Role for ^{11}C-choline PET in active surveillance of prostate cancer

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Abstract

Introduction: Active surveillance (AS) is an increasingly popular management strategy for men diagnosed with low-risk indolent prostate cancer. Current tests (prostate-specific antigen [PSA], clinical staging, and prostate biopsies) to monitor indolent disease lack accuracy. ^{11}C-choline positron emission tomography (PET) has excellent detection rates in local and distant recurrence of prostate cancer. We examine ^{11}C-choline PET for identifying aggressive prostate cancer warranting treatment in the AS setting.

Methods: In total, 24 patients on AS had clinical assessment and PSA testing every 6 months and ^{11}C-choline PET and prostate biopsies annually. The sensitivity and specificity to identify prostate cancer and progressive disease (PD) were calculated for each ^{11}C-choline PET scan.

Results: In total, 62 biopsy-paired, serial ^{11}C-choline PET scans were analyzed using a series of standard uptake value-maximum (SUVmax) cut-off thresholds. During follow-up (mean 25.3 months), 11 of the 24 low-risk prostate cancer patients developed PD and received definitive treatment. The prostate cancer detection rate with ^{11}C-choline PET had moderate sensitivity (72.1%), but low specificity (45.0%). PD prediction from baseline ^{11}C-choline PET had satisfactory sensitivity (81.8%), but low specificity (38.5%). The addition of clinical parameters to the baseline ^{11}C-choline PET improved specificity (69.2%), with a slight reduction in sensitivity (72.7%) for PD prediction.

Conclusions: Addition of ^{11}C-choline PET imaging during AS may help to identify aggressive disease earlier than traditional methods. However, ^{11}C-choline PET alone has low specificity due to overlap of SUV values with benign pathologies. Triaging low-risk prostate cancer patients into AS versus therapy will require further optimization of PET protocols or consideration of alternative strategies (i.e., magnetic resonance imaging, biomarkers).

Introduction

Prostate cancer is the most common solid organ cancer and the third leading cause of cancer-related death in men.[1] For many patients, prostate cancer behaves as an indolent disease; the cancer is not expected to progress to a clinically significant disease within a patient's lifetime.[2] With improved screening techniques and increased awareness to undergo screening for prostate cancer, it has been estimated that 27% to 56% of patients diagnosed with prostate cancer will have indolent disease,[3] and only a subpopulation of those will suffer from signs of progressive disease (PD) during their lifetime.

Active surveillance

Multiple studies on active surveillance (AS) have suggested the feasibility of AS for low-risk prostate cancer allowing patient to avoid unnecessary treatment and associated toxicities. Up to two-thirds of men enrolled in AS protocols are spared any treatment.[4] AS is an increasingly popular management strategy for men diagnosed with low-risk indolent prostate cancer, where disease is closely monitored and treatment is deferred unless there are signs of PD.[2,5,6] For an AS program to be successful, it is critical that disease progression is promptly detected. Unfortunately, using serum prostate-specific antigen (PSA) levels, clinical stage, and the Gleason score (GS) on prostate biopsies to monitor a patient's disease have demonstrated an accuracy of only 61% to 74% in predicting organ confined disease.[7,8] Hence, there is a need for more ways to distinguish aggressive from indolent prostate cancer. Imaging is emerging as an additional screening method, with multiparametric magnetic resonance imaging (MRI) being recommended by some guidelines at baseline for stratification of risk.[9,10]

Biological imaging in prostate cancer ^{11}C-choline-PET

Positron emission tomography (PET) imaging has been used to identify and localize prostate cancer, with Carbon-11 labelled choline (^{11}C-choline) PET currently demonstrating the greatest potential along with other radiotracers like Fluorine-18-fluorodeoxyglucose (^{18}F-FDG).[11,12] Although ^{18}F-FDG is routinely used in other cancer sites (e.g., breast), it has limited efficacy for visualizing low-risk prostate cancer due to its low glycolytic activity. Cancer is associated with cell proliferation and up-regulation of choline-kinase, the enzyme that catalyzes the phosphorylation of choline. As a result, malignant cells have an elevated level of choline metabolites, allowing for the utilization of ^{11}C-choline PET imaging in oncology. Several studies have demonstrated the utility of ^{11}C-choline PET in prostate cancer detection and progression, but there are no published reports in the AS setting. This novel investigation assessed the utility of biological imaging with ^{11}C-choline PET in the context of AS to determine if it can be used to distinguish indolent from aggressive prostate cancer.

Methods

Study design

This was a single-institution, prospective, phase II clinical trial. Research ethics approval was obtained from the local research ethics committee. All eligible patients provided written informed consent prior to enrollment and participation in the trial. All patients were followed as per schedule: clinical assessment and PSA testing were performed every 3 months for the first year and biannually thereafter; ^{11}C-choline PET and prostate biopsies were taken at baseline (minimum of sextant biopsies with 8-12 samples taken) and annually thereafter.

Patient population

In total, 24 patients with low-risk prostate cancer were enrolled into this study from April 2009 to May 2012. The inclusion criteria were: histologically proven adenocarcinoma of the prostate classified as low-risk with clinical stage ≤T2a, composite GS ≤6, PSA ≤10 ng/mL, ≤50% of each core and ≤3 cores biopsies involved with disease from one set of biopsies. PD was identified during follow-up by: Gleason pattern ≥4, ≥50% of biopsies involved from one set of biopsies, clinical stage ≥T3a, or PSA doubling time <2 years. Patients with PD were offered treatment with any one or combination of standard treatment options.

^{11}C-choline PET

^{11}C-choline was produced by the Edmonton PET Centre. ^{11}C-choline PET scans were performed prior to prostate biopsies at specified time intervals to minimize potential artifact. Patients were administered 400 MBq (±10%) of ^{11}C-choline intravenously. Five minutes after injection, dynamic images of the prostate were acquired over about 30 minutes, preceded by a non-diagnostic computed tomography (CT) scan for positioning and attenuation correction. All ^{11}C-choline PET scans were acquired using the Allegro PET (Phillips Healthcare, Andover, MA) or Gemini PET/CT camera (Phillips).

Interpretation of ^{11}C-choline PET

Radiological review of all the anonymized scans was performed individually and reported upon without the other results known. The radiologist reported the presence of imaging characteristics compatible with a malignancy, the presence or absence of increased uptake as well as standardized uptake value (SUV) in each of the sextants of the prostate (base, mid-gland and apex in the right and left lobes of the prostate). Upon receiving these results, the radiologist defined the index of suspicion for each lesion using a score of 0 to 4.[13] After reviewing each individual set of images, the radiologist reviewed the collection of images for a particular patient to determine if there were signs of PD over time. The radiologist reported signs of progression, including new lesions, increased area of uptake within the prostate above a threshold SUV, or other changes suggestive of disease progression (using modified Positron emission tomography Response Criteria in Solid Tumors [PERCIST] criteria).[14] PERCIST is based on ^{18}F-FDG PET and, as such, not all recommendations can be utilized. We examined SUVmax rather than lean body mass (SUL), but utilized the 30% increase as the measure of disease progression.

Correlation of ^{11}C-choline PET with pathology

The pathological information provided by the prostate biopsies was used as a "gold standard" to determine the presence or absence of prostate cancer in each sextant of the prostate. The pathological information of a particular sextant of the prostate was correlated with the ^{11}C-choline PET to determine the ability of this investigation to accurately identify prostate cancer and PD. A true-positive finding was defined as concordance of ^{11}C-choline PET with the pathological biopsy result (e.g., presence of measurable lesion with a SUVmax above a certain threshold in the same sextant as a pathologically confirmed lesion). Descriptive statistics were used to analyze ^{11}C-choline PET data to calculate sensitivity and specificity of prostate cancer detection rate and PD.

Results

Patient demographics

In total, 24 patients consented to the study (Table 1). Among all patients, 69 sets of biopsies were analyzed and the median number of biopsies per patient was 3. All biopsy sets contained 833 cores (average 12.25 cores per biopsy set [range: 6–17]), with 146 cores positive for prostate cancer (average 2.1 positive cores per biopsy set [range: 0–9]) with 5 sets of biopsies having greater than 50% positive cores. The mean number of cores per biopsy at baseline was 12.0 and during AS was 12.2. Twenty-one biopsies in 8 patients showed no cancer (benign) and only 1 of these patients subsequently had PD during follow-up.

Table 1. Patient demographics and disease characteristics at baseline

Characteristic	Value
Age, years	63.8 (51–75)
PSA, ng/mL	6.0 (1.6–9.7)
Clinical stage, n (% total)	
cT1c	21(87.5)
cT2a	2 (8.3)
cT2b	1 (4.2)
Gleason score 6 (3+3), n (% total)	24 (100%)
% biopsies positive per patient	19.0 (0*–58.3)
Density of tumour in positive biopsies (% core)	15.4 (1.0–38.5)
HGPIN, n (% total)	7 (29.2)
PNI, n (% total)	4 (16.7)
LVI, n (% total)	0 (0.0)

Data are represented as mean (range), unless otherwise specified. *2 patients had benign biopsies at study enrollment but previous positive biopsies.
PSA: prostate-specific antigen; HGPIN: high-grade prostate intraepithelial neoplasia; PNI: perineural invasion; LVI: lymphovascular invasion.

Disease progression

During the mean follow-up of 25.3 months (range: 9.9–48.8), 11 of 24 (45.8%) low-risk prostate cancer patients developed PD and received definitive treatment. The mean time from study enrolment to PD requiring treatment was 20.3 months (range: 6.2–37.9 months).

The main factor for upstaging to PD was higher GS (Table 2). Five of the 11 patients with higher GS also had ≥50% of cores involved and 2 of these also had PSA doubling time <2 years. Subsequent management for patients with PD included: 5 low-dose rate prostate brachytherapy, 2 radical prostatectomies, 2 external beam radiation therapy and 2 continued AS despite disease progression.

^{11}C-choline PET

Among the 24 patients, 67 randomized ^{11}C-choline PET scans were analyzed (median of 3 scans per patient) and a total of 117 PET-CT measurable lesions (mean diameter of 15.2 mm [range: 8.0–45.0]) were identified by the radiologist. Mean SUV of detected prostate lesions was 3.5 [range: 1.9–6.4] (Fig. 1). Background mean SUV uptake in uninvolved prostate was 1.8 (range: 0.8–2.5) and obturator muscle was 0.8 (range: 0.1–1.5).

To determine the ability of ^{11}C-choline PET to detect prostate cancer, scans within 6 months of prostate biopsy results were compared. There were 62 evaluable pairs of scans and biopsies. The sensitivity of ^{11}C-choline PET to detect prostate cancer varied from 57.7% to 95.4% with different SUV cut-offs and regional analyses (Table 3). Whole prostate gland included any lesions on ^{11}C-choline PET corresponding with any involved biopsies, whereas left/right division and sextant data required lesions on ^{11}C-choline PET to correspond with cancer identified in the same half or sextant for biopsies.

Of the 24 patients, 17 had positive baseline ^{11}C-choline PET scans (measurable lesions with SUVmax ≥3.3); of these, 9 patients developed PD. Serial ^{11}C-choline PET scans revealed subsequent presence of PD with a sensitivity of 63.0%, in contrast to baseline ^{11}C-choline PET scans, where sensitivity to predict future PD was 81.8% (Table 4). Using the modified PERCIST criteria, an increase in 30% of SUVmax as a measure of PD had a sensitivity of 58.3%.

The mean SUVmax increased with GS (4.6 for GS 8 vs. 4.0 in GS 7 (p = 0.47) and was 3.4 in patients with GS 6 (p = 0.07) although it was not statistically significant, probably due to small numbers (Table 5). All patients had confirmed disease, although some biopsies did not have positive cores and were listed as benign. This was likely due to undersampling and GS 6 disease.

Combination of baseline ^{11}C-choline PET (SUV ≥3.3) with clinical characteristics of age-adjusted PSA ≥1.5-times the upper-limit-of-normal and percent of positive cores at baseline ≥25% increased the specificity to predict PD from 38.5% to 69.2%, with a small reduction in sensitivity from 81.8% to 72.7%.

Table 2. Characteristics for PD in 11 patients

	GS ≥7	≥ 50% of cores biopsies involved	PSADT <2 years	Clinical stage ≥T3a
Patients with PD, n (%)	11 (100)	5 (45.5)	2 (18.2)	0

PD: progressive disease; GS: Gleason score; PSADT: prostate-specific antigen doubling time.

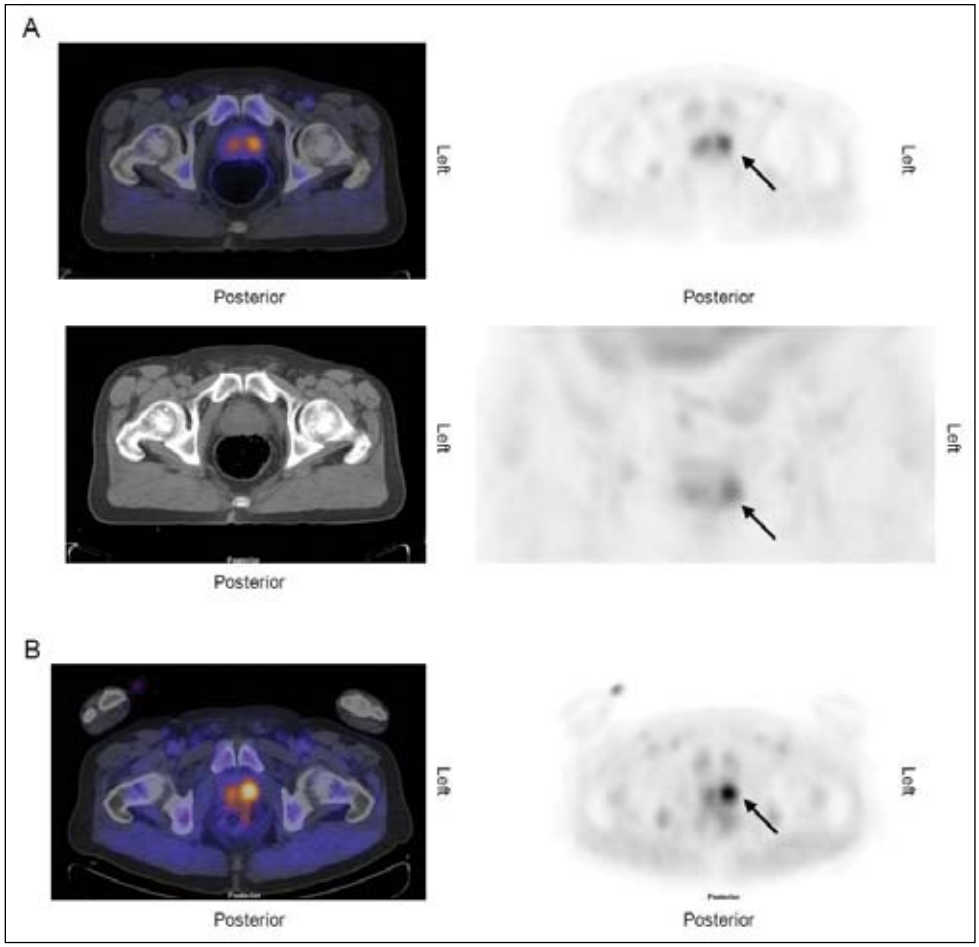

Fig. 1. Representative [11]C-choline positron emission tomography (PET) scan. (A): Biopsy proven Gleason score (GS) 6 prostate adenocarcinoma in the left apex. A 1.8-cm nodule with focal uptake (standard uptake value [SUV] maximum = 3.8) is seen in the left apex of prostate gland on axial and coronal [11]C-choline PET scans (right top and bottom corners respectively) and the axial fused image (left top corner) using the computed tomography image (left bottom corner) for anatomical information. (B): Consecutive [11]C-choline scan shows increase uptake of the tracer in the nodule of the left apex (SUV maximum = 6.4). This represented progression of disease by PERCIST (Positron emission tomography Response Criteria in Solid Tumors) criteria and GS 7 was confirmed by biopsy.

Discussion

Active surveillance

Prostate cancer shows variable biologic behaviour and causes death in a relatively small proportion of men.[2,15,16] Therefore, identifying aggressiveness early in the disease process is beneficial for therapeutic decision-making. During surveillance, about 30% of patients will be reclassified as higher-risk and offered definitive treatment.[2] Although comparable, our study had a higher proportion of patients (45.8%) that met the criteria for higher-risk prostate cancer on re-biopsy during the course of AS (mean follow-up time 25.3 months), perhaps reflecting differences in criteria for AS protocols.

A major limitation with current surveillance protocols is the inaccurate tools used to follow patients. Non-invasive means of monitoring patients with indolent disease and identifying patients who will develop PD would strengthen AS in prostate cancer management. To our best knowledge, this is the first study to identify a role of [11]C-choline PET in AS of indolent prostate cancer.

[11]C-choline PET

[11]C-choline PET for primary prostate cancer remains controversial. Some authors report a significant overlap of [11]C-choline SUVmax between prostate cancer and benign prostate hyperplasia (BPH) tissue,[17,18] while other studies showed that [11]C-choline PET effectively differentiated malignant from benign prostate lesions.[19,20] These differences may be due to heterogeneity of patient population, differences in study methodology, and application of different PET scanners. In our study, the SUVmax of histologically benign lesions was slightly higher than that of GS 6 lesions (3.6 vs. 3.4, $p = 0.45$). All patients had confirmed disease so the biopsies that were benign were likely due to undersampling. The issue of significant overlap of uptake from BPH and predominantly small low-grade lesions is worth considering when interpreting results.

Various studies comparing imaging modalities in prostate cancer patients have illustrated [11]C-choline PET sensitivity and specificity for prostate cancer detection rates ranging from 54% to 100% and 43% to 84%, respectively.[21] Our analysis showed whole prostate [11]C-choline PET sensitivity

Table 3. Sensitivity and specificity of ^{11}C-choline PET to detect PCa

	Detecting PCa	
	Sensitivity, %	Specificity, %
Whole prostate gland		
SUV >1	95.4	0.0
SUV ≥2.5	88.6	15.0
SUV ≥3.0	74.4	25.0
SUV ≥3.3	72.1	45.0
Left/right division		
SUV >1	80.4	12.9
SUV ≥2.5	73.2	24.3
SUV ≥3.0	65.5	42.3
SUV ≥3.3	57.9	47.8
Individual sextant biopsies		
SUV >1	81.4	71.2
SUV ≥2.5	73.3	75.3
SUV ≥3.0	65.9	81.6
SUV ≥3.3	57.7	83.3

PET: positron emission tomography; PCa: prostate cancer; SUV: standard uptake value.

and specificity of 72.1% and 45.0%, respectively. Left/right and sextant division had lower sensitivity likely due to the spatial resolution of PET imaging and the inconsistent sampling of prostate sextant biopsies. One weakness in our study is that it required utilization of transrectal ultrasound biopsy which can lead to false negatives due to undersampling. Additional limitations were the small sample size and the use of a single radiologist to report the ^{11}C-choline PET scans, which limited our ability to quantify interobserver variability.

SUV

The wide SUVmax range of histologically confirmed cancer foci reflects differences in metabolic state and the general heterogeneity of prostate cancer. The optimal criteria for ^{11}C-choline PET in prostate cancer detection remains unclear. Some authors use visual interpretation as the main criteria to reach the final diagnosis: any uptake higher than background was suspected for malignancy,[22] while others have specific SUVmax cut-offs ranging from 2.5 to 3.3.[17,18,20,23,24] These studies examined ^{11}C-choline PET for prostate cancer detection and localization, with sensitivity and specificity ranges of 66%–81% and 43%–87%, respectively.

Due to the significant overlap of ^{11}C-choline uptake between GS 6 and GS 7 prostate cancer lesions, especially in this low-risk population, the parameter of SUV alone cannot be an optimal marker of tumour biologic behaviour. Incorporation of other clinical criteria, such as PSA and positive core percentage, along with ^{11}C-choline PET in the AS setting, may be necessary to improve triaging. The protocol of this trial would not be convenient in the real clinic setting. Due to the short half-life, ^{11}C-choline PET can only

Table 4. Sensitivity and specificity of ^{11}C-choline PET to detect current/future PD

	Detecting PD	
	Sensitivity, %	Specificity, %
SUV >3.3 and index of suspicion >2	81.8	30.8
PERCIST	58.3	46.7
Baseline whole prostate gland		
SUV >1	100.0	7.69
SUV ≥2.5	90.9	7.69
SUV ≥3.0	90.0	9.09
SUV ≥3.3	81.8	38.5

PD: progressive disease; SUV: standard uptake value; PERCIST: Positron Emission Tomography Response Criteria in Solid Tumors.

be used at specialized sites with a cyclotron. In addition to challenges of accessibility, there is also the additional risk of infection from repeated annual biopsies and radiation from annual PET scans.

Additional studies will allow for optimization of ^{11}C-choline PET being incorporated in AS triage procedures. Alternative strategies to identify aggressive prostate cancer may involve other imaging modalities (i.e., multiparametric MRI,[25] MR spectroscopy[26]) or biomarkers (i.e., TMPRSS2:ERG gene rearrangement, PCA3).[27,28]

Gleason score

GS remains the most predictive available factor for prostate cancer mortality and the presence of Gleason 4 pattern often serves as a trigger for intervention.[16] We found that the SUVmax was highest in patients with GS 8 (4.6) versus GS 6 or 7 (3.4, $p = 0.07$; 4.0, $p = 0.47$, respectively). We found that SUVmax of benign biopsies was slightly higher than in GS 6 biopsies, but as all patients had confirmed GS 6 disease prior to enrollment it is likely that due to undersampling the GS 6 disease was not detected. Similarly, Piert and colleagues found that high GS (≥4+3) and Ki-67 index (≥5%) were significantly associated with an increased SUV in ^{11}C-choline PET imaging.[29]

Table 5. Mean SUVmax of ^{11}C-choline PET in each Gleason score group

	Benign (n = 20)	GS 6 (n = 33*)	GS 7 (n = 5*)	GS 8 (n = 4)
Mean SUVmax, SEM	3.6 ± 0.05	3.4 ± 0.03	4.0 ± 0.25	4.3 ± 0.26
Unpaired, 2-tailed t-test vs. benign	–	0.684	0.462	0.195
Unpaired, 2-tailed t-test vs. GS 8	0.195	0.168	0.745	–

*62 scans paired with biopsies were analyzed (3 patients with GS 6 biopsies did not have ^{11}C-choline PET within 6 months and 7 patients had GS 7 biopsies but only 5 had ^{11}C-choline PET within 6 months).
SUV: standard uptake value; PET: positron emission tomography; GS: Gleason score; SEM: standard error of the mean.

Conclusion

The addition of ^{11}C-choline PET to AS protocols may be beneficial. The preliminary data from our work suggest that assessment with ^{11}C-choline PET for PD risk in AS patients requires further investigation to optimize cut-off values and co-variables. Alternatively, other strategies to identify at-risk low-risk prostate cancer patients may include other imaging modalities or biomarkers.

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