Utility of FDG-PET in Clinical Neuroendocrine Prostate Cancer

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BACKGROUND. Fluorodeoxyglucose (FDG) positron emission tomography (PET) has well-characterized limitations in prostate adenocarcinoma (PCA). However, data assessing the utility of PET in neuroendocrine prostate cancer (NEPC) is limited to isolated case reports. Herein, we describe the first case series to assess the utility of FDG-PET in NEPC.

METHODS. Inclusion criteria consisted of clinically progressive metastatic PCA in the setting of a chromogranin-A levels $>1.5\times$ the upper limit of normal, and ≥ 1 FDG-PET scan after the diagnosis of NEPC, which yielded 23 patients. All metastatic lesions on CT, PET, and bone scan were read by two independent physicians.

RESULTS. Five hundred ninety two unique lesions were identified across all imaging modalities, 510 were bone metastases, and 82 were soft tissue metastases. Of bone lesions, 22.2%, 92.7%, and 77.6% were detected by PET, CT, and bone scan, respectively. Of soft tissue lesions, 95.1% and 97.5% were detected by PET and CT, respectively. Stratified by the median survival from NEPC diagnosis, patients who survived <2.2 versus ≥ 2.2 years had more PET avid bone (8 vs. 2, $P = 0.06$) and soft tissue lesions (7 vs. 1, $P = 0.01$), and higher average SUVmax of bone (5.49 vs. 3.40, $P = 0.04$) and soft tissue lesions (8.02 vs. 3.90, $P = 0.0002$).

CONCLUSIONS. In patients with clinical NEPC, we demonstrate that FDG-PET has clinical utility in the detection of metastatic disease. In addition to detection, PET allows for treatment response to determine tumor viability. With novel therapies on the horizon to treat NEPC, consideration to investigate the use of FDG-PET to monitor response is warranted. *Prostate 74:1153–1159, 2014.* © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

Neuroendocrine prostate cancer (NEPC) is a rare malignancy that carries a devastating prognosis with a median survival of approximately 12 months [1]. The pathogenesis of NEPC is controversial with multiple competing theories postulated over the past four decades to describe the cell of origin. Initially, NEPC was felt to be derived from an amine precursor uptake and decarboxylase cell lineage [2]. However, embryologic and clinic observations did not fully support this theory [3], and modern rationales pose that NEPC is more commonly a progression of final dedifferentiation from prostate adenocarcinoma (PCA) [4,5]. This is supported by preclinical in vitro and xenograft data, which have shown that long-term androgen deprivation therapy (ADT) promotes the transformation from PCA to NEPC [6–8]. Additionally, molecular studies of mixed tumors analyzing for ERG gene rearrangements demonstrate a concordance of ERG status between PCA and NEPC foci [9].

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Contrasted to the 233,000 cases of PCA that are anticipated to occur in 2014 in the United States, the true incidence of NEPC in largely unknown [10]. Estimates of 1,000–5,000 cases of NEPC are often cited (<2% of all cases of prostate cancer), but data suggests that 10–100% of PCA have a neuroendocrine subpopulation [11–14]. Furthermore, greater than 30% of the 34,000 cases of lethal PCA transform into NEPC [15]. These estimates are expected to continue to increase secondary to the prevalent usage of ADT in nearly all stages of prostate cancer in conjunction with the surge of available novel second generation anti-androgen therapies [16–18].

NEPC is often a clinical diagnosis, as pan-biopsies of metastatic sites are not routinely performed. NEPC is commonly diagnosed in the context of clinical progression on ADT, formation of lytic bone metastases (contrasted to the more common blastic form from PCA) and visceral metastases, all in the setting of a low serum PSA [15]. Elevated neuroendocrine serum markers, such as chromogranin A or neuronal serum enolase, are used to support the clinical diagnosis of NEPC. However, these markers have not been established to monitor response to treatment in NEPC.

Currently, clinical trials conducted on NEPC use cross-sectional imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI) to monitor response to therapy [1]. Unfortunately most NEPC patients have undergone years of treatment and the lesions seen may often represent treatment changes or non-active disease. The use of fluorodeoxyglucose (FDG) positron emission tomography (PET) can provide valuable metabolic information to aid in diagnosis of viable tumor. However, FDG-PET has numerous limitations for use in PCA [19], and the utility for NEPC has only been reported in single person case reports [20]. As PET has proven benefit in other small cell malignancies [21], we hypothesized that PET may have improved detection ability in NEPC, and herein report the first series of use of PET in NEPC.

METHODS

Institutional review board approval was obtained to perform this study. Patients diagnosed with NEPC from 2003 to 2013 were queried via our institution's prospectively maintained database. Inclusion criteria consisted of biopsy proven PCA in the setting of castration-resistant disease and a chromogranin-A (CrA) levels $>1.5\times$ the upper limit of normal (ULN). In addition, patients were required to have ≥ 1 FDG-PET scan after the diagnosis of NEPC. Reference values for the ULN of CrA were set at 30 ng/ml. Patients were excluded if they had a history of or active lymphoma or other small cell malignancies. Twenty-three men met eligibility criteria and form the study cohort.

Baseline demographic details were collected including race, gender, and age. Staging information for the original PCA, including Gleason score, pre-treatment PSA, and clinical TNM stage were collected. Treatment details of patient's original PCA treatment were recorded (primary ADT, radiotherapy, or prostatectomy). Dates of initial and maximum CgA levels, FDG-PET/CT scans, and ^{99m}Tc-bone scans were collected.

All patients had a combined PET/CT scan after the diagnosis of NEPC. PET/CT examinations were performed on one of our institutions PET/CT scanners (Discovery STE; GE Healthcare, Milwaukee, WI). The low-dose CT (~140 kV) was performed with 5 mm section thickness and pitch of 0.75–1.5. The PET scan was acquired approximately 60 min after 370 MBq of FDG was injected intravenously. As per our institutional protocols, patients were scanned from the base of skull to upper thighs.

The first PET/CT scan after the diagnosis of NEPC was used for all lesion analyses. In addition, 20 of the 23 patients also had a ^{99m}Tc bone scan within 6 months of the PET/CT scan. Previously used methods to comprehensively quantify all metastatic lesions were used [22]. In brief, a template consisting of 94 discrete anatomic skeletal sites, and 15 discrete soft tissue sites consisting of major nodal basins and viscera was used. Two physicians, a radiologist (L.T.) and a nuclear medicine physician (S.G.), independently evaluated all imaging examinations. Lesions that could not be agreed upon were resolved by a third reader, a dually trained radiologist and nuclear medicine physician (J.O.). All readers were blinded to baseline characteristics, treatment details, and oncologic outcomes. The FDG scans were imported to a dedicated workstation and coregistered to the CT and bone scans. All lesions were quantified by measuring the maximum standardized uptake value (SUVmax) adjusted to body weight. Efforts were made to quantify each individual lesion, however at times there were confluent clusters of lesions that could not be accurately isolated. In such cases, the confluent lesions were counted as a single metastasis. For skeletal sites, the PET, CT, and bone scan (if available) were compared. For soft tissue sites, only the PET and CT were compared. SUVmax was recorded for all individual lesions.

Overall survival (OS) rates were calculated for both PCA and NEPC: (1) For PCA the date of initiation of therapy for PCA until date of last follow-up or death was used; (2) for NEPC the date of diagnosis of NEPC until death or last follow-up was used. Exploratory analyses were conducted for predictors of OS, and the cohort was stratified into two subgroups by the median OS from time of NEPC diagnosis (2.2 years).

Correlative analyses were conducted on CrA levels and the number of PET avid lesions, and SUVmax. The CrA value in closest proximity to the FDG-PET scan was used with a median interval from CrA to FDG-PET of five days. Two-sided *P*-values ≤ 0.05 were considered statistically significant. Statistical analysis was performed using R version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Prostate Adenocarcinoma Clinical and Treatment Characteristics

At the time of PCA diagnosis the cohort was classified as high and very high risk by National Comprehensive Cancer Network (NCCN) criteria; 74% (n = 17) of patients had a Gleason score ≥8, 30% (n = 7) had clinical ≥T3 disease, the median percent biopsy core positivity was 100%, and 48% (n = 11) had radiographic metastatic disease (Table I). The median pre-treatment PSA value was only 11.7 ng/ml.

Fifty-seven percent (n = 13) of patients had definite treatment for their PCA with either prostatectomy (n = 6) or radiation therapy (n = 7). Patients who did not receive definitive therapy were treated with primary ADT (44%, n = 10). Of the seven patients who underwent radiotherapy, five received neoadjuvant and concurrent ADT. Of the six patients who underwent surgery, four had pathologically involved lymph nodes. The median OS from initiation of treatment for PCA was 5.7 years.

Neuroendocrine Prostate Cancer Clinical Characteristics

The median time from diagnosis of PCA until development of NEPC was 4.6 years (range 0–20.8 years), and the median OS from time of NEPC diagnosis to death was 2.2 years. The median age of patients diagnosed with NEPC was 70.1 years (range 56.4–90.4 years). Ninety-one percent (n = 21) of patients were diagnosed by an elevated CgA value alone, and the remaining 9% (n = 2) had histopathological confirmation in conjunction with an elevated CgA level. The median CgA value at time of diagnosis was 110.0 ng/ml (range 45–442 ng/ml), and the mean CgA was 130.5, which corresponds to 4.4× the ULN. The median peak CrA value was 142 ng/ml (range 88–444 ng/ml).

Radiographic Analyses of Neuroendocrine Prostate Cancer

A total of 592 unique lesions were identified across all imaging modalities, of which 86.1% (n = 510) were

TABLE I. Baseline and Treatment Characteristics

Variable	N	%
Race		
White	19.0	82.6
Other	4.0	17.4
Age[a]		
Median	70.1	
Range	56.4–90.4	
Prostate adenocarcinoma details		
Clinical T-stage		
T1	8	34.8
T2	7	30.4
T3	5	21.7
T4	2	8.7
NA	1	4.3
Biopsy Gleason Score		
≤6	1	4.3
7.0	4	17.4
8–10	17	73.9
NA	1	4.3
Pre-treatment PSA (ng/ml)		
Median	11.7	
Range	1.1–100.0	
Number of cores taken		
Median	10.0	
Range	4–16	
Percent core positivity (%)		
Median	100%	
Range	25–100	
Metastases at diagnosis	11.0	47.8
Treatment of adenocarcinoma		
Radiotherapy	7	30.4
Prostatectomy	6	26.1
Primary ADT	10	43.5
Radiotherapy details		
EBRT alone	5	21.7
EBRT + brachytherapy	2	8.7
NeoADT	5	21.7
Surgery details		
Pathologic t-stage		
T1, T2, T4	0	
T3	6	26.1
Pathologic n-stage		
N0	2	8.7
N1	4	17.4
Salvage EBRT	2	8.7
Neuroendocrine prostate cancer details		
Method of initial diagnosis		
Biopsy	2	8.7
Elevated CrA	21	91.3
Initial CrA level		
Median	110.0	
Mean	130.5	
Range	45.0–442.0	
Highest CrA level		
Median	142.0	

(Continued)

TABLE I. Continued.

Variable	N	%
Mean	170.9	
Range	88.0–444.0	
Number of FDG-PET scans after NEPC diagnosis		
Median	2	
Range	1–9	
Extent of disease		
0–5 sites	6	26.1
6–25 sites	8	34.8
26–50 sites	6	26.1
50–110 sites	3	13.0

[a]From date of NEPC diagnosis.

bone metastases (Table II). Three patients did not have bone scans, so the total number of bone lesions for these 20 patients was 396. One patient did not have visible disease by any imaging modality, 65% (n = 15) had PET avid lesions, 96% (n = 22) had lesions detected by CT, and 85% (n = 17) had lesions detectable by bone scan. One patient had skeletal disease predominantly detected only by PET, and not CT nor bone scan.

Of the bone lesions, 22.2% (n = 113), 92.7% (n = 473), and 77.6% (n = 230) of the total bone lesions were detected by PET, CT, and bone scan, respectively (Table II). PET identified 5.4% (n = 28) and 6.8% (n = 27) new lesions not detected by CT or bone scan, respectively. The average SUVmax of all lesions was 4.52 (range 2.00–8.77).

A total of 82 unique soft tissue metastases were detected (Table III). Thirty-nine percent (n = 9) of patients had no detectable soft tissue lesions by either PET or CT, and of the remaining 14 patients, PET and CT detected lesions in 86% (n = 12) and 93% (n = 13) of patients, respectively. One patient had soft tissue disease predominantly detected only by PET, and not CT. Of the total soft tissue lesions, 95.1% (n = 78) versus 97.5% (n = 80) were detected by PET versus CT, respectively. PET identified two new lesions that were

TABLE II. Skeletal Lesion Analysis Per Patient

	Number of lesions identified by					Unique lesions identified by PET but not	
Patient #	PET	Average SUVmax	CT	Bone scan	Total unique lesions	CT	Bone scan
1	16	4.00	16	13	16	0	3
2	0	NA	0	1	1	0	0
3	0	NA	12	0	12	0	0
4	0	NA	4	5	6	0	0
5	0	NA	37	34	37	0	0
6	1	2	31	2	31	0	0
7	1	3.5	3	3	4	1	0
8	1	2.3	85	1	85	0	0
9	2	3.75	9	12	12	0	0
10	0	NA	0	0	0	0	0
11	17	9.1	18	19	19	0	0
12	3	3.13	17	NA	17	0	NA
13	9	3.54	25	24	27	0	0
14	1	4	12	NA	12	0	NA
15	1	4.8	1	1	1	0	0
16	27	4.92	1	9	28	27	19
17	17	8.77	85	NA	85	0	NA
18	12	6.02	12	9	12	0	3
19	4	3.23	5	2	5	0	2
20	0	NA	34	31	34	0	0
21	1	4.7	2	2	2	0	0
22	0	NA	2	0	2	0	0
23	0	NA	62	62	62	0	0
Total (average)	113	(4.52)	473	230	510	28	27
Percent of total lesions (%)	22.2		92.7	77.6[a]	100	5.5	6.8[a]

NA, not available.
[a]Total number of lesions was 396 for patients who had bone scans performed.

TABLE III. Soft Tissue Lesion Analysis Per Patient

Patient #	Number of lesions identified by			Totalunique lesions	Unique lesions identified by PET but not: CT
	PET	Average SUVmax	CT		
1	2	3.80	2	2	0
2	2	3.30	0	2	2
3	0	NA	0	0	0
4	1	4.30	1	1	0
5	2	9.10	2	2	0
6	0	NA	0	0	0
7	0	NA	3	3	0
8	0	NA	0	0	0
9	1	4.90	1	1	0
10	0	NA	0	0	0
11	16	10.21	16	16	0
12	0	NA	0	0	0
13	7	9.00	7	7	0
14	0	NA	1	1	0
15	1	4.2	1	1	0
16	11	8.67	11	11	0
17	22	7.68	22	22	0
18	12	8.48	12	12	0
19	0	NA	0	0	0
20	0	NA	0	0	0
21	0	NA	0	0	0
22	1	6.1	1	1	0
23	0	NA	0	0	0
Total (average)	78	(6.65)	80	82	2
Percent of total lesions (%)	95.1		97.5	100	2.4

NA, not available.

not detected by CT. The average SUVmax for soft tissue lesions was 6.65 (range 3.30–10.21).

Patients who survived <2.2 versus ≥ 2.2 years had more PET avid bone lesions (8 vs. 2, respectively, $P = 0.06$), and significantly more soft tissue PET avid lesions (7 vs. 1, respectively, $P = 0.01$). Furthermore, patients who survived <2.2 versus ≥ 2.2 years had a significantly higher average SUVmax of bone lesions (5.49 vs. 3.40, $P = 0.04$), and soft tissue lesions (8.02 vs. 3.90, $P = 0.0002$).

Using the CrA in closest proximity before the FDG-PET, there was no correlation between number of PET avid lesions and CrA level. Furthermore, there was no correlation with average SUVmax of the lesions and the CrA level. This held true for both bone and soft tissue lesions (all correlation R-square values <0.1).

DISCUSSION

We report the first series of FDG-PET in a cohort of clinically transformed NEPC, and demonstrate the utility of PET, CT, and bone scan in this rare disease. FDG-PET appears to have excellent detection rates of nodal and visceral metastases (95%) for patients with NEPC. The present study has practical clinical applicability as most patients are diagnosed with NEPC based on clinical and laboratory features, rather than by biopsy. However, it must be emphasized that without a systematic and comprehensive biopsy of all metastatic sites, a truth standard cannot be established from any imaging study; hence the true rate of detection of NEPC metastases cannot be quantified.

FDG-PET has had a disappointing history for use in PCA compared to many other hematologic and solid tumors [19]. FDG-PET for primary prostate cancer has limited utility secondary to high uptake of adjacent organs, primarily the bladder, as well as the low glycolytic activity of PCA. Currently, FDG-PET is not recommended by the NCCN as a routine part of staging in PCA [23]. Likewise, the American Society of Clinical Oncology put out a statement on five of the most important ways to reduce costs and improve

care. Ranking in at number two was to avoid use of advanced imaging technology in patients with localized prostate cancer, such as FDG-PET [24]. This culminated in a statement released in March of 2013 from the Centers for Medicare & Medicaid Services (CMS) to no longer provide coverage of FDG-PET for use in PCA. This decision was based on the decades of use of FDG-PET in PCA, often in localized disease, with no clear demonstrable benefit. Eventually, this decision was overturned to cover a limited number of FDG-PET scans based on the apparent applicability in more advanced forms of the disease [19]. However, what is not known is if the improved detection rate of FDG-PET in CRPC is secondary to the increased incidence of NEPC (>30% in this stage of disease), or a true improvement in tracer uptake in PCA independent of NEPC transformation [15]. Furthermore, as neither CT nor bone scan provide information to tumor viability, many of the skeletal lesions detected by these modalities may represent treatment effects.

Consistent with the theory that NEPC is a terminal process in the progression of PCA, it would be rational to assume that there is a heterogenous mixture of NEPC and PCA lesions in metastatic patients. This theory is supported in part by data over the last decade using 16β-18F-fluoro-5α-dihydrotestosterone (FDHT) PET [25]. DHT is the dominant ligand for PCA that activates the androgen receptor (AR), which as a complex is translocated to the nucleus and binds DNA. NEPC has been shown to lose AR expression, which occurs late in the dedifferentiation process of PCA to NEPC [26]. Studies with FDHT have occurred in patients with advanced castration resistant disease, and often result in mixed uptake of lesions visible by other modalities (<80% detection rate) [25]. This is thought by some to be a limitation of the radiotracer; however this may simply be insight into the biology of lesions that have transformed to NEPC and lost the ligand binding target. For this reason, it is unclear if the 22% PET detection rate of bone lesions is a reflection of the lack of NEPC detection, or the limitation of PET to detect PCA.

A hallmark of NEPC is the predilection for soft tissue metastases, especially visceral metastases [15]. FDG-PET has demonstrated utility in other small cell malignancies that metastasize to soft tissue sites, such as small cell lung cancer [21]. We found a 95% detection rate of all soft tissue lesions using PET, which was comparable to CT (98%). Bone lesions however were detected at a markedly lower frequency with PET compared to CT (22% vs. 93%). Despite the limited detection rate of bone lesions in the present series, FDG-PET may have potential to monitor treatment response in NEPC for those with a dominant soft tissue disease burden. This is of increasing importance in the current landscape of oncology. Precision medicine is being applied even in less common malignancies, and next-generation RNA sequencing and oligonucleotide arrays have been employed even in NEPC to detect new drugable targets [27]. One promising target that was recently identified is the serine/threonine kinase Aurora kinase A (AURKA), that when inhibited can cause complete suppression of neuroendocrine biomarkers both in vitro and in vivo. With new therapies on the horizon to treat NEPC there is a pressing need for improved methods of detection and treatment response monitoring.

Despite our efforts to rigorously analyze all available patient data and present it in a transparent manner, limitations exist in our study. As previously stated, without comprehensive histopathology of every lesion, a true sensitivity/specificity rate cannot be generated and was not reported. The study is retrospective, and the reason for obtaining the FDG-PET scan varied for each patient, but predominantly was for enrollment on institutional protocols. This may have introduced a selection bias. In addition, patients had heterogenous treatment histories, which may impact the detection ability of certain modalities (prior radiotherapy or systemic therapy).

CONCLUSIONS

In patients with clinically diagnosed NEPC we demonstrate that FDG-PET has clinical utility in the detection of predominantly soft tissue metastases. However, secondary to the known limitations of FDG-PET for PCa bone lesions, FDG-PET for NEPC may provide utility in detection and monitoring of response in both soft tissue and bone metastases. With novel therapies in development to treat NEPC, future trials should consider utilizing PET/CT as part of treatment response monitoring in addition to serum biomarkers.

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