Comparison of Ga 68 PSMA-11 and F 18 Choline for detection of prostate cancer during biochemical relapse

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Abstract

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Prostate Cancer (PCa) is the most common cancer in men. In 2020, there were 1.4 million new cases and 375,000 deaths worldwide. The most important biomarker for PCa is the prostate-specific antigen (PSA), which is helpful for the initial screening, detection, and follow-up after surgery.

Serum PSA level is also used as a sensitive marker for tumor recurrence. Any increase in PSA level during the follow-up period after the complete prostatectomy procedure is interpreted as a biochemical cancer relapse. Since 15-30% of patients experience a biochemical relapse after curative treatment of radical prostatectomy (RP) or radiation therapy, development of new technologies and therapeutic strategies for diagnosing and treating PCa biochemical relapse is of major significance. The objective of the current study was to assess the utility of Ga 68 PSMA-11 (a target molecule and inhibitor of the prostate-specific membrane antigen), and F 18 Choline (a molecule that increases in level along with increases in cancer cells) in identifying biochemical

relapse of PCa. The U. S. Food and Drug Administration (FDA) has approved Gallium 68 PSMA-11 (Ga 68 PSMA-11) as the first marker for detecting PSMA-positive lesions in men with PCa in the United States.

Our study was based on anonymized data from the Clinical Physiology and Nuclear Medicine Unit of the Helsinki University Hospital (HUS) in Finland. A total of 199 participants examined from January 2015 to June 2016 were included in this study. Positron Emission Tomography-Computed Tomography (PET/CT) imaging was used as the gold standard.

Cross-tabulation tables were constructed to assess the performance (sensitivity, specificity, and overall accuracy, with respective 95% confidence intervals [95% CI]) of both diagnostic tests (based on Ga 68 PSMA-11 and F 18 Choline) in detecting biochemical relapse of PCa among patients with PSA > 2 μg/L. The screening test using F 18 Choline had a specificity of 92.9% (95% CI 83.0% - 98.1%), and an overall accuracy of 93.1% (95% CI 83.3% - 98.1%). The screening test using Ga 68 PSMA-11 had a specificity of 59.6% (95% CI 44.3% - 73.6%), and an overall accuracy of 60.4% (95% CI 45.3% - 74.2%). For both markers, we did not report sensitivity since the 95% CIs had a wide range (95% CI 2.5% - 100.0%). Further investigations are necessary to investigate sensitivity of these diagnostic tests.

Our results did not agree with previous reports of better sensitivity and specificity for Ga 68 PSMA-11, compared with F 18 Choline. While we were unable to compare the two markers directly due to HUS regulations, the current study demonstrated that Ga 68 PSMA-11 can be used in HUS settings to detect PCa in patients with biomedical relapse. Future studies of Ga 68 PSMA-11, particularly those that perform direct comparisons with other diagnostic tests, are needed.

1. Introduction

1. Prostate and Prostate Specific Antigen

Prostate Cancer (PCa) is the most common cancer in men. In 2020, there were 1.4 million new cases and 375,000 deaths worldwide (AstraZeneca and MSD Launch Prostate Cancer Awareness Campaign, n.d.; Cardoso et al., 2022).

The prostate gland is located below the bladder and in front of the rectum. The prostate glandular epithelium is a falsely deposited cylindrical epithelium that produces and secretes various glycoproteins, enzymes, and prostaglandins (Oliffe, 2005). One of the most essential enzymes produced by the prostate is the prostate-specific antigen (PSA). The PSA is a 34 kD glycoprotein that acts as a serine protease enzyme that helps coagulated semen liquify, allowing sperm to move freely in semen. The concentration of PSA is highest in semen. However, it also enters the systemic circulation through the blood vessels of the prostate gland, allowing the concentration of PSA to be measured in the blood (Zambelli et al., 2010)

2. Prostate cancer and Prostatic Intraepithelial Neoplasia Risk factors

About 98% of prostate cancer (PCa) cases are adenocarcinomas originating in the glandular epithelium. PCa may locally progress to the bladder, rectum, and ureters (Harryman et al., 2021). Metastases are usually found in the bones and lymph nodes. Typical symptoms of PCa include painful or difficult urination, increased frequency of urination, weakness of the urine stream, bloody urine, urinary retention, urinary tract infection, and pain in the pelvis or back. Bone pain, anemia, and weight loss generally indicate metastatic cancer. Bone metastases are common, especially in the pelvic bones and spine (Hsiao et al., 2007). Prostatic intraepithelial neoplasia (PIN) is a neoplastic transformation of the epithelium that envelops the ducts of the prostate. PIN changes may be the first sign of future PCa. Currently, the only way to diagnose PIN changes is

through a biopsy. PIN lesion detection varies across a variety of settings (e.g., 0.7-20% in screening biopsies, 4.4-25% in clinical biopsies, 32-83% in prostate removed without cancer, and 73-100% in prostate removed due to cancer) (Zhou, 2018).

Family history, race, hypertension, overweight/obese status, smoking, Age, and genetic factors are the main risk factors for PCa. In addition, lifestyle and prostate infections can also increase the risk of developing PCa (Prostate Cancer: Risk Factors and Prevention, 2022) (Prostate Cancer: Risk Factors and Prevention, 2022).

PCa in one first-degree relative doubles the risk, while PCa in two or more first-degree relatives increases the risk five-fold. According to one study, race/ethnicity has been associated with the risk of PCa. For example, having an African background increases the risk of PCa ten-fold if two or more first-degree relatives also have PCa (Martin et al., 2010).

High blood pressure has been identified as a risk factor for PCa. Men who are older than 45 years with a systolic blood pressure >150 mmHg have a 35% increased risk of PCa compared with men with normal systolic blood pressure (<130 mmHg) (Stikbakke et al., 2022).

Obesity after a diagnosis of PCa has been shown to increase biochemical relapse and mortality (Hjartåker et al., 2005). High body mass index (BMI) correlates with more severe cancer (Haque et al., 2014).

Smoking increases the likelihood of developing aggressive PCa and the chance of PCa biochemical relapse (Fowke et al., 2015) . The risk of PCa increases with Age, especially after age 50, and around 60% of PCa cases are diagnosed in people 65 or older (Coughlin, 2020).

As in other cancers, genetic variations also play significant roles in the onset of PCa. Several single-nucleotide polymorphisms (SNPs), including 5q14.3 SNPs (rs35148638)(15), 19p13.33 SNP rs266849 and 19p13.33 SNP rs2735839), are associated with aggressive PCa. (Lindstrom et al., 2011).

3. Finnish Cancer Registry

The current study was based in Finland. PCa is the most common cancer among men in Finland. In 2018, there were 5,016 cases of PCa, corresponding to approximately 28% of all cancers diagnosed among men in Finland in 2018. Fortunately, the prognosis for PCa survival in Finland is good. The relative age-standardized survival rate five years after diagnosis is about 93%, and the mortality rate in 2018 was 33.59 per 100,000 when 914 men died of PCa (Santala et al., 2019)(*Finnish Cancer Registry*, 2021).

4. Biopsies and Classifications of Prostate Cancer

Biopsy is the gold standard for PCa diagnosis. (Yuan et al., 2019). Unfortunately, compared to other diagnostic methods, this is the most invasive of all and carries the highest risk of side effects. Before the biopsy, the patient receives a prophylactic antibiotic, and the prostate is anesthetized transrectally (*Urology*, n.d.). Six test pieces are usually taken from each lateral lobe when taken transrectally. If no carcinoma is found in biopsies taken transrectally, but cancer is strongly suspected based on the symptom picture and PSA changes, biopsies can be taken transperitoneally. Then, a pathologist examines the biopsies based on the Gleason cancer classification (Djavan et al., 2001). The Gleason classification is the most common classification used to differentiate prostate cancer. The classification is based on the glandular architecture of the tumor and how likely the cancer is to advance and spread. Using the numerical order used to

determine the aggressiveness of the tissue, type 1 is the least aggressive, and type 5 is the most aggressive. Based on the Gleason classification, the prognosis of cancer worsens significantly if the score is more than 7 points. The numerical values of the Gleason scores and corresponding characteristics are shown in Table 1 (Gleason, 1992).

5. PSA based Screening

The total PSA predicts the probability of prostate cancer. The higher the total PSA, the greater the probability of cancer. PSA is mainly bound to serum proteins in the bloodstream. High concentrations of PSA (>10 μg/L) indicate a high probability of PCa.

There is a diagnostic gray area (1-10 μg/L) where new diagnostic tools might be needed to assess whether additional examinations are recommended for the patients. Table 2 describes the relationship between serum total PSA and the probability of PCa (Catalona et al., 1998*).*

6. PSA rise speed and doubling time

The PSA rise speed (velocity, PSAV) refers to the speed at which the concentration of PSA rises in the blood in a year. For men aged 60 to 70, if the PSA velocity is ≥0.75 μg/L/year, further studies are recommended by the physician to determine the possibility of prostate cancer (Loeb et al., 2007).

PSA doubling time (PSADT) refers to the time during which the concentration of PSA doubles (What Is an Acceptable PSA Velocity?, 2020).For example, a patient with a current PSA of 2 μg/L and a PSA velocity of 0.5 μg/L/year would be expected to have a PSA of 2.5 μg/L in the next 12 months. Therefore, this example patient's PSA doubling time would be 48 months (Vickers

& Brewster, 2012). PSADT might be used to assess the aggressiveness of the PCa's biochemical relapse (O'Brien et al., 2009).

7. Imaging

Different imaging modalities have been used to assess the spread of PCa, including ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission tomography (SPECT), and combinations of those (PET/CT, SPECT/CT, and PET/MRI). In PET/CT, the anatomical precision obtained from CT is combined with the visualization of receptor concentration obtained from PET, depending on the tracer used. One of the primary advantages of the PET/CT system is the reduction in imaging time and the detection of tumor recurrence earlier than with other diagnostic modalities. The radionuclides used in PET are positron emitters. A decaying radionuclide emits a position that loses kinetic energy as it travels through the medium. When the kinetic energy decreases enough, the positron reacts with an electron from material in the body, and an annihilation event occurs. In annihilation, two 511 keV gamma photons are generated, which are emitted at an angle of 180^0 to each other. The emitted gamma photons are detected with gamma detectors, after which the location of the decayed radioactive tracer in the body can be calculated.

Various markers are used in PCa diagnostic efforts, including Choline, PSMA, and gastrin-releasing peptide receptors. The most common radionuclides used are ^{11}C (T1/2=20 min), ^{18}F (T1/2=110 min), and ^{68}Ga (T1/2=68 min) (Kader et al., 2021).

8. Sensitivity and Specificity

Sensitivity is used to calculate how well a screening test can detect the existence of a disease when the disease does exist. Specificity calculates how well the screening test correctly identifies absence of disease when the disease does not exist. Sensitivity, therefore, describes how many actual positive findings were found (in patients with cancer) and specificity describes how many correct negative findings were found (for patients with no cancer). For prostate cancer, the gold standard is prostate biopsies which serves as the comparison for screening tests.

Positive (PPV) and negative (NPV) predictive values are closely related to sensitivity and specificity. PPV describes the likelihood of confirmed disease among those with positive test results. Similarly, the NPV describes the likelihood of confirmed absence of disease among those with negative test results. Low PPV indicates that the study has a lot of false positive results, and low NPV indicates that the study has a lot of false negative results. Overall accuracy is the probability that an individual will be correctly classified by a test. Overall accuracy is the sum of true positives plus true negatives divided by the total number of individuals tested.

9. Choline

Choline is present in the components of the cell membrane as phosphatidylcholine. The Choline kinase enzyme catalyzes the first reaction in the Choline reaction chain to phosphatidylcholine, and it has been shown that Choline kinase is overexpressed in PCa (de Molina et al., 2002). Choline is usually found in different organs and tissues, with the highest concentration found in the liver, kidneys, and pancreas, as well as in the lacrimal and salivary glands.

Umber *et al.,* in a review (12 studies and 1055 patients) article, compared C 11 Choline and F 18 Choline to detect PCa biochemical relapse using PET/CT. Umber reported a “pool”

(combining the results of 12 studies) sensitivity of 85% (95% CI:79-89%) and a specificity of 88% (95% CI: 73-95%) for F 18 Choline (Umbehr et al., 2013).

10. Prostate-Specific Membrane Antigen (PSMA)

PSMA is a type II integral membrane protein overexpressed in PCa cells and during the neovascularization of solid cancers. Despite its name, PSMA is also found in small amounts in other tissues, including the nervous system, kidneys, small intestine, and salivary glands. PSMA is in the cell cytosol of the prostate gland. PSMA production increases in cancer cells, moving to the cell membrane, where it hydrolyzes folates. Folate promotes the growth of cancer cells and thus promotes the transformation of PIN lesions into adenocarcinoma (Ghosh & Heston, 2004).

Hope *et al*. discussed 29 studies with a total of 4,790 patients who had PCa biochemical relapse after treatment. The review concluded that the sensitivity and specificity of Ga 68 PSMA-11 (unspecified cutoff) in cancer diagnosis were 74% (95% CI: 51-89%) and 96% (95% CI: 85-99%), respectively. In PCa biochemical relapse, the PPV (positive predictive value) of Ga 68 PSMA-11 was 99% (95% CI:96-100%). For PSA < 2.0 ug/L, the detection rate was 63% (95% CI: 55-70%), while it was 94% for PSA > 2.0 ug/L (95% CI: 91-96%) (Hope et al., 2019).

Another study by Perera *et al.* discussed 37 studies with a total of 4,790 patients who had PCa biochemical relapse. They found that the PSA levels affect the detection rate of Ga 68 PSMA-11 PET. When the PSA was 0-0.19 µg/L, the detection rate was 33%. When the PSA was 0.2-0.49 µg/L, the detection rate was 45%. When the PSA was 0.5-0.99 µg/L, the detection rate was 59%. When the PSA was 1-1.99 µg/L, the detection rate was 75%. Finally, when the PSA was >2 µg/L, the detection rate was 95% (Perera et al., 2020).

2. Research Objectives

On December 1, 2020, the U. S. Food and Drug Administration (FDA) approved Gallium 68 PSMA-11 (Ga 68 PSMA-11) as the first marker for detecting PSMA-positive lesions in men with PCa (U. S. Food & Drug Administration, 2020). Since then, few studies have been published comparing Ga 68 PSMA-11 with other markers, such as 18 F-Choline. At the time of this study, F 18 Choline was used routinely as a biomarker in the Clinical Physiology and Nuclear Medicine Unit of the Medical Hospital of the University of Helsinki's (HUS) department for the diagnosis of PCa with biochemical relapse, where a retrospective study was designed to assess the utility of the two markers (Ga 68 PSMA-11 and 18 F-Choline). Asfhar-Oromieh *et al.* published a similar study "assessing PET imaging with 68-Ga-labelled PSMA ligand and 18F-Choline-based PET/CT" in patients with PCa in Germany (Afshar-Oromieh et al., 2015) To our knowledge, this is the first clinical study of Ga 68 PSMA-11 done in Finland.

Overall Aim. The overall aim of the current study was to determine the utility of Ga 68 PSMA-11 and F 18 Choline to detect prostate, lymph nodes, and bone lesions in patients with PCa biochemical relapse.

Specific objectives include:

- To characterize patient characteristics in terms of age, body mass index (BMI), Gleason score, serum PSA (both at the time of diagnosis and at relapse), PSA velocity, and PSA doubling time.

- To assess whether Ga 68 PSMA-11 marker and F 18 Choline have no differences in detecting tumors/metastases at different PSA serum concentrations when compared against the gold standard (CT).

- To determine sensitivity, specificity, and overall accuracy of diagnostic tests based on Ga 68 PSMA-11 marker and F 18 Choline.

3. Methods

3.1 Study Design, Study Population, Data Collection, and Data Analysis

This retrospective study was conducted among patients examined by imaging with PET/CT for suspected biochemical relapse of PCa in the Clinical Physiology and Nuclear Medicine Unit of the Medical Hospital of the University of Helsinki (HUS), Finland between January 13, 2015, and June 28, 2016.

A total of 199 patients were examined, of which 56 were excluded because they did not have a PCa biochemical relapse. The HUS hospital granted the necessary permissions to process patient data in an anonymized form in the study. Of the remaining 143 patients, 76 patients were examined with F 18 Choline PET/CT, while 67 were examined using Ga 68 PSMA-11 PET/CT (Figure 1).

All patients were examined with ONLY one marker; therefore, the patients formed two different groups (independent groups). Participants in each group were also assessed using the gold standard (CT scan). The PET and CT scans detect possible lesions in each patient's prostate, lymph nodes, and bones. We also examined the size of the lesion(s) identified by PET or CT.

Patients were divided into three groups according to the PSA concentration at relapse: <1, 1-2, and >2 μg/L). In addition, patients were examined for lesions from the three tissues in which most metastases occur: prostate, lymph nodes, and bone.

Mean and standard deviation were calculated for the two groups of patients to summarize age, Gleason score, serum PSA at the time of diagnosis and relapse, PSA doubling time, and calculated body mass index (BMI). We examined the degree to which Ga 68 PSMA-11 and F 18 Choline biomarkers detect tumors/metastases at different PSA serum concentrations using PET/CT scans as a gold standard. Chi-square testing was used to analyze "scan positivity" at different PSA concentrations in prostate, lymph nodes, and bones.

Additional cross-tabulation tables were constructed to assess the performance of the diagnostic tests (sensitivity [SN], specificity [SP], and overall accuracy [OA]with respective 95% confidence intervals [95% CI]). All analyses were performed using SPSS Version 29 (Armonk, NY: IBM Corp.), GraphPad Prism 9.5.1, and R software, version 3.2.5. Statistical significance was determined using the p-value < 0.05 cutoff.

4. Results

4.1 Patient Characteristics and Dose Parameters

Figure 2a-g describes patients' characteristics (age, BMI, Gleason score, serum PSA at diagnosis and relapse, PSA Velocity, and PSA doubling time) among the two groups. In general, the characteristics of the patients between the two groups were similar and as follows: age [F 18 Choline group (M =69 years, SD = 6.6) versus Ga 68 PSMA-11 (M= 70 years, SD = 6.7)], BMI [F 18 Choline group (M =25.8 kg/m^2, SD =3.8) versus Ga 68 PSMA-11 (M= 26.1 kg/m^2, SD = 3.4)], PSA levels at the beginning of detection [F 18 Choline group (M= 10.2 μg/L, SD=70.2)

versus Ga 68 PSMA-11 (M =8.3 µg/L, SD =31.9)], PSA levels at relapse [F 18 Choline group (M= 3.1 µg/L, SD =7.6) versus Ga 68 PSMA-11 (M=3.2 µg/L, SD=16)], Gleason Score [F 18 Choline group (M= 7, SD = 1.2) versus Ga 68 PSMA-11 (M=7, SD=1.2)], PSA velocity [F 18 Choline group (M= 0.2 µg/L/year, SD = 1.3) versus Ga 68 PSMA-11 (M=0.2 µg/L/year, SD= 0.6)], and PSA doubling time [F 18 Choline group (M= 6.5 months, SD = 13.3) versus Ga 68 PSMA-11 (M= 6.8 months, SD= 8.8)].

Table 3 shows the device's CT parameters, such as CT dose index (CTDI) and Dose-length product (DLP). CTDI (measured in mGy) is a standardized measure of a CT scanner's radiation dose output, allowing the user to compare the radiation output of different CT scanners (*Computed Tomography*, 2023). In addition, the Marker Activity is also reported in Table 3 for the two markers. As shown, the dose parameters and activity of F 18 Choline was (M= 298.2 MBq, SD= 37.5), and the activity for the Ga 68 PSMA-11 was (M= 152.6 MBq, SD =23.3). Marker Activity/patient weight were higher for F 18 Choline (M= 3.6 MBq/kg, SD= 0.4) MBq/kg than Ga 68 PSMA-11 (M=1.8 MBq/kg, SD =0.3).

4.2 Biomarkers' ability to detect lesions compared to CT

Tables 4A, 4B, 4C and 4D show the lesions detected with F 18 Choline and Ga 68 PSMA-11 at different PSA concentrations at relapse versus the Gold Standard, CT. Overall, in this study, PET identified more lesions than CT. CT did not identify some positive results that were detected using the F 18 Choline marker based PET scan.

Table 5 shows the detection rate for each subgroup as the number of lesions detected divided by the total number of patients in each subgroup. The findings indicate that Ga 68 PSMA-

11 identified more prostate and lymph node lesions than CT. On the other hand, F 18 Choline has a better ability to detect bone metastases than CT.

Subgroup analysis of Ga 68 PSMA-11 revealed **a prostate lesion** detection rate of 7.1% (1/14) for PSA less than 1 µg/L, 20% (1/5) for PSA between 1 to 2 µg/L, and 41.6% (20/48) for PSA higher than 2 µg/L. Subgroup analysis of Ga 68 PSMA-11 revealed **lymph node les**ion detection rate of 35.7% (5/14) for PSA less than 1 µg/L, 40% (2/5) for PSA between 1 to 2 µg/L, and 45.8% (22/48) for PSA higher than 2 µg/L. Subgroup analysis of Ga 68 PSMA-11 revealed **bone lesion** detection rates of 7.14% (1/14) for PSA less than 1 µg/L, 20% (1/5) for PSA between 1 to 2 µg/L, and 31.2% (15/48) for PSA higher than 2 µg/L.

Subgroup analysis of F 18 Choline revealed a **prostate lesion detection** rate of zero percentage (0/4) for PSA less than 1 µg/L, 7.1% (1/14) for PSA between 1 to 2 µg/L, and 8.6% (5/58) for PSA higher than 2 µg/L. Subgroup analysis of F 18 Choline revealed **lymph node lesion** detection rates of 50% (2/4) for PSA less than 1 µg/L, 28.5% (4/14) for PSA between 1 to 2 µg/L, and 39.6% (23/58) for PSA higher than 2 µg/L. Subgroup analysis of F 18 Choline revealed **bone lesion** detection rates of 0% (0/4) for PSA less than 1 µg/L, 7.14% (1/14) for PSA between 1 to 2 µg/L, and 31% (18/58) for PSA higher than 2 µg/L.

4.3 Sensitivity and specificity

Since the best detection rates for both markers were at PSA higher than 2 µg/L, we focused on that subgroup for the analysis of sensitivity and specificity.

Table 6 shows cross-tabulation tables used to calculate sensitivity and specificity, using CT as the gold standard, among participants with PSA > 2 µg/L. Table 7 shows the findings from analyses to assess the performance of the diagnostic tests (sensitivity, specificity, and overall accuracy with respective 95% confidence intervals [95% CI]) for patients with PSA > 2 µg/L according to the lesion site.

For the prostate location, the sensitivity of F 18 Choline at baseline with CT scan was 100% with 95% CI ranging from 2.5 % to 100.0%. The specificity was 92.9%, with a 95% CI ranging from 83.0% to 98.1%. The overall accuracy was 93.1%, with a 95% CI ranging from 83.3% to 98.1%.

The sensitivity of Ga 68 PSMA-11 at baseline with CT scan for the prostate location was 100.0% with 95% CI ranging from 2.5% to 100.0%. The specificity was 59.6%, with a 95% CI ranging from 95% CI 44.3% to 73.6%. The overall accuracy was 60.4%, with a 95% CI ranging from 45.3% to 74.2%.

Comparing the sensitivity of F 18 Choline and Ga 68 PSMA-11 for the prostate location was conducted using McNemar's chi-square analysis as the tests were conducted in two independent groups. We found statistically significant differences between the diagnostic tests in terms of specificity, $X2(1) = 16.69$, $p < 0.00004$, and overall accuracy, $X2(1) = 16.52$, $p = 0.00005$.

For the lymph node's location, the sensitivity of F 18 Choline at baseline with CT scan was 100% with 95% CI ranging from 7.8% to 100.0%. The specificity was 77.8%, with a 95% CI ranging from 60.9% to 89.9%. The overall accuracy was 84.3%, with a 95% CI ranging from 71.4% to 93%.

The sensitivity of Ga 68 PSMA-11 at baseline with CT scan for the lymph node location was 100% with 95% CI ranging from 63.1 % to 100%. The specificity was 65.0%, with a 95% CI ranging from 48.3% to 79.4%. The overall accuracy was 70.8%, with a 95% CI ranging from 55.9% to 83.1%.

Comparison of sensitivity of F 18 Choline and Ga 68 PSMA-11 for the lymph node location showed marginally significant differences in terms of specificity ($X2(1) = 2.86$, $p < 0.09$) and overall accuracy ($X2(1) = 3.77$, $p = 0.052$).

For bone location, the sensitivity of F 18 Choline at baseline with CT scan was 100% with 95% CI ranging from 29.2% to 100.0%. The specificity was 72.7%, with a 95% CI ranging from 59.0% to 83.9%. The overall accuracy was 74.1%, with a 95% CI ranging from 61.0% to 84.7%.

The sensitivity of Ga 68 PSMA-11 at baseline with CT scan for the bone location was 75.0% with 95% CI ranging from 34.9% to 96.8%. The specificity was 77.5%, with a 95% CI ranging from 95% CI 61.6% to 89.2%. The overall accuracy was 77.1%, with a 95% CI ranging from 62.7% to 88%.

The chi-square analysis did not find statistically significant differences between the diagnostic tests in sensitivity and specificity ($p = 1.0$ and $p = 0.60$, respectively), and marginal difference in overall accuracy ($p = 0.073$).

In Figure 3, we show CT/PET scans of the two markers, F 18 Choline and Ga 68 PSMA-11, for detecting prostate, lymph node, and bone lesions in patients who present with PCa biochemical relapse in this study.

5. Discussion

While we were unable to compare the two markers F 18 Choline and Ga 68 PSMA-11 directly due to HUS regulations, our study demonstrated that Ga 68 PSMA-11 is a good candidate for screening for PCa biochemical relapse in patients. We found Ga 68 PSMA-11 based detection rates of 41.6% and 45.8% for prostate and lymph node lesions, respectively, among patients with PSA value >2 µg/L .

Asfhar-Oromieh *et al.* did a study comparing PET imaging with 68-Ga-labelled PSMA ligand and 18F-Choline-based PET/CT (Afshar-Oromieh et al., 2015). Asfhar-Oromieh *et al.*'s hypothesis suggested that PSMA is overexpressed in PCa patients in contrast with choline, which is not increased in PCa patients. Our study had the same hypothesis as this published study.

The number of participants in the study by Asfhar-Oromieh *et al.* was 319 and participants comprised of patients who underwent Ga 68-PSMA screening from 2011 to 2014. PSA level, Gleason score, androgen deprivation therapy, and age were evaluated in the Asfhar-Oromieh *et al* study. Our study consisted of two groups: 76 patients in the F 18 Choline group and 67 patients in the Ga 68 PSMA-11 group. We found that The PSA level was 3.1 ± 7.6 µg/L for the F 18 Choline group and 3.2 ± 16 µg/L for Ga 68 PSMA-11 group in our study. Mean PSA level was lower among our study participants (Mean 3.15 µg/L) compared with PSA level among participants of the Asfhar-Oromieh *et al.* study (Mean 161.0, median 4.59 µg/L) . Since previous studies have identified a gray area for the diagnosis test when the PSA level is between 2 and 10 µg/L, in our study, we used 2 µg/L as a cutoff.

In the Asfhar-Oromieh *et al.* study, the dose parameters for F 18 Choline and Ga 68 PSMA-11 were 237 MBq (range 114-374) and 132 MBq (range 59-263), respectively. Patients received

injections of both tracers within less than 30 days. The authors claimed that there were no adverse detectable pharmacological effects from the injections. Asfhar-Oromieh *et al.* did not examine subgroups of PSA levels or different locations as we did in our study. Asfhar-Oromieh *et al.* reported detection rates (at least one lesion) of 86.5% for Ga 68 PSMA-11 and 70.3% for F 18 Choline.

In our study, the dose parameters for F 18 Choline and Ga 68 PSMA-11 were 298.2 MBq (SD= 37.5) and 152.6 MBq (SD =23.3), respectively. One weakness of our study was that the groups were independent and not compared against each other. Due to institutional regulations, patients were injected with only one tracer and each patient had only one scan as data. In our study, we divided participants into three subgroups based on PSA levels and three subgroups based on targeted locations (prostate, lymph nodes, and bones).

Morigi *et al.* reported findings of a trial conducted among thirty-eight prostate cancer patients with a rising PSA level after radical prostatectomy or radiotherapy and were not yet on systematic therapy (Morigi et al., 2015). The mean PSA level was 1.74 ± 2.54 ng/mL. The scan results were 54% positive for Ga 68 PSMA and 4% with 18F-fluoromethylcholine. We reported a detection rate of 41.6% at a PSA value >2 μg/L in the prostate and a detection rate of 45.8% at a PSA value >2 μg/L in lymph nodes using Ga 68 PSMA-11.

Kallur *et al.* reported that the transmembrane location of PSMA with a large extracellular domain allows for its internalization after ligand binding, providing an accurate target for prostate carcinoma-specific imaging and therapy (Kallur et al., 2017).. Kallur *et al.*'s study had 262 patients and 336 scans. About 20% of patients received two or more scans to clarify suspicious findings. The mean patients' age was 67.6 ± 8.8 years, and the patients' Gleason's score for intermediate risk

(7–8) was 47% and for high risk (9–10), it was 27.2%. Kallur *et al.* reported that Ga 68 PSMA detection did not vary with varying grades of Gleason's score. Kallur *et al.* reported that the sensitivity of Ga 68 PSMA at baseline with PSA levels ≥2 ng/dl and histopathological diagnosis was 95% (95% CI ranging from 86% to 98%) (Kallur et al., 2017). Our study showed that Ga 68 PSMA is more likely to detect prostate, lymph node, and bone lesions than Choline.

Compared to the CT scan, we obtained sensitivity of Ga 68 PSMA-11 for prostate lesions at 100% with 95% CI ranging from 2.5% to 100%. Since the 95% CI range is wide, we decided not to report a value for sensitivity. One possible bias in our study was the gold standard selected, CT. For future studies, setting the gold standard as MRI scan or combining both techniques (CT and MRI) would be beneficial. CT scan has a limitation of low rate of positive imaging for prostate cancer detection; however, CT is an excellent technique to scan the whole body in a limited time (MSK CC, 2022).

We also noticed that the number of false positives for Ga 68 PSMA-11 was higher than F 18 Choline, especially in prostate and lymph nodes (Tables 6D and 6E). Evangelista *et al*. mentioned that the determination of true positive or actual negative results for two markers Ga 68 PSMA and F 18 Choline is impossible without biopsy results. In addition, there is a need for clear image acquisition parameters since many CT instruments do not have the same settings, limiting comparisons (Evangelista et al., 2016).

It is possible to see that Ga 68 PSMA-11 has a better uptake than F 18 Choline in the prostate of BCR patients (Figure 3). PSMA is a validated molecular target for PCA, overexpressed in >90% of tumor cells (PYLARIFY® 18F Radioisotope, n.d.) PSMA expression is associated with higher Gleason scores and lower survival rates (Sanchez-Crespo, 2013). PET/CT with ^{18}F has

higher sensitivity and better resolution than PET/CT with ^{68}Ga. However, it has been reported that Ga 68 PSMA PET has better sensitivity than choline-based PET in detecting prostate cancer recurrence (Papa et al., 2017; Xue et al., 2022; Zattoni et al., 2017).

In sum, we can conclude that the gold standard selection is critical for the determination of the sensitivity and specificity of any marker. Our results for sensitivity and specificity were not the best for Ga 68 PSMA-11, as other authors have published. However, the current study demonstrated that Ga 68 PSMA-11 can be used in HUS settings to detect PCa in patients with biomedical relapse. Future research is needed on PSMA PET and there is a need for more robust sensitivity and specificity data (Matushita et al., 2021; Zequi, 2021). In addition, future research is essential to investigate the use of Ga 68 PSMA-11 PET/MRI instead of CT to improve tumor detection rates.

Table 1. Gleason Score Rating and Characteristics (Gleason, 1992).

Gleason Score	Grade Group	Characteristics
6	Grade Group 1	Less aggressive, very slow growing, low risk.
3 + 4 = 7	Grade Group 2	Slightly aggressive, slow growing, low to intermediate risk.
3 + 4 = 7	Grade Group 3	Moderately aggressive, fast-growing, intermediate to high risks.
8	Grade Group 4	Aggressive, rapidly growing, high risks
9-10	Grade Group 5	High aggressive, rapidly growing, high risks.

Table 2. PSA concentration ratio to the probability of PCa (Catalona et al., 1998).

Total PSA content (µg/L)	Likelihood of prostate cancer (%)
0-2	1
2-4	15
4-10	25
> 10	> 50

Figure 1. Design of the study and Flow chart of patient selection.

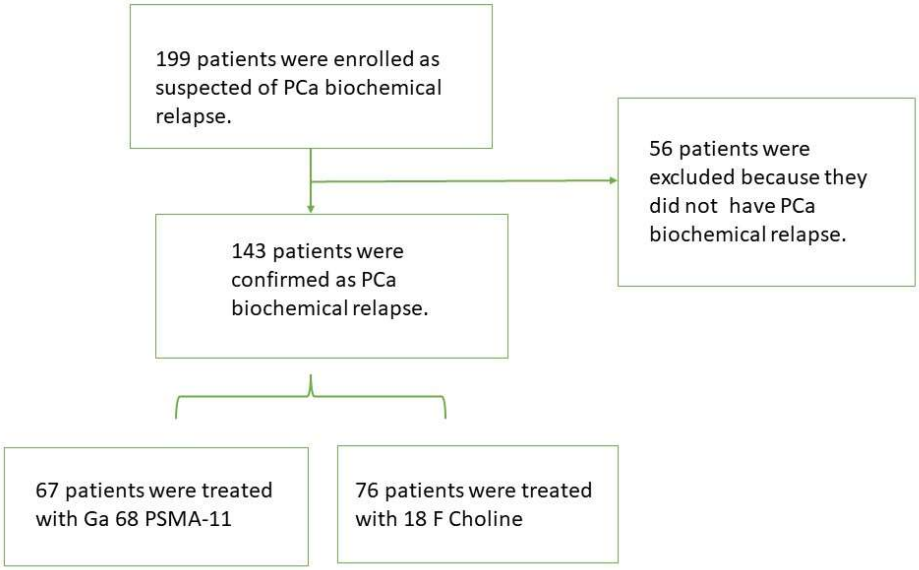


Figure 2. Selected characteristics of Patients by Groups of Examination.

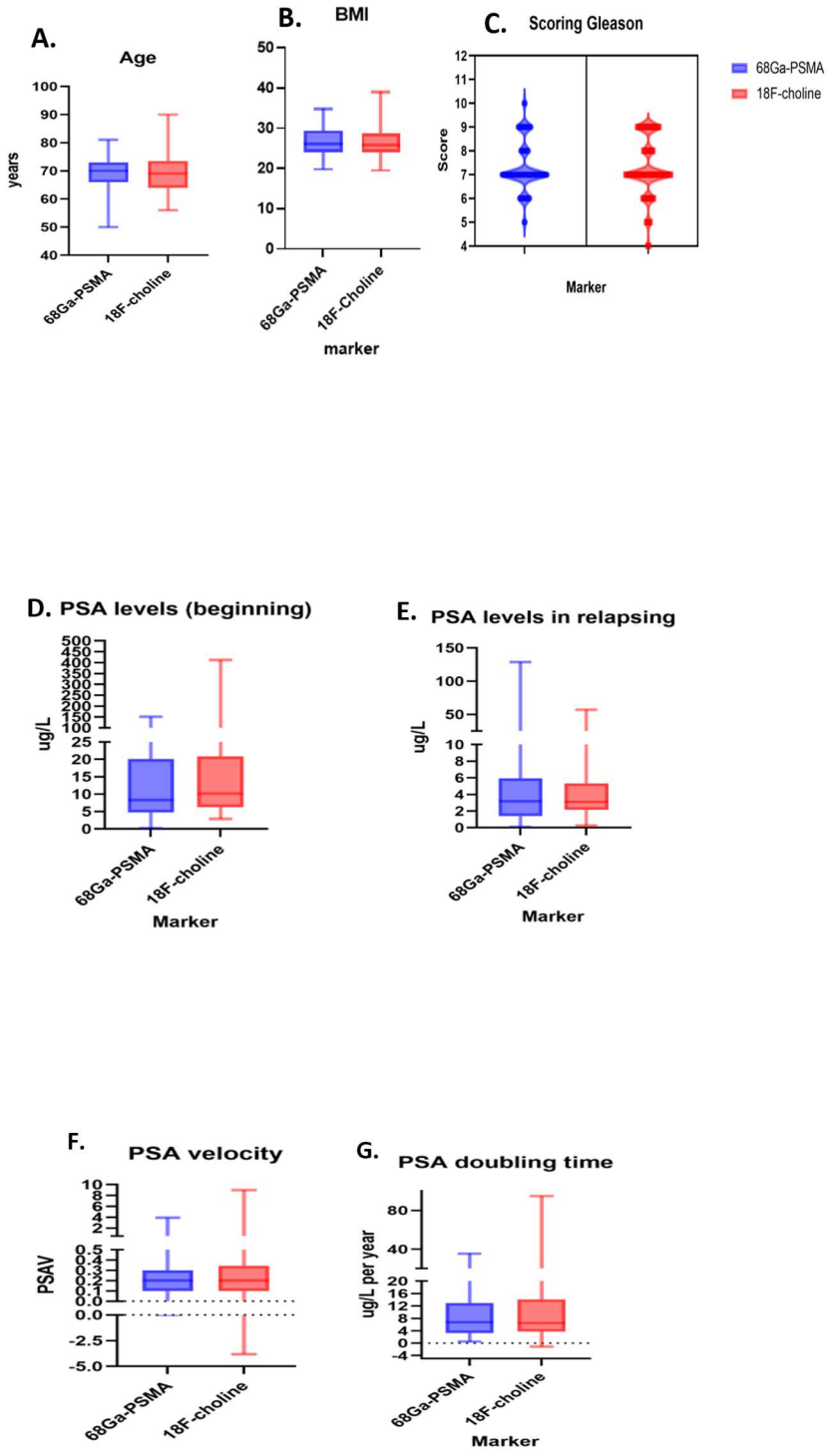


Table 3. Dose Parameters and dose tracer for PET/CT.

			^{68}Ga-PSMA	^{18}F-Choline
	CTDI (mGy)	Mean	2.4	4.2
		SD	1.1	1.1
	DLP (mGy*cm)	Mean	240.9	424.5
		SD	114.1	123.2
	Activity (MBq)	Mean	152.6	298.2
		SD	23.3	37.5
	Activity/Weight (MBq/kg)	Mean	1.8	3.6
		SD	0.3	0.4

Footnote: Computed Tomography dose index (CTDI) , mGy (milligray), Dose-length product (DLP), cm (centimeter), MBq (Megabecquerels), SD (Standard Deviation).

Table 4. Lesions were identified in patients using **F 18 Choline or Ga 68 PSMA-11** tracer at any PSA at relapse (µg/L) value with PET and CT scans.

			Patients with Lesions identify by		
Marker	Location	PSA in relapse (ug/L)	PET	CT	Total Number Patients
18 F-Choline	A. Prostate	<1	0	0	4
		[1-2]	1	0	14
		>2	5	1	58
		all concentrations	6	1	76
	B. Lymph Nodes	<1	2	2	4
		[1-2]	4	1	14
		>2	23	15	58
		all concentrations	29	18	76
	C. Bones	<1	0	0	4
		[1-2]	1	0	14
		>2	18	3	58
		all concentrations	19	3	76
Ga 68 PSMA-11	A. Prostate	<1	1	0	14
		[1-2]	1	0	5
		>2	20	1	48
		all concentrations	22	1	67
	B. Lymph Nodes	<1	5	2	14
		[1-2]	2	0	5
		>2	22	8	48
		all concentrations	29	10	67
		<1	1	1	14
		[1-2]	1	0	5
		>2	15	8	48
		all concentrations	17	9	67

Table 5. The detection rate of F 18 Choline and Ga 68 PSMA biomarkers

Marker	Location	PSA in relapse (ug/L)	PET	CT	*P value*
18 F-Choline	A. Prostate	<1	0% (0/4)	0% (0/4)	NA
		[1-2]	7.1% (1/14)	0% (0/14)	NA
		>2	8.6% (5/58)	1.7% (1/58)	0.13
		all concentrations	7.9% (6/76)	1.3% (1/76)	
	B. Lymph Nodes	<1	50% (2/4)	50% (2/4)	NA
		[1-2]	28.5% (4/14)	7.1% (1/14)	0.25
		>2	39.6% (23/58)	25.9% (15/58)	0.013
		all concentrations	38.2% (29/76)	23.7% (18/76)	
	C. Bones	<1	0% (0/4)	0% (0/4)	NA
		[1-2]	7.1% (1/14)	0% (0/14)	NA
		>2	31% (18/58)	5.2% (3/58)	<0.001
		all concentrations	25% (19/76)	3.9% (3/76)	
Ga 68 PSMA-11	A. Prostate	<1	7.1% (1/14)	0% (0/14)	NA
		[1-2]	20% (1/5)	0% (0/5)	NA
		>2	41.6% (20/48)	2.0% (1/48)	<0.001
		all concentrations	32.8% (22/67)	1.5% (1/67)	
	B. Lymph Nodes	<1	35.7% (5/14)	14.3% (2/14)	0.25
		[1-2]	40% (2/5)	0% (0/5)	NA
		>2	45.8% (22/48)	16.6% (8/48)	<0.001
		all concentrations	43.3% (29/67)	14.9% (10/67)	
	C. Bones	<1	7.1% (1/14)	7.1% (1/14)	1
		[1-2]	20% (1/5)	0% (0/5)	NA
		>2	31.2% (15/48)	16.6% (8/48)	0.07
		all concentrations	25.4% (17/67)	13.4% (9/67)	

Tables 6. Cross-tabulation tables (Table A to F) describing the diagnostic testing calculations (sensitivity [SN], specificity [SP], and overall accuracy [OA]with respective 95% confidence intervals [95% CI]) for patients with PSA > 2 µg/L

Marker	Location		CT (control)			
18 F-Choline	A. Prostate	PET (test)		**YES**	**NO**	**TOTAL**
			YES	1	4	5
			NO	0	53	53
			TOTAL	1	57	58
			CT (control)			
	B. Lymph Nodes	PET (test)		**YES**	**NO**	**TOTAL**
			YES	15	8	23
			NO	0	35	35
			TOTAL	15	43	58
			CT (control)			
	C. Bones	PET (test)		**YES**	**NO**	**TOTAL**
			YES	3	15	18
			NO	0	40	40
			TOTAL	3	55	58
Ga 68 PSMA-11	A. Prostate	PET (test)		**YES**	**NO**	**TOTAL**
			YES	1	19	20
			NO	0	28	28
			TOTAL	1	47	48
			CT (control)			
	B. Lymph Nodes	PET (test)		**YES**	**NO**	**TOTAL**
			YES	8	14	22
			NO	0	26	26
			TOTAL	8	40	48
			CT (control)			
	C. Bones	PET (test)		**YES**	**NO**	**TOTAL**
			YES	6	9	15
			NO	2	31	33
			TOTAL	8	40	48

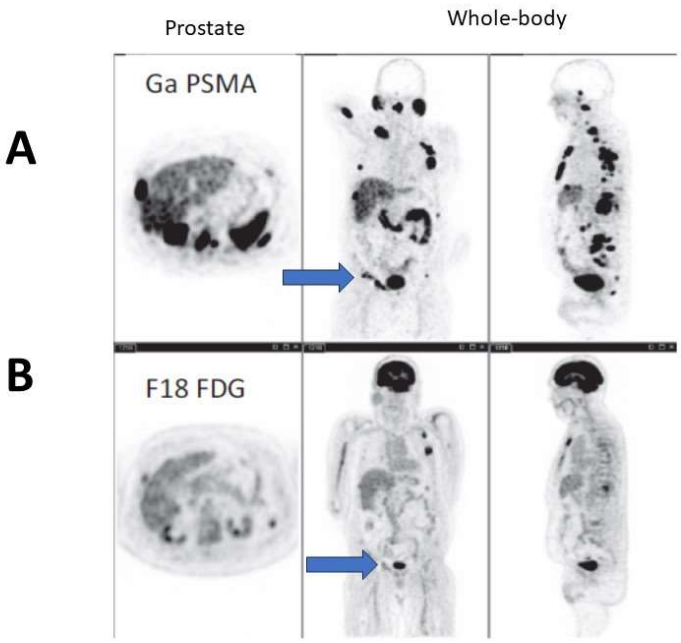
Table 7. Sensitivity, specificity, OA and PPV, and NPV of A: F 18 Choline and B: Ga 68 PSMA-11 concentration >2 and lesion site.

Location		**18 F-Choline**			
	Overall Accuracy % (95% CI)	**SN % (95%CI)**	**SP % (95%CI)**	**PPV % (95%CI)**	**NPV % (95%CI)**
Prostate	93 (83.2-98.1)	100 (2.5-100)	93 (83-98)	20 (0.5-71)	100 (93-100)
Lymph nodes	86.2 (74.6-93.8)	100 (78-100)	81.4 (66-6-91.6)	65 (43-83.6)	100 (90-100)
Bones	74.1 (61-84.7)	100 (29-100)	73 (59-84)	16.6 (4-41)	74.13 (91-100)

Location		**Ga 68 PSMA-11**			
	Overall Accuracy % (95% CI)	**SN % (95% CI)**	**SP % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% I)**
Prostate	60.42 (45.3-74.2)	100 (2.5-100)	59.6 (44.3-74)	5 (0.13-24.8)	100 (87.6-100)
Lymph nodes	70.8 (55.9-83.1)	100 (63-100)	65 (48-79)	36 (17.2-59.3)	100 (86.7-100)
Bones	77.1 (62.7-88)	75 (34.9-96.8)	77.5 (61.6-89.2)	40 (16.3-67.7)	93.9 (79.7-99.26)

Footnote: sensitivity [SN], specificity [SP], and overall accuracy [OA]with respective 95% confidence intervals [95% CI]

Figure 3. Comparison of CT/PET prostate scans with Ga 68 PSMA-11 and F-18 FDG: Ga 68 PSMA-11 concentration >2 and lesion site.



68Ga-PSMA PET show multiple sites of metastatic prostate cancer. There is an intense PSMA uptake (blue arrow). Additional lymph nodes are observed in the whole-body imagen.

F18 FDG PET show minimal activity of metastatic prostate cancer. There is a minimal FDG uptake (blue arrow).

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