Incidentalomas of the prostate detected by 18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography

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Abstract

Introduction: Prostate incidentalomas are prostatic lesions suspicious for cancer discovered by imaging patients without a known history of prostatic cancer (PCa) for other reasons. 18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG PET) is used to diagnose, stage, and assess response to treatment for numerous cancers, but it is not routinely used for PCa. We aimed to determine the rate of detection of prostate incidentalomas in patients undergoing FDG PET and to evaluate the natural history of these lesions.

Methods: A retrospective review was conducted of all FDG PET scans performed between 2005 and 2017 at a single institution. Patients were selected who had prostatic uptake without a history of PCa. Clinical data were collected from electronic medical records to determine how the prostate incidentalomas were further evaluated and to define the rate of malignancy.

Results: A prostate incidentaloma was identified in 309 (1.0%) of 31 019 FDG PET scans performed on men. A prostate-specific antigen (PSA) test was obtained in 40.1% of patients within six months of prostate incidentaloma detection. Six patients underwent a multiparametric magnetic resonance imaging (mpMRI) of the prostate, which identified PCa in one case. Overall, PCa was diagnosed in 33 cases, representing 10.7% of the prostate incidentalomas and 0.1% of the scanned patients. PCa was intermediate- or high-risk in 27 (8.7%) of the prostate incidentalomas.

Conclusions: Incidental lesions detected in the prostate by FDG PET may represent clinically significant PCa. Referral to a urologist for further evaluation should be considered if the patient is otherwise in reasonable health.

Introduction

The shift towards an increase in aerobic glycolysis, known as the Warburg effect, is a well-characterized metabolic derangement in cancer.[1] 18-fluoro-2-seoxy-D-glucose positron emission tomography/computed tomography (FDG PET) detects this increase in glycolysis and, as such, is routinely used in the diagnosis and surveillance of many cancers, including melanoma, lung cancer, squamous cell carcinoma of the head and neck, and lymphoma.[1,2] Prostate cancer (PCa), however, does not routinely experience the Warburg effect and FDG PET is not part of the routine staging of PCa.[3-7] An investigation of FDG PET in localized PCa revealed 51.9% sensitivity and 75.7% specificity in the context of an elevated prostate-specific antigen (PSA).[3]

Incidental focal uptake in any organ on FDG PET that is not directly associated with the disease under investigation is referred to as an incidentaloma. Incidentalomas are commonly observed, occurring in approximately 10–14% of FDG PET scans.[1,2] Some of these incidentalomas are located within the prostate in the absence of known PCa. The rate of prostate incidentaloma on FDG PET has been reported in two series as 0.086%[8] and 1.4%.[4,5] This elevated prostatic FDG uptake may represent both benign and malignant conditions, including especially PCa, benign prostatic hyperplasia, and prostatitis.[6]

To our knowledge, FDG PET prostate incidentalomas have yet to be investigated in a North American population. We aimed to further characterize the etiology, rate of malignancy, aggressiveness of malignancy identified, FDG PET characteristics of identified malignancy, and the adequacy of subsequent investigation once they have been identified. There are also no guidelines to aid in the investigation of these lesions and we sought to develop recommendations for investigation once FDG PET prostate incidentalomas are identified.

Methods

A retrospective review was conducted of all FDG PET scans performed in men ≥18 years of age between September 2005 and June 2017 at the British Columbia (BC) Cancer Agency. This facility serves the entire population of BC (over 4.4 million residents in 2016) as the sole PET scanner for the duration of this study period.[7] This study was approved by the Clinical Research Ethics Board of the BC Cancer Agency (H17-01483).

A search was conducted for all FDG PET reports on male patients that contained the word "prostate." These reports were further narrowed by reviewing the context in the electronic reports. Men with a history of PCa were excluded from further analysis. Full clinical review of the remaining patients was conducted.

A prostate incidentaloma was considered PCa if this was determined by biopsy (ultrasound-guided transrectal [TRUS] biopsy, magnetic resonance imaging (MRI)-TRUS fusion biopsy, or transurethral resection of prostate [TURP]) and was considered benign if a biopsy was negative. A prostate incidentaloma was also considered benign if a multiparametric (mp) MRI of the prostate was normal, as defined by absence of a Prostate Imaging – Reporting and Data System (PIRADS) ≥3 lesion. The prostate incidentalomas were otherwise categorized based on age-standardized PSA gathered from provincial databases that capture results from almost all bloodwork in BC. If the PSA was less than the age-standardized cutoff value (PSA <2.5ug/L for age <50 years; PSA <3.5 ug/L for age 50–59 years; PSA <4.5 ug/L for age 60–69 years; and PSA <6.5ug/L for age >70 years), the lesion was considered "likely benign."[9] Prostate incidentalomas were considered suspicious for PCa if the PSA was above the age-standardized cutoff level and a biopsy or mpMRI was not performed. The status of the prostate incidentaloma was considered unknown if a PSA could not be located in the databases within 10 years of the FDG PET.

One-way ANOVA and mean statistical testing were performed using Prism 7, version 7.0e.

Results

In the study period, 31 019 FDG PET scans were performed on men over 18 years of age. The number of scans performed per year increased during the study period from 570 per year in 2005 to 9551 per year in 2017, but the rate of detection of prostate incidentalomas remained constant. A prostate incidentaloma was identified in 309 men undergoing FDG PET scanning, representing 1.0% of all men scanned. The mean age of all men undergoing FDG PET was 63.7 (18–98) years, compared to 70.5 (18–93) years in the patients with a prostate incidentaloma.

Fig. 1 shows how the patients were evaluated after FDG PET. The diagnostic categorization of prostate incidentalomas is summarized in Fig. 2. A prostate TRUS biopsy was performed in 24 (7.8%) patients within 12 months of detection of the prostate incidentaloma identified on FDG PET, and in 13 (4.2%) patients beyond 12 months. PCa was diagnosed in 18 (75.0%) of the early biopsies and 12 (92.3%) of the delayed biopsies (Table 1). The mean PSA of all patients together was 7.3 ug/L around the time of FDG PET. The mean PSA of patients not undergoing prostate biopsy was 5.9 ug/L, while the PSA of patients undergoing biopsy was 12.1 ug/L. Of patients who went on to be diagnosed with PCa, the mean PSA was 14.9 ug/L. As summarized in Table 2, of patients who went on to have a prostate biopsy and were diagnosed with PCa, 87.1% of prostate incidentalomas represented clinically significant PCa defined as Gleason grade group ≥2. Evaluation of the incidentaloma revealed metastatic PCa in one patient and 12 others progressed to metastatic PCa during subsequent followup.

A mpMRI of the prostate was performed in six cases. Two patients had no abnormal findings and did not undergo biopsy. A targeted biopsy was performed in two patients with a PIRADS 3 lesion and two with a PIRADS 4 lesion. These lesions corresponded to the prostate incidentaloma in all cases. One patient with a PIRADS 4 lesion was diagnosed with a Gleason grade group 2 PCa. This 68-year-old patient had a PSA of 1.9 and PSA density of 0.07. The biopsy was benign in the other cases.

Only 124 (40.1%) patients underwent PSA testing within six months of FDG PET and 147 (47.6%) patients underwent PSA

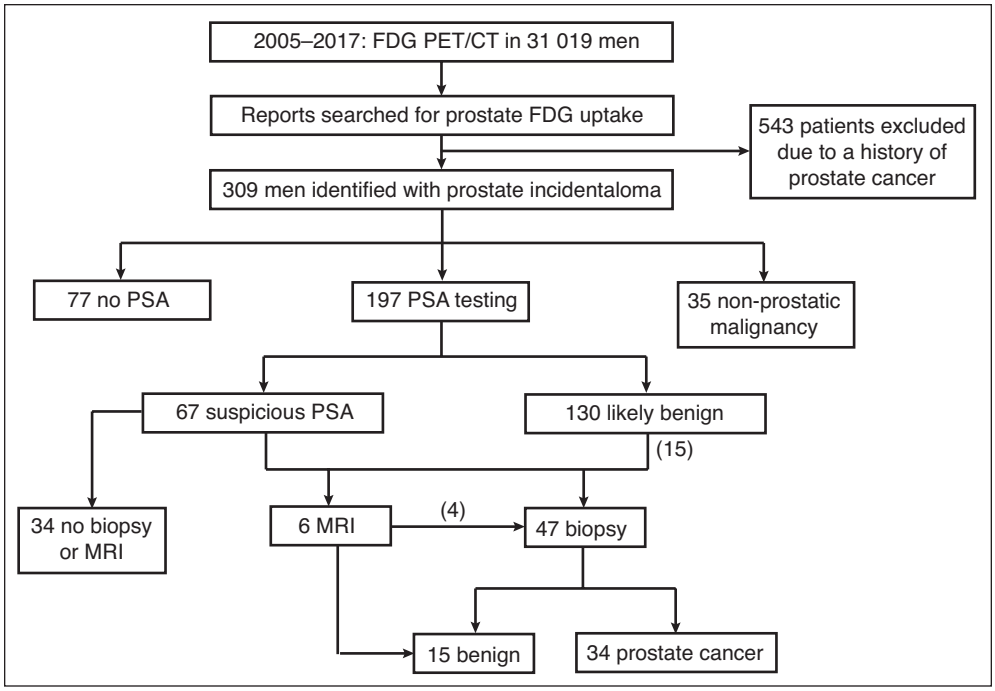

Fig. 1. Summary of investigations performed to evaluate prostate incidentalomas discovered on FDG PET. FDG PET: 18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography; MRI: magnetic resonance imaging; PSA: prostate-specific antigen.

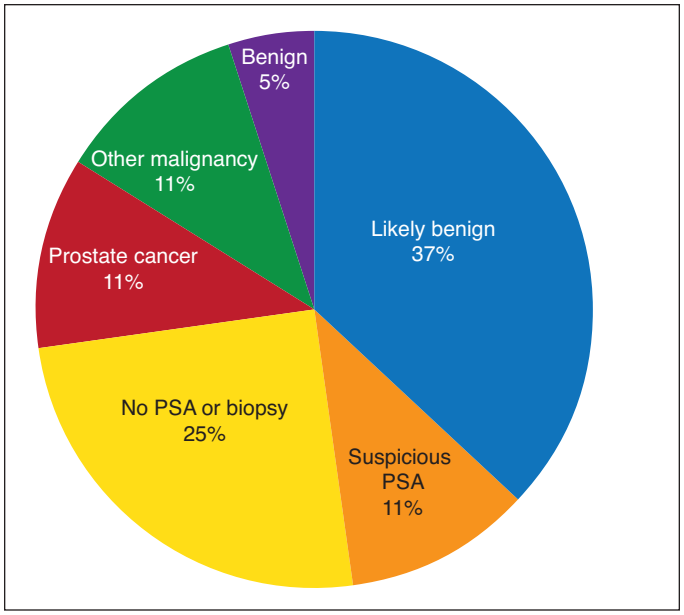

Fig. 2. Classification of prostate incidentalomas based on prostate-specific antigen (PSA) testing and/or prostate biopsy.

testing at any point after FDG PET. Based on age-standardized PSA cutoffs, the incidentaloma was deemed likely benign in 117 (37.9%) patients and suspicious for PCa in 34 (11.0%) patients who did not undergo prostate biopsy or mpMRI (Fig. 1). In 77 (24.9%) cases no PSA was measured.

The prostate incidentaloma represented a non-prostate malignancy in 35 (11.3%) patients. In 22 (7.1%) patients it was indicative of direct invasion of rectal carcinoma, and in 13 (4.2%) patients it was associated with urothelial carcinoma. Eight of these incidentalomas represented urothelial carcinoma with histological confirmation of prostatic stromal invasion. Five patients had a prior history of non-muscle-invasive bladder cancer and intravesical therapy, but recurrence in the prostate was not confirmed. In no case was the prostate incidentaloma identified to be a metastatic lesion. Furthermore, all PCa cases were adenocarcinoma.

The FDG PET scans were performed to stage different cancers: 34% lung, 17% colorectal, 11% head and neck, 11% lymphoma, 11% upper gastrointestinal or hepatobiliary, 4% melanoma, and 6% for cancer of 10 other origins. Metastatic cancer other than PCa was present in 137 (44.3%) patients. Four of these patients underwent prostate biopsy, which was benign in all cases, and 81 (59.1%) were tested for PSA. The mean followup of patients after FDG PET was 5.1 years. The mean duration of survival and five-year survival of patients with a prostate incidentaloma was 3.0 years (range 0–11 years) and 43.2%, respectively. Three of the 34 patients with a prostate incidentaloma confirmed to be PCa have died of PCa.

One-way ANOVA statistical testing was conducted to investigate whether patient age at time of FDG PET or prostate incidentaloma maximum standardized uptake value (SUVmax) correlated with subsequent diagnosis of PCa. Mean age was not statistically different between likely benign (69.9; 95% confidence interval [CI] 68.11–71.79), suspicious PSA (71.4; 95% CI 67.45–75.18), PCa on biopsy (71.8; 95% CI 69.7–74.0), and patients without a PSA measurement (71.4; 95% CI 68.76–73.84; p=0.66) (Fig. 3). Similarly, there was no statistically significant difference between the mean SUVmax of likely benign (8.06; 95% CI 6.93–9.32), suspicious PSA (8.60; 95% CI 6.85–10.35), biopsy-confirmed PCa (9.83; 95% CI 7.92–11.74), and patients without a PSA measurement (7.37; 95% CI 5.94–8.80; p=0.2) (Fig. 4). In the reporting of prostate incidentalomas, only 204 patients had quantitative measurements of SUVmax, 11 qualitative, and 94 had no description other than stating there was abnormal uptake.

Discussion

We describe a 1.0% incidence of prostate incidentalomas in men without a history of PCa undergoing FDG PET imaging for staging of a non-PCa. Since PCa is the most commonly diagnosed and third leading cause of cancer-related death in Canadian men,[8] it is not surprising that it can be found incidentally using other imaging modalities. The identification of PCa relies on digital rectal examination (DRE), PSA, and tissue sampling, with mpMRI also taking on a growing role.[10,11] With increasing use of FDG PET in oncology, it has become more common to encounter patients with prostate incidentalomas, even though PCa is not typically FDG-avid.

Table 1. Time to diagnosis of prostate cancer after detection of prostate incidentaloma on FDG PET

Time to diagnosis	Number of patients	Gleason grade group
<1 year	20	1–5
1–2 years	7	1–3
2–3 years	2	5
3–4 years	1	3
4–5 years	3	2 and 5
5–6 years	1	5

FDG PET: 18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography.

Table 2. Prostate cancer diagnosed after FDG PET

Gleason grade group	Number of patients
1	5
2	6
3	6
4	3
5	12
De novo metastatic disease	1

FDG PET: 18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography.

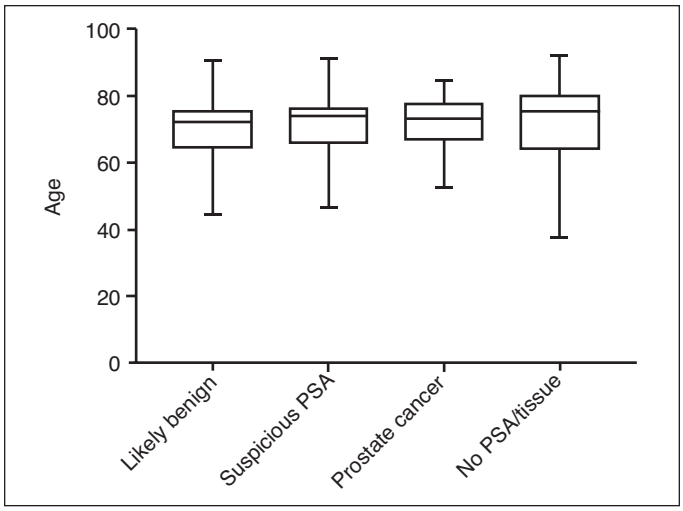

Fig. 3. Patient age at time of prostate incidentaloma detection. PSA: prostate-specific antigen.

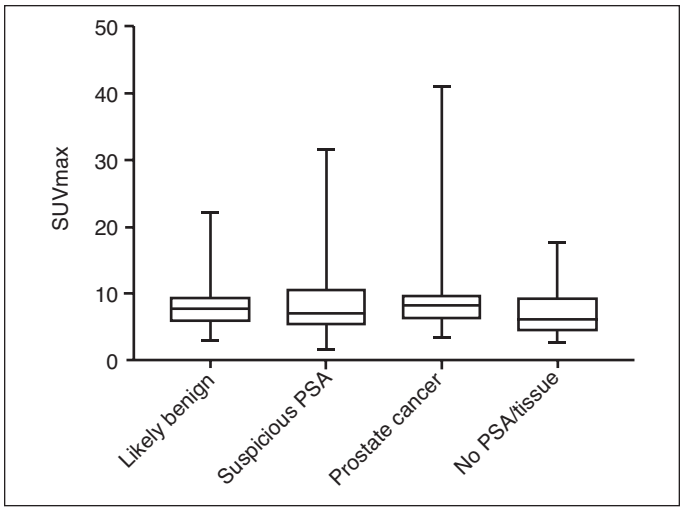

Fig. 4. Prostate incidentaloma maximum standardized uptake value (SUVmax). PSA: prostate-specific antigen.

Bertagna et al previously identified equal distribution of incidentalomas between peripheral and transitional zones; however, incidentalomas in the peripheral zone were significantly more often PCa.[12] Studies have been unable to detect differences in signal intensity (SUV_{max}) between prostate incidentalomas that are found to be benign or malignant.[4,6] The rate of PCa detected in FDG PET prostate incidentalomas is variable in prior reports.[1] Han et al evaluated 87% of patients with a prostate incidentaloma and found that 5.4% represented PCa.[12] Bertagna et al evaluated 22.5% of patients with PSA and biopsy and found PCa in 55.5% of evaluated cases, or 12.5% of the overall cohort.[13] Hwang et al evaluated 12.5% of cases and found that 12% of cases contained PCa with Gleason score ≥7.[6] Though variant subtypes of PCa, such as neuroendocrine or ductal PCa, represent <10% of all cases, these cancers are more frequently FDG-avid on PET.[14,15] The aggressive clinical behavior of these tumors is associated with metabolic derangements that allow them to use glucose metabolism preferentially. There is evidence that mRNA expression of GLUT1, the first rate-limiting step in glucose metabolism, is associated with Gleason score and is upregulated in poorly differentiated castrate-resistant PCa, which may correlate to increased FDG uptake.[14-16] However, histological variants were not detected in our cohort.In general, it is believed that patients likely benefit from treatment of intermediate- and high-risk localized PCa if they have a life expectancy of ≥10 years.[17] Although in our series only 40.1% of patients underwent PSA testing within six months of the prostate incidentaloma identification, and 64.1% eventually underwent PSA testing or underwent prostate tissue sampling, we are unable to characterize the health status of our patients and are, therefore, unable to comment on the appropriateness of the delayed investigation of prostate incidentalomas. The competing risk of morbidity and mortality from comorbidities and the cancer that the FDG PET was used to stage need to be taken into account.

We have proposed an evaluation algorithm for patients with a prostate incidentaloma on FDG PET without a prior history of PCa (Fig. 5). We suggest that all patients should have a serum PSA test and undergo DRE, unless they have a severely limited life expectancy (e.g., <2 years). Further evaluation with prostate MRI and/or TRUS-guided biopsy would depend on the balance between the patient's general health and the degree of PSA rise or abnormal DRE. We suggest that a patient with a life expectancy >10 years who would be eligible for definitive PCa treatment should undergo prostate MRI and/or TRUS-guided biopsy to rule out clinically significant PCa. This recommendation is based on the overall experience of detecting aggressive PCa variants in prostate incidentalomas.

There are significant limitations to this retrospective study. Prostate incidentalomas were identified based on review of FDG PET reports without review of original FDG PET scans. Age-standardized PSA was used to classify lesions and exclude PCa; however, patients concluded to have likely benign disease certainly had the possibility to be harboring clinically significant PCa. PSA and followup of the cohort was based on electronic medical record review and patients could have had followup or lab results not discovered through this review.

Conclusions

Prostate incidentalomas are an infrequent finding on FDG PET. If the incidentaloma was deemed appropriate for prostate biopsy, then typically, clinically significant cancer is found. Our results and prior reports in the literature are inadequate to define optimal evaluation of prostate inci-

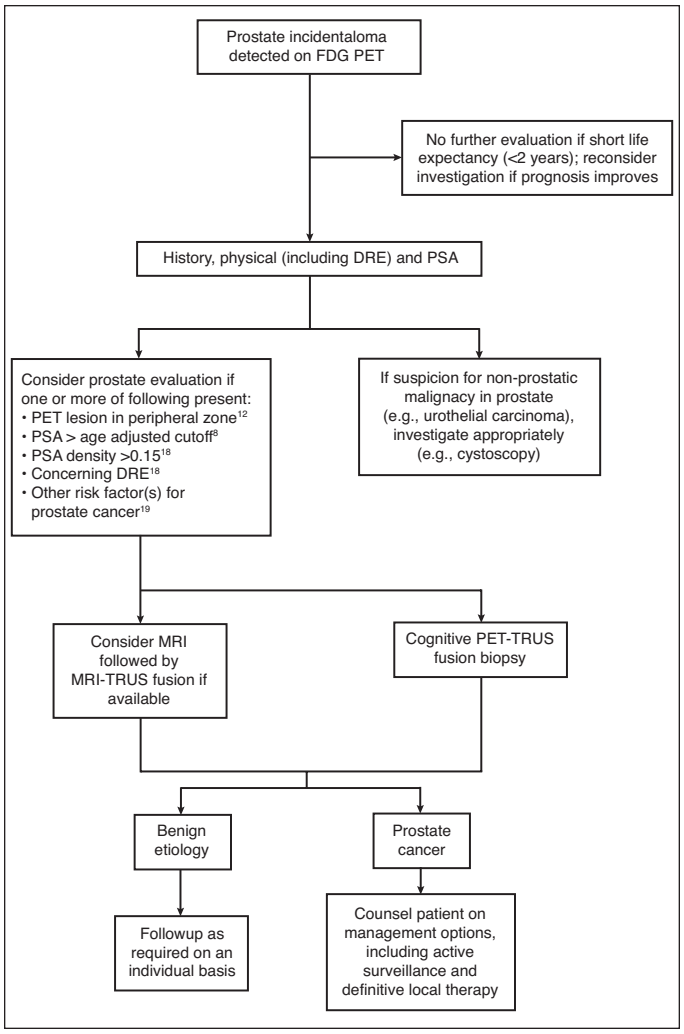

Fig. 5. Proposed algorithm to investigate prostate incidentalomas detected on 18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG PET). DRE: digital rectal exam; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; TRUS: transrectal ultrasound.

dentalomas because many patients have undergone no or only very delayed investigation. Depending on other patient variables, this may prove to be the most appropriate management. However, it is important for oncologists to recognize the risk of significant PCa and to initiate further investigation dependent on the patient's underlying prognosis and other factors (age, general health, family history PCa, race). Referral to a urologist should be considered in patients with favorable prognosis to consider MRI and/or prostate biopsy.

Competing interests: Dr. Black has been advisory board member or equivalent for Abbvie, Asieris, Astellas, AstraZeneca, Bayer, Biosyent, BMS, EMD-Serono, Fergene, H3-Biomedicine, Janssen, Merck, Roche, Sanofi, and Urogen; a speakers' bureau member for Abbvie, Biosyent, Ferring, Janssen, Pfizer, and TerSera; has received grants and/or honoraria from Bayer, GSK, iProgen, and Sanofi; has participated in clinical trials supported by Astellas, AstraZeneca, BMS, Genentech, Janssen, MDx Health, Pacific Edge, Sitka, and Therelase; and shares a patent with Decipher Biosciences. The remaining authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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