT