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A Review of the Role of PET / CT Scan in the Assessment and Management of Biochemical Failure Following Treatment of Carcinoma of the Prostate Gland with Curative Intent: An Update

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Abstract

A number of patients who undergo treatment of curative intent for localized carcinoma of the prostate gland subsequently develop biochemical failure. There is no global consensus opinion regarding which radiological imaging modality should be the used in the first instance in the investigation of biochemical failure in order to identify localized and distant recurrent disease early. PET/CT scan does not tend to be used frequently in the investigation of biochemical failure; however, recent reports have indicated that PET/CT scan would be a useful tool which could be used in the early investigation of biochemical failure. The Aim of the article was to review the recent literature relating to the use of PET/CT scan in the investigation of biochemical failure emanating from treatment of prostate cancer with curative intent in order to confirm or negate the suggestion that PET/CT scan would be useful for the identification of localized and distant recurrent diseases in cases of biochemical failure. Various internet data bases were searched including: Google, Google Scholar, Educus, and PUBMED. The search words that were used included: PET/CT Scan in carcinoma of the prostate, PET/CT scan in prostate cancer, PET/CT scan and prostate cancer, PET/CT scan and carcinoma of the prostate. Twenty manuscripts have been published between 2013 and 2016 relating to the use of a form of PET/CT scan in the investigation of carcinoma of the prostate gland. One of the articles published in Dutch was a review article. Another paper reported the use of PET CT scan in the diagnosis of Hurtle tumour (a benign tumour) in association with carcinoma of the prostate gland. The remaining manuscripts contained case reports and studies regarding the use of various types of PET/CT scan in the investigation of biochemical failure. On the whole almost all of the papers had confirmed the high sensitivity and high specificity of PET/CT scan in detecting localized and distant metastatic lesions in the scenario of slight elevations of serum PSA. There have been reports of PET/CT scan being able to detect localized and distant metastasis when conventional computed tomography scan and isotope bone scan failed to detect metastases. In one case when the serum PSA was high isotope bone scan and CT scan failed to detect bone metastases but PET/CT scan detected bone metastases. PET/CT Scan is a very useful imaging modality that detects localized and distant metastases in biochemical recurrence of prostate cancer and this modality of imaging should be used more often from now onwards. PET/CT scan would detect smaller sized lesions at slightly raised levels of serum PSA. The detection of small localized metastasis at a slightly elevated serum PSA values would make it easier for a second-line treatment of curative intent in the form of salvage lymphadenectomy or salvage radiotherapy targeted at the lesion to be undertaken. Perhaps PET/CT scan should be the first-line imaging modality which should be used in investigating biochemical recurrence and this should be done when the serum PSA is slightly elevated.

Key Words: Positron emission tomography scan; carcinoma of prostate; biochemical recurrence; isotope bone scan, computed tomography scan; magnetic resonance imaging scan; radical prostatectomy;

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Introduction

The recent incidence statistics of carcinoma of the prostate in the United Kingdom has been summarized as follows: [1]. There were about 47,300 new cases of carcinoma of the prostate gland diagnosed in the United Kingdom in 2013 which would amount to 130 cases of carcinoma of the prostate gland diagnosed every day in the United Kingdom. [1] In 2013 carcinoma of the prostate gland was the second most common cancer encountered in the United Kingdom [1] Carcinoma of the prostate gland accounted for 13% of all cases of cancer reported in the United Kingdom in 2013. [1] With regard to males in the United Kingdom, it has been documented that carcinoma of the prostate gland was the commonest cancer reported which amounted to approximately 47,300 cases. [1] Between 2011 and 2013 about 54% of cases of carcinoma of the prostate cancer were diagnosed in men who were 70 years old or older than 70 years old. [1] It has been stated that since the 1970s the incidence of carcinoma of the prostate gland had increased by 155% due to the advent of serum PSA testing. [1] It has been documented that over the preceding decade the incidence rate of carcinoma of the prostate gland in the United Kingdom had increased by about 5% and that majority of cases of carcinoma of the prostate gland are diagnosed at an early stage (see figure 1). [1] It has also been stated that 1 out of 8 men would be diagnosed with carcinoma of the prostate gland within their life-times and that within England carcinoma of the prostate gland tends to be less common amongst men who live in deprived areas. [1] It has been iterated that carcinoma of the prostate gland tends to be most common among black males, followed by in white males and the disease is least common among Asian males. [1] It has been documented that within the United Kingdom more than 181,000 men were still alive by the end of 2006 and that these men had been alive for more than 10 years pursuant to being diagnosed as having carcinoma of the prostate gland. [1] It has also been stated that within Europe, about 417,000 new cases of carcinoma of the prostate gland were estimated to have been diagnosed in 2012 and that the United Kingdom incidence of carcinoma of the prostate gland ranks as the 17th highest within Europe . [1] It has been documented that globally in 2012 it had been estimated that 1.11 million men had been diagnosed as having carcinoma of the prostate gland and the incidence of carcinoma of the prostate gland has varied across the world. [1]

A large number of patients globally would be diagnosed as having localized adenocarcinoma of the prostate gland and they may be managed by (a) active surveillance, (b) treatment with curative intent in the form of radical prostatectomy or radiotherapy by means of external beam radiotherapy or brachytherapy and in some developing countries where there is lack of radiotherapy facility such patients may be treated by means of bilateral orchidectomy as surgical hormonal therapy to slow down the disease due to the relatively high-cost of the medical hormonal treatment medicaments which the patients cannot afford to pay for. A number of patients who undergo treatment of curative intent for localized disease would subsequently develop biochemical recurrence which could either be (a) biochemical recurrence without radiological evidence of a recurrent lesion, or (b) localized recurrence, or (c) distant metastasis. Patients who develop localized recurrence could be managed by (a) salvage lymph node excision (salvage lymphadenectomy), (b) salvage radiotherapy, (c) watch and wait, or (d) hormonal treatment. A second-line treatment of salvage lymph-adenectomy or salvage radiotherapy offers the patient a second line treatment of curative intent whilst reserving hormonal treatment for further subsequent biochemical recurrence as 3rd line treatment. Some of the patients who undergo second-line treatment of curative intent may not develop biochemical recurrence following their treatment and may not have to undergo hormonal treatment. Various radiological imaging techniques are available to identify the cause of biochemical recurrence and these include: (a) trans-rectal ultrasound scan and ultrasound scan of abdomen and pelvis, (b) computed tomography (CT) scan of thorax abdomen and pelvis, (c) magnetic resonance imaging (MRI) scan of thorax abdomen and pelvis, (d) PET/CT scan. CT scan and MRI scan of the thorax would exclude metastasis within the thorax. Isotope bone scan tends to be undertaken to exclude bone metastasis but this modality of investigation is not used to identify localized recurrence. There is no consensus opinion regarding which radiological imaging technique would best identify a localized recurrent tumour and at what stage of the development of biochemical recurrence a patient should undergo radiological imaging investigation to identify localized recurrence in order to undertake further early treatment of curative intent. From 2013 to 2016 a number of case reports and reports from studies related to the use of PET/CT scan have been published in various journals. The ensuing manuscript relating to the use

of PET/CT scan as a mode of investigating biochemical recurrence following treatment of adenocarcinoma of the prostate gland with curative intent is divided into two parts: (A) Overview and (B) miscellaneous narrations and discussions from some reported cases and studies related to the use of PET/CT scan in the assessment of patients who developed biochemical recurrence pursuant to undergoing treatment of curative intent for adenocarcinoma of the prostate gland.

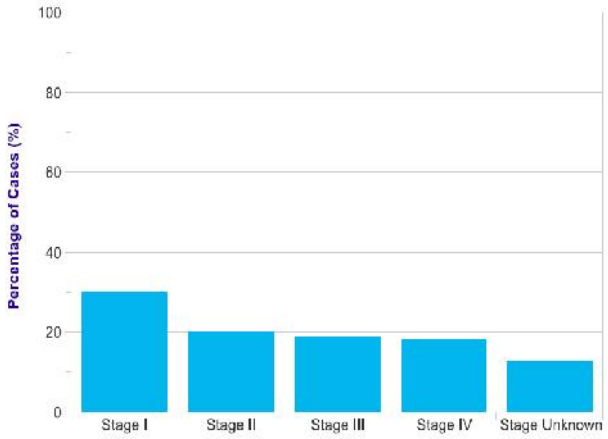

Figure 1: Prostate Cancer (C61): 2014. Proportion of Cancers Diagnosed at Each Stage, All Ages, England

Stage at Diagnosis	Percentage of Cases (%)
Stage I	30.2%
Stage II	20.1%
Stage III	19.0%
Stage IV	18.1%
Stage Unknown	12.6%

Source: Cruk.org/cancers/stats. Cancer Research UK as the primary source [1] Cancer Research UK Prostate cancer statistics Cancer | Research UK. URL: http://www.cancerresearchuk.org/health-profiles Accessed 9th October 2016.

Methods

Various internet data bases were searched including Google, Google Scholar, Educus, and PUB MED, for information related to the use of positron emission tomography (PET) / computed tomography (CT) scan with regards to the detection recurrent tumours in the investigation of biochemical (serum PSA) recurrence following treatment of carcinoma of the prostate gland. The search words that were used included: Positron Emission Tomography / Computed Tomography scan in carcinoma of prostate; PET/CT scan and carcinoma of prostate; PET/CT scan and prostate cancer. In all 27 references were identified and used in writing the article.

Literature Review

(A) Overview

General Comments

- Various radiological imaging modalities have been used globally in the assessment of patients who develop biochemical failure after undergoing treatment of curative intent for adenocarcinoma of prostate including trans-rectal ultrasound scan of prostate, computed tomography scan, magnetic resonance imaging scan and PET/CT scan but there is no consensus regarding which radiological imaging techniques offer the best chance to identify early localized recurrent tumour. Isotope bone scan also tends to be used to confirm presence or absence of bone metastasis.

Trans-rectal ultrasound scan

- Trans-rectal ultrasound scan is very useful as a guide to taking biopsies from the prostate gland for histological examination for the confirmation of the diagnosis of carcinoma of the prostate gland and for the Grading of the tumour.
- Trans-rectal ultrasound scan of the prostate also tends to be used as a guide to taking subsequent biopsies of the prostate when a patient is undergoing active surveillance to ascertain whether or not the grade of the tumour had changed with time.
- If a patient has had radical radiotherapy for localized prostate cancer trans-rectal ultrasound scan of prostate can be undertaken in the scenario of biochemical failure to assess the prostate in order to identify any lesion or lesions that can be biopsied for histological examination to confirm presence of adenocarcinoma of the prostate as well as to establish the Gleason grade of any recurrent lesion of the prostate.
- Ultrasound scan of renal tract abdomen and pelvis can be used to assess the renal tract and abdomen and pelvis which could identify a lesion or lesions in the prostate or seminal vesicle or within the pelvis in the form of enlarged lymph nodes or other lesions within the abdomen and pelvis.

Computed tomography scan

- Computed tomography scan can be used in the initial stating of carcinoma of the prostate gland as baseline which can be compared with other CT-scan images that are taken in the follow-up assessment of the patient.
- CT scan of the thorax, abdomen, and pelvis tends to be undertaken in the staging process of a newly diagnosed carcinoma of the prostate to assess for

extension beyond the prostate but especially to establish whether or not there is nodal disease.

- CT scan can be used to confirm presence or absence of bone metastasis; however, isotope bone scan and magnetic resonance imaging scan tend to be superior to CT scan in confirming bone metastasis in that some small lesions may be missed by CT scan but isotope bone scan and MRI scan would be able to detect such lesions.
- When an isotope bone scan shows a hot spot in a bone, CT scan may be used to further assess the features of the lesion and to confirm metastasis.
- In cases of cord compression CT scan may be undertaken to show whether there is a localized lesion that could be removed surgically by a neurosurgeon as an emergency or there is disseminated disease which should be amenable to urgent/emergency radiotherapy in the scenario of cord compression. Nevertheless, MRI scan tends to be superior in situations like this but MRI scan may not necessarily be available everywhere globally.
- CT scan is not absolutely necessary in all cases of carcinoma of the prostate in the first instance. The guideline indicators for CT scan in carcinoma of the prostate include (a) serum PSA of 20 UG/L or greater, or (b) Gleason score higher than 7, and or (c) clinical stage T3 or higher.
- CT scan can also be used in the assessment of the prostate in order to plan for external beam – radiotherapy; CT scan is useful for targeting biopsy of the prostate gland in some cases of previous negative prostate biopsies and rising serum PSA. CT scan is used in the planning and performance of brachytherapy.

Magnetic resonance imaging (MRI) Scan

- Magnetic resonance imaging (MRI) scan can be used for the detection of carcinoma of the prostate gland; however, it is not commonly used for this purpose. MRI scan tends to be undertaken only if despite negative prostate biopsy findings there is suspicion of carcinoma of the prostate because of persistent rising serum PSA.
- As a result of high resolution T2 weighted MRI scans, MRI spectroscopy, and dynamic contrast-enhancement, there has recently been a trend for MRI scanning to be seen and used as a method that can improve the detection of carcinoma of the prostate gland and MRI scan is also being used for the characterization, staging, treatment and follow-up of patients with carcinoma of the prostate gland.
- MRI scan of the prostate has the ability to detect abnormal areas within the prostate gland that should be targeted for biopsy in case of previous negative prostate biopsies when there is persistently rising serum PSA with a suspicion of carcinoma of the prostate gland.
- MRI scan of thorax, abdomen and pelvis can be undertaken for staging the disease but this is not routinely undertaken for everybody. It can also be used in the follow-up re-staging of the disease in cases of biochemical recurrence following treatment of curative intent in the form of radical prostatectomy or radiotherapy / brachytherapy in order to plan salvage treatment of the patient.
- MRI scan of the spine is useful for the diagnosis of bone metastasis and it tends to be more superior to CT scan of the spine

Isotope bone scan

- Radioisotope bone scan generally is not used for the diagnosis or staging of carcinoma of the prostate but traditionally isotope bone scan has been the main stay approach to the diagnosis of bone metastasis. [2]
- Generally there is no need to undertake a bone scan when the serum PSA is less than 10 ng / mL because almost invariably the overwhelming majority of such cases would be negative (less than 1% of patients would have positive scan); when the serum PSA level is between 10 and 50 ng / mL up to about 10% of the patients would tend to have a positive bone scan; when the serum PSA level is greater than 50 ng / m L up to about 50% of patients would have positive bone scan. [2]
- The fact that a bone scan is negative does not mean that the patient does not have bone metastasis because a case report in the second part of the paper would illustrate how a patient with a negative isotope bone scan had been shown to have a positive PET/CT scan showing bone metastasis.

Positron Emission Tomography Scan

Previous reports relating to the use of 18 F fluorodeoxyglucose PET/CT in carcinoma of the prostate gland had not been encouraging; nevertheless, as a result of newer reconstruction techniques as well as a result of the use of newer PET/CT scan agents including (11) C choline, (11) C acetate, (11) C methionine, and (18) fluoro-dihydrotestosterone, [2] the use of PET/CT scan in biochemical recurrence has recently been reported to be yielding encouraging results with regard to the detection of lesions responsible for biochemical recurrence following treatment of carcinoma of the prostate with curative intent. From 2013 up to 2016 a number of case reports, and studies had been published which had documented the reliability, sensitivity and specificity and level of accuracy of the

use of various analogues of choline PET/CT scan in the detection of lesions responsible for biochemical recurrence of prostate cancer which is discussed in the second section of this paper.

Approach to imaging with regard to treatment of adenocarcinoma of the prostate

Hricat et al. [2] had outlined the approach to imaging of prostate cancer during treatment as follows:

- The role of radiological imaging pursuant to treatment for the carcinoma of the prostate would depend upon the treatment option used including active surveillance, watchful waiting, treatment of curative intent by radical prostatectomy or radical radiotherapy, or treatment by androgen deprivation.
- The role of radiological imaging would also depend upon the clinical and laboratory findings of the patient.
- Irrespective of the type of therapy administered to the patient, serial measurements of serum PSA, and digital rectal examination findings are standard ways to assess and monitor the patient for tumour recurrence.
- The earliest and commonest indication for recurrence of adenocarcinoma of the prostate gland is rising serum PSA level and routine CT scan imaging is not needed if the patient's serum PSA is not detectable and there are no new clinical findings.
- In the event of a subsequent rise in serum PSA levels, three main categories of recurrence of carcinoma should be considered including: (a) PSA only biochemical recurrence, (b) local recurrence of tumour either in the post-prostatectomy bed or within the prostate gland pursuant to radical radiotherapy, (c) distant metastasis which quite commonly tends to be occurrence of nodal disease or osseous disease.
- The pivotal consideration with regard to the evaluation of a patient who could possibly have recurrence from carcinoma of the prostate gland is to differentiate between local and distant metastasis.
- It had been stated that the occurrence of distant metastasis would be suggested by a short serum PSA doubling time of less than 10 months in a patient who had undergone treatment for a high-grade adenocarcinoma of prostate Gleason 8 to Gleason 10, or a high pathological stage tumour with seminal vesicle involvement or lymph node metastasis. But on the other hand, the occurrence of local metastasis would tend to be associated with a prolonged serum PSA doubling time of more than 10 months in a patient who had undergone treatment for a tumour that had been scored as Gleason 2 to Gleason 7, a positive surgical margin, and no involvement of seminal vesicles or lymph node. [3]
- It has been intimated that with regard to the patient who had undergone surgery (radical prostatectomy), the serum PSA level should drop to an undetectable level within 21 days to 30 days after the surgical operation and the serum PSA level should remain undetectable thereafter. [4] [5]
- It had also been intimated that serum PSA level tends to decrease more slowly pursuant to definitive radiotherapy in comparison with after radical prostatectomy and the serum PSA level may not reach a nadir until 18 months to 20 months pursuant to the radiotherapy. [6] [7]
- Even though any increase in serum PSA level pursuant to radical prostatectomy would indicate recurrence of the carcinoma of prostate, the American Society for Therapeutic Radiation Oncology had defined a biochemical recurrence for a post-irradiation patient as three consecutive increases in serum PSA level from the nadir, with the date of recurrence assigned half-way between the dates of nadir and the first increase. Nevertheless, later on, it had been demonstrated that the definition of PSA failure (biochemical failure) as nadir PSA + 2.0 ng / m L does provide a better surrogate for treatment failure in patients who had undergone treatment with curative intent by means of permanent brachytherapy of the prostate or external beam radiotherapy [8]
- Trans-rectal ultrasound scan, CT scan and MRI scan have been evaluated for detection of local recurrence after prostatectomy.

When there is evidence of biochemical recurrence following radical prostatectomy the options of management would include salvage lymph adenectomy, salvage radiotherapy, and hormonal treatment. Whilst salvage lymph node excision and salvage radiotherapy could be regarded as treatment of curative intent hormonal treatment would not be regarded as treatment of curative intent. It would also be argued that it does not matter which radiological imaging that is used to diagnose local recurrence at an earlier stage following radical prostatectomy and that early detection of local recurrence would offer the patient a possibility of longer survival as a result of the second treatment of curative intent. Not all patients who undergo second treatment with curative intent would necessarily be cured. However, those who have good response to second line treatment of curative intent could still be considered for hormonal treatment as a subsequent 3rd line treatment should the need arise. The question may be asked which

radiological imaging should be used if there is evidence of biochemical failure following treatment of localized prostate for adenocarcinoma of the prostate and at what time should the radiological-imaging be undertaken? It is conjectural but it may be further argued that it does not matter which imaging technique that is used to detect local recurrence after treatment of prostate cancer with curative intent and that there is no point in waiting till the patient's serum PSA has risen to 6 ng/ml or above as well as the sooner a diagnosis of biochemical failure is confirmed radiological imaging should be undertaken to ascertain presence of local recurrence or distant metastasis to enable early planning of second line treatment of curative intent.

From 2013 to date in 2016, a number of case reports and studies related to the use of PET/CT scanning to evaluate biochemical failure pursuant to treatment of carcinoma of the prostate gland by curative intent have been published in different journals. The following section contains miscellaneous narrations and discussions from reported cases of the use of various PET/CT scan procedures in the assessment of a number of patients who had developed biochemical failure after they had undergone treatment for carcinoma of the prostate gland with curative intent.

(B) Miscellaneous narrations and discussions from reported cases, case series and various studies on the use of PET/CT Scan in carcinoma of the prostate gland

Ceci et al. [9] evaluated the usefulness of 11 C-choline PET/CT scan in patients who had recurrent carcinoma of the prostate gland and hormone-sensitive disease that had been treated by intermittent anti-androgen treatment regime. Ceci et al. [9] retrospectively evaluated 10 patients pursuant to having had radical prostatectomy in the case of 8 patients and two after having had external beam radiotherapy for curative intent as primary treatment. All of the ten patients had undergone sequential 11 C-choline PET/CT scans. The first PET/CT (PET1) was undertaken during an anti-androgen therapy (ADT) and the second PET/CT scan (PET2) was undertaken following interruption of the anti-androgen therapy for at least 6 months. It was only patients who had negative results in the PET1 who were included in the study. At the time of performing PET1 all the patients were undergoing anti-androgen therapy from at least 6 months and their mean serum PSA was 0.54 ng / m L. At the time of performing PET2 all the patients had completed their anti-androgen therapy for a mean period of 7 months. The 11 C-choline PET/CT scan findings had been validated by a follow-up of at least a minimum of 12 months or by histological confirmation of diagnosis in the case of local recurrence. With regard to the results Ceci et al. [9] reported that PET2 was able to detect the site of recurrence in all cases and that at the time of PET2 scanning the mean serum PSA was 3.88 ng / m L as well as the mean serum PSA doubling time (PSAdt) was 2.46 months. Furthermore, the mean serum PSA velocity (PSAvel) was 6.94 ng / mL / year. Four out of the ten patients had a single lesion, 5 out of the ten patients had PET2 scan evidence of 2 lesions and 1 patient had multiple lymph node lesions on the PET2 scan. Ceci et al. [9] made the following conclusions.

- When performed during interruption of anti-androgen therapy, 11 C-choline PET/CT scan had been able to identify the site of tumour recurrence during a rising serum PSA level detection.
- Within this context 11 C-choline PET/CT scan could help in the assessment of the burden of disease or in the change of therapeutic approach by the use of more aggressive and addressed therapies like guided radiotherapy or salvage lymph node dissection.

Souvatzouglou et al. [10] evaluated the performance of conventional [(11)C]choline PET/CT scan in comparison with PET/MRI scan in carcinoma of the prostate gland. Souvatzouglou et al [10] studied 32 patients who had carcinoma of the prostate gland and who had undergone a single-injection dual-imaging protocol with PET/CT scan and subsequent PET/MRI scan. The PET/CT scans were undertaken applying standard clinical protocols (5 minutes pursuant to injection of 793 ± 69Mbq [(11)C]choline, 3 minutes per bed, intravenous contrast agent). Subsequently (52±15 minutes after injection) PET/MRI scan was undertaken (4 minutes per bed position). The PET images had been reconstructed iteratively (OSEM 3D), scatter and attenuation correction of emission data and regional allocation of [(11)C] choline foci were undertaken using CT data for PET/CT scan and a segmental Dixon MRI, T1 and T2 sequences for PET/MRI scan. The image quality of the respective PET scans as well as PET alignment with the respective morphological imaging modality had been compared with the use of a four point scale (0 to 3). Additionally, the number, the location, and conspicuity of the detected lesions had been evaluated. The SUVs for suspicious lesions, lung, liver, spleen, vertebral bone, and muscle were compared. With regard to the results, Souvatzouglou

et al. [10] reported that 80 lesions overall had been scored visually in 29 out of the 32 patients. No significant difference was found between the two scans with regard to the number or conspicuity of the identified lesions (P not significant). PET/MRI scan had T1 and T2 sequences performing better than PET/CT scan in anatomical allocation of the lesions (2.87 ± 0.3 versus 2.72 ± 0.5: P = 0.05). The quality of PET/CT images (2.97 ± 0.2) had been better in comparison with that of the respective PET scan of the PET/MRI scan (2.69± 0.5; P = 0.007). On the whole the maximum and mean lesional SUVs did exhibit high correlations between PET/CT scan and PET/MRI scan (P = 0.87, and P = 0.86, respectively; both P < 0.001). Souvatzouglou et al. [10] made the following conclusions:

- Despite the fact of a substantially later imaging time-point, the undertaking of simultaneous PET/MRI scan was comparable with that of PET/CT scan in the detection of lesions with increased [(11)C] choline uptake in patients who have carcinoma of the prostate.
- The anatomical allocation of lesions was found to be better with simultaneous PET/MRI scan in comparison with PET/CT scan especially in bone and in the pelvis
- These promising findings would suggest that [(11)C] choline PET/MRI scan might have a diagnostic benefit in comparison with PET/CT scan in patients who have carcinoma of the prostate gland, and now needs to be evaluated in prospective trials.

Kang et al. [11] evaluated the clinical value of incidental prostate of 18F-FDG uptake in PET/CT scans. Kang et al. [11] reviewed the 18F-FDG PET/CT scan reports from September 2009 to September 2013 and they selected cases that had been reported to have shown focal/diffuse FDG uptake in the prostate gland. Kang et al. [11] analysed the correlation between 18F-FDG PET/CT scan finding and data which had been collected during evaluations including serum prostate specific antigen (PSA) levels, digital rectal examination (DRE) findings, trans-rectal ultrasound scan of prostate (TRUSP) findings, and or pathological reports of biopsy of prostate to confirm carcinoma of the prostate gland. Out of a total of 18,393 cases 106, (0.6%) did exhibit abnormal hyper-metabolism in the prostate gland. Additional evaluations were undertaken in 66 patients. Serum prostate-specific antigen (PSA) were found not to be significantly correlated with maximum standardized uptake values (SUV max) in all patients (rho 0.483; P = 0.132). Biopsies of the prostate gland were undertaken in 15 patients, and carcinoma of the prostate gland was confirmed in 11 patients. The median serum PSA level was 4.8 (range 0.55 – 7.06) ng/ml, and 127.4 (1.06 – 495) ng/ml, in the benign and the carcinoma of prostate groups respectively. The median SUVmax was higher in the carcinoma of prostate gland group (mean 10.1, range 3.8 to 24.5) than in the benign group (mean 4.3, range 3.1 to 8.8), but the difference was found not to be statistically significant (P = 0.078). No significant correlations were found between SUVmax, and serum PSA levels, prostate volume or Gleason grade. 18F-FDG PET/CT scan was found not to reliably differentiate malignant, or benign from abnormal uptake lesions within the prostate gland, and routine prostate biopsy had not been routinely recommended in patients who had abnormal FDG uptake. However, Kang et al. [11] recommended that patients who had incidental prostate uptake on 18F-FDG PET/CT scans should not be ignored and they should undergo further evaluations in the form of serum PSA level determinations and digital rectal examinations.

Hodolic et al. [12] reported a 59-year-old man who presented with urinary frequency. Six months prior to his presentation, his serum prostate-specific antigen (PSA) level was 1.56 ng/ml and at the time of his current presentation his serum PSA level was 3.5 ng/ml (PSA doubling time 6 months; PSA velocity = 0.19 ng/ml per month). Histological examination of his prostate biopsy showed features consistent with Gleason 5+5 = 10 adenocarcinoma of the prostate gland. He underwent staging of his tumour by having (18)F-fluorocholine PET/CT scan which showed lymph node metastasis. Following six months of having hormonal treatment with goserelin, his serum PSA level had decreased to 0.38 ng/ml. He then had (18) F-FCH PET/CT re-staging scan which showed a global reduction of (18) F-FCH lesion uptake with the disappearance of some mediastianal lymph node activity and iliac as well as pelvic lymph node activity.

Vargas et al. [13] undertook a retrospective study to compare the features of bone metastases at computed tomography (CT) to tracer uptake at fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) and fluorine 1816β-fluoro-5-dihydrotestosterone (FDHT) PET and to ascertain the association between these imaging characteristics and the overall survival in men who have castration-resistant carcinoma of the prostate

gland. In this study, two readers independently evaluated computed tomography (CT) scans, FDG PET scans, and FDHT PET scans of 38 patients for features of bone metastases. The associations between imaging findings and the overall survival of the patients were determined by utilizing univariate Cox proportional hazards regression. With regard to the results, Vargas et al. [13] reported that reader 1 detected in 38 patients, 881 lesions and reader 2 detected 867 lesions. They found that attenuation coefficients at computed tomography scanning had correlated inversely with FDG (reader 1: r = -0.3007); P < 0.001; reader 2: r = -0.3147, P < 0.001) and FDHT (reader 1: r = -0.2680; P = 0.001, reader 2: r = -0.3656; P < 0.001) uptake. The number of lesions on the CT scans was significantly associated with the overall survival of the patients (reader 1: hazard ratio [HR] 1.025; P = 0.05; reader 2: hazard ratio [HR] 1.021; P = 0.04). The numbers of lesions on the FDG and the FDHT PET scans were found to be significantly associated with survival by reader 1 (hazard ratio [HR] 1.051 – 1.109, P < 0.001; and also significantly associated with survival by reader 2 (hazard ratio [HR] 1.026 1.082; P ≤ 0.009). The patients who had higher FDHT uptake (lesion with the highest maximum standardized uptake value) did have significantly shorter survival (reader 1: hazard ratio [HR] 1.078; P = 0.02; reader 2: hazard ratio [HR] 1.092; P = 0.02). FGD uptake intensity was found not to be associated with overall survival of the patients (reader 1: P = 0.65; reader 2: P = 0.38). Vargas et al. [13] concluded that in patients who have castrate resistant carcinoma of the prostate gland, the numbers of bone lesions on CT scan, FDG PET/CT scan, and FDHT PET/CT scan and the intensity of the FDHT uptake tend to be significantly associated with the overall survival of the patients.

Buchegger et al. [14] reported the results of a comparative, prospective PET/CT scan study of both tracers that had been in the same patients who had developed recurrence of their carcinoma of the prostate and low serum PSA in order to compare the diagnostic information provided by the two tracers. Buchegger et al. [14] stated that they had studied 23 patients who had developed rising serum PSA following treatment of curative intent. Seven patients had undergone radical prostatectomy and subsequently developed rising serum PSA ≤3 ng/mL; 7 patients had undergone radiotherapy of curative intent and subsequently developed rising serum PSA 0f ≤ 5 ng/mL; 9 patients had undergone radical prostatectomy and salvage radiotherapy and subsequently developed rising serum PSA levels of ≤ 5 ng/ml. Both FCG and ACE PET/CT scans were undertaken on all patients in a random sequence with a mean of 4 days and a range of 0 to 11 days apart. FCH PET/CT scan was started at injection (307 ± 16 MBq) with a 10 minutes dynamic acquisition of the prostate bed ensued by a whole-body PET scan and late (45 minutes later) imaging of the pelvis. ACE PET/CT scan was undertaken as double whole-body PET scan starting 5 minutes and 22 minutes after following the injection (994 ± 72 MBq), and a late view (45 minutes later) of the prostate bed. The PET/CT scans had been blindly reviewed by two independent pairs of two experienced nuclear medicine physicians, and discordant sub-group results were discussed to obtain consensus for positive, negative, or equivocal results. With regard to the results, Buchegger et al. [14] reported that the PET results had been concordant in 88 out of 92 local, regional, and distant findings (Cohen's kappa 0.929). The results were adjudged to be concordant in all of the patients with regard to local status, bone metastases, and distant findings. Buchegger et al. [14] also reported that the lymph node results had been concordant in 19 patients and different with regard to 4 patients. With regard to per patient basis, the results were found to be concordant in 22 out of 23 patients (14 positive, 5 negative, and 3 equivocal). However, in one patient ACE PET/CT scan was positive for nodal metastasis and whilst FCH PET/CT scan was overall negative. Furthermore, interestingly the ACE-positive and FCH negative lymph nodes were found to be positive in a second FCH PET/CT scan which was undertaken a few months later. Buchegger et al. [14] concluded that on the whole, ACE and FCH PET/CT scans did exhibit excellent concordance, on both a per-lesion, and per-patient basis which would indicate that both tracers had performed equally for recurrent prostate cancer staging.

Castellucci et al. [15] undertook a study to assess the factors that could influence (11) C-choline PET/CT scan detection rate within a population of recurrent carcinoma of prostate gland patients who had been listed for salvage radiotherapy in an early phase of biochemical relapse, in order to select which of the patients could benefit most by the performance of re-staging (11) C-choline PET/CT scan prior to having salvage radiotherapy. Castellucci et al. [15] included in their study 605 patients who had undergone radical prostatectomy with curative intent for carcinoma of the prostate who had developed

rising serum PSA levels pursuant to their primary therapy and had been listed for salvage radiotherapy. The patients' serum prostate-specific-antigen (PSA) levels were greater than 0.2 ng/mL, and less than 2 ng/mL (mean, 1.1.05 ng/mL, median, 1.07 ng/mL, range 0.2 to 2.0 ng/mL, standard deviation, ± 0.59). All the patients had been classified as not having nodal disease (N0) after their radical prostatectomy. Seventeen of the 605 patients had adjuvant radiotherapy together with radical prostatectomy; on the other hand 148 of the patients had androgen deprivation therapy at the time of having their PET/CT scans. In order to assess which factor could influence PET/CT scan positivity, and the detection of local versus distant metastasis, the serum PSA levels, serum PSA kinetics, Gleason score, the ages of the patients, time to biochemical recurrence, androgen deprivation therapy, and the initial stage of the tumours, were analysed statistically. With regard to the results, Castellucci et al. [15] reported that (11) C-choline PET/CT was positive in 28.4% (positive in 172 out of the 605 patients). Eighty three out of the 605 patients had positivity within the pelvis (Group A), distant metastases were found in 72 out of the 605 patients (Group B), and local as well as distant sites of recurrence were found in 17 out of the 605 patients (Group C). The results of multivariate analyses did reveal that serum PSA level, and serum PSA doubling time (PSAdt), and on-going androgen deprivation therapy (ADT) had constituted significant predictors for obtaining positive scan results; however, the serum PSA level, serum PSA doubling time (PSAdt) had been significantly related to the detection of distant recurrence ($P < 0.05$). Receiver-operating-characteristics analysis revealed that a serum PSA level of 1.05 ng / mL, and a serum PSA doubling (PSAdt) time of 5.95 months were the optimal cut-off values with regard to the prediction of a positive (11) C-choline PET/CT scan, with an area under the curve (AUC) of 0.625 for serum PSA and 0.677 for serum PSA doubling time (PSAdt). Castellucci et al. [15] made the following conclusions:

- (11) C-choline PET/CT scan may be suggested prior to salvage radiotherapy during the early phase of biochemical recurrence in order to select those patients who could benefit from this aggressive therapy.
- Especially, patients that show fast serum PSA kinetics or serum PSA increasing levels despite receiving androgen deprivation therapy (ADT) should undergo (11) C-choline PET/CT scan studies prior to undergoing salvage radiotherapy, taking into consideration that they tend to be associated with higher probability for the detection of positive findings outside the pelvis.

Poulsen et al. [16] compared the diagnostic accuracy of the ensuing imaging techniques with regard to the detection of spine metastases, with the use of magnetic resonance imaging (MRI) scan as a reference: whole body scintigraphy (WBS) with technetium-99m-MDP; [18F]-Sodium fluoride, [18F]-sodium fluoride (NaF) positron emission tomography (PET) / computed tomography (CT) and [(18)F]-fluoromethylcholine (FCH) PET/CT. Poulsen et al. [16] stated that the entry criteria for their study included biopsy proven carcinoma of the prostate gland, a positive whole body scan (WBS) consistent with bone metastases, and no history of androgen deprivation therapy. Within 30 days of obtaining informed consent, the trial scans were undertaken in random fashion. The scans were interpreted blindly for the aim of a lesion-based analysis. The target variable for the study was bone lesion (malignant/benign). The gold standard was magnetic resonance imaging (MRI) scan findings. With regard to the results, Poulsen et al. [16] reported that they had enrolled 50 men with a mean age of 73 years, between May 2009 and March 2012. The median serum PSA level of the patients was 84 ng/mL, and the mean Gleason score of the tumours was 7.7. Forty six (46) of the patients had had all of the four scans, and 4 patients had missed one PET/CT scan. A total of 526 lesions were identified in the 50 patients and according to the MRI scan 353 of the lesions were benign and 163 of the lesions were not malignant. The sensitivity, specificity, positive and negative predictive values and accuracy of the study were recorded as: Whole body bone scan (WBS) – 51%, 82%, 86%, 43%, and 61% respectively; NAF-PET/CT scan – 93%, 54%, 82%, 78%, and 81% respectively; FCH PET/CT scan – 85%, 91%, 95%, 75%, and 87% respectively. Poulsen et al. [16] made the following conclusions:

- They had found that FCH PET/CT scan and NaF PET/CT scan were superior to WBS with regard to the detection of carcinoma of the prostate gland bone metastases within the spine.
- The results of their study would call into question the use of whole body scan (WBS) as the method of choice in patients with hormone-naïve carcinoma of the prostate gland.

Evangelista et al. [17] evaluated the efficiency of (18)F-Fluorocholine positron emission tomography /computed tomography (FCH PET/CT) in the detection of lymph node and bone involvement in comparison with conventional imaging such as abdominal-pelvic CT scan and bone scan in the initial staging of carcinoma of the prostate gland. Evangelista et al. [17] evaluated 48 patients who had undergone FCH PET/CT scanning for the initial staging of carcinoma of the prostate gland. At the same time 32 out of the 48 patients had had a bone scan and 26 out of the 48 patients had also had CT scan of abdomen and pelvis. The diagnostic performance of the FCH PET/CT including the sensitivity, specificity, accuracy, was evaluated based upon patient basis for the entire population and also separately based upon risk-classification, and later in comparison with conventional imaging. Histological findings of specimens or follow-up data had been used as the standard of reference. With regard to the results, Evangelista et al. [17] reported that the overall accuracy associated with FCH PET/CT scan for lymph node involvement was 83.3%. The sensitivity of FCH was found to be higher in the case of the higher-risk subset of patients which was 83.3% than in the intermediate-risk group which was 33.3%, on the other hand, FCH specificity was similar compared with dedicated CT scan, FCH PET / CT scan was associated with a higher sensitivity and similar specificity (46.2%, versus 69.2%, 92.3% versus 92.3%) respectively. Additionally, the sensitivity and specificity of PET/CT scan were found to be higher than the sensitivity and specificity of bone scan (100% versus 90%, and 86.4% versus 77.2% respectively). As opposed to conventional imaging, PET/CT scan did change the staging of the carcinoma of the prostate gland in 33.3% of patients. Evangelista et al. [17] made the following conclusions:

- The efficiency of FCH PET/CT in the detection of both bone and lymph node involvement in carcinoma of the prostate gland at the initial staging was found to be higher in comparison with that of conventional imaging
- Prospective clinical trials would be required to confirm their findings.

Suardi et el. [18] had stated that traditionally patients who have been treated for adenocarcinoma of the prostate gland by means of radical prostatectomy who subsequently develop lymph node recurrence had tended to be managed by androgen deprivation approach. Suardi et al. [18] also said that even though there are no documented prospective studies, salvage lymph node dissection has been proposed as an alternative treatment option for lymph node recurrence pursuant to radical prostatectomy undertaken for localized carcinoma of the prostate gland. Suardi et al. [18] examined the long-term outcomes of salvage lymph node dissection in patients who developed local lymph node recurrence diagnosed based upon 11C-choline positron emission tomography/computed tomography (PET/CT) scan. Suardi et al. [18] reported on 59 patients who had developed biochemical recurrence with 11C-choline with 11C-choline PET/CT scan showing pathologic activity who had undergone salvage lymph node dissection between 2002 and 2008. The patients did undergo pelvic and or retroperitoneal salvage pelvic lymph node dissection. With regard to outcome measurements and statistical analysis, Suardi et al. [18] defined biochemical response as serum prostate-specific antigen (PSA) level of < 0.2 at 40 days pursuant to the surgical operation of salvage lymph node dissection. Biochemical recurrence for those who achieved biochemical response was defined by Suardi et al. [18] as serum PSA level of > 0.2 ng/mL. Clinical recurrence was defined by Suardi et al. [18] as positive PET/CT scan pursuant to salvage lymph node dissection and in the presence of a rising serum PSA level. Kaplan-Meier curves were used to assess time to biochemical recurrence, clinical recurrence, and cancer-specific mortality. Cox regression had been fitted to assess the predictors of clinical recurrence. With regard to the results and limitations of the study, Suardi et al. [18] reported the following: The median follow-up of the patients was 81.1 months. On the whole, 35 patients (59.3%) did achieve biochemical response. The 8-year biochemical recurrence-free survival rate in patients who had achieved complete biochemical response was 23%. On the whole the 8-year clinical recurrence-free rate was 38% and the cancer-specific mortality-free rate was 81%. Suardi et al. [18] also reported that multivariable analyses were used to evaluate pre-operative variables and this showed that the serum PSA level at salvage lymph node dissection was the only predictor of clinical recurrence ($P = 0.03$). When post-operative parameters were taken into consideration, biochemical response and the presence of retroperitoneal lymph node metastases were found to be significantly associated with the risk of clinical recurrence ($P \leq 0.04$). Suardi et al. [18] were of the opinion that the limitation with regard to their study is the fact that there was no control group in the study

for comparison. Suardi et al. [18] made the following conclusions.

- Salvage lymph node dissection could represent a therapeutic option in the treatment of patients who develop biochemical recurrence and nodal pathologic uptake at 11C-cholnie PET/CT scan pursuant to radical prostatectomy.
- Even though majority of the patients subsequently developed biochemical recurrence after salvage lymph node dissection, about 40% of the patients had experienced clinical recurrence-free survival.

Rowe et al. [19] reported a 45-year-old man who had presented 2 years prior to the time of having PET/CT imaging with elevated serum PSA level of 39ng/mL and a suspected clinically localized carcinoma of the prostate gland. Histological examination of his trans-rectal ultrasound scan biopsy of his prostate gland showed features consistent with Gleason 5+4 = 9 adenocarcinoma of the prostate which had involved all biopsy cores. He had conventional imaging which did not reveal any evidence of metastasis. He underwent radical retro-pubic prostatectomy and during the operation there was evidence of extra-prostatic extension, seminal vesicle invasion, and positive bilateral pelvic lymph nodes. Pursuant to his prostatectomy his serum PSA level dropped to 10.5 ng/mL, and he later on received treatment by means of leuprolide and docetaxel which resulted in his serum PSA level dropping to 1.0 ng/mL. He was next enrolled in a series of clinical trials in which he received in succession, sipuleucel-T, anti-PDL1 therapy and enzalutamide with persistent elevation of his serum PSA up to 15.6 ng/mL, but the serum PSA level reduced to 1.0 ng/mL whilst he was receiving enzalutamide. At this point of his therapy he did have radiological imaging with whole body planar ^{99m} TC MDP bone scan, Na^{18}F PET/CT scan, and ^{18}F DCFPyL PET/CT scan. With regard to the results of the scans, Rowe et al. [19] reported that in all 89 lesions had been identified by at least one modality of scanning. Planar ^{99m} TC MDP bone scan did demonstrate 12 suspicious sites, Na^{18}F PET/CT scan did demonstrate 39 suspicious sites, and ^{18}F DCFPyL PET/CT scan did demonstrate 87 suspicious sites, of abnormal radiotracer uptake within the bones. Rowe et al. [19] stated that with the assumption of all the 89 suspicious lesions being positive would yield a sensitivity of 13.5% for bone scan, 43.8% for the Na^{18}F PET/CT scan, and 97.7% for the ^{18}F DCFPyL PET/CT scan. Lesions that had been occult for planar ^{99m} TC MDP bone scan, and Na^{18}F PET/CT scan but had been apparent by ^{18}F DCFPyL PET/CT scan did include lesions that were entirely within the marrow cavity of the affected bone as well as in subtle sites that had abnormal cortical based uptake. Rowe et al. [19] stated that traditionally, imaging of bone metastases in carcinoma of the prostate gland had involved planar ^{99m}TC-methylene diphosphate (^{99m} TC MDP) bone scan with or without the use of supplemental tomographic imaging. However, over recent times, Na18 F positron emission tomography / X-ray computed tomography (PET/CT) scan had been found to have led to an improvement in the sensitivity and specificity for sites of osseous metastatic involvement. Rowe et al. [19] further stated the following:

- Prostate-specific membrane antigen (PSMA) is a cell surface enzyme which is encountered highly in carcinoma of the prostate gland and it had been explored as a target for the imaging of carcinoma of the prostate gland.
- PSMA-targeted PET/CT scan could offer improved sensitivity by binding directly to tumour cells, as opposed to localizing to sites of bony reaction.
- Their preliminary anecdotal finding should be explored in larger studies.

Agarwal et al. [20] reported a 55-year-old man who had metastatic Gleason 5+4=9 adenocarcinoma of the prostate gland for which he was undergoing Docetaxel chemotherapy. He was noted to have rising serum PSA levels and his serum PSA was recorded as 340 ng/mL and for this reason he had an isotope bone scan which did show diffusely increased skeletal accumulation with increased bone to soft tissue (renal uptake) ratio which was suggestive of a metastatic super-scan. He additionally had gallium-68-prostate-specific membrane antigen 68 (^{68}GaPSMA) PET/CT scan in order to evaluate him for Lu-PSMA therapy. His maximum intensity projection image did show generalized increased tracer uptake in the entire axial as well as appendicular skeleton and reduced physiological uptake in bilateral lacrimal and salivary glands, spleen, small intestine, and kidneys. The sagittal and trans-axial positron emission tomography / computed tomography (PET/CT) scan fusion images did illustrate sclerotic changes in the whole axial skeleton with increased tracer uptake. Agarwal et al. [20] stated that all the aforementioned features were suggestive of metastatic super-scan on (^{68}GaPSMA) PET/CT scan. Based upon this case report it would

be argued that PET/CT scan has the capability of demonstrating super-scan from disseminated adenocarcinoma of the prostate gland.

Su et al. [21] reported a 54-year-old man who had undergone radical prostatectomy and hormonal therapy for adenocarcinoma of the prostate gland. At his 7-years follow-up his serum PSA was noted to be elevated and he had magnetic resonance imaging scan as well as isotope bone scan which did not reveal any metastasis. He underwent radiotherapy under the presumption that he had local recurrence to no avail. One more year later he had F-FDG PET/CT scan which did show 3 FDG-avid lesions in the right lung and mediastinum. He underwent video-assisted thoracoscopic surgery and pathological examination of the excised lesions confirmed lung and lymph node metastases of adenocarcinoma of the prostate gland and at that time he also had bone scan which remained negative. The finding from this report would indicate that at times magnetic resonance imaging scan and isotope bone scan may not detect cases of early metastases of carcinoma of the prostate gland but F-FDG PET/CT scan could identify such recurrences that magnetic resonance imaging scan and bone scan are not able to detect.

Tong et al. [22] stated that carcinoma of the prostate gland constitutes a major health problem, and that routine radiological imaging does show only modest results in the detection and in the re-staging of localized carcinoma of prostate recurrence. Tong et al. [22] also stated that reports from studies undertaken recently had indicated promise of radiolabelled analogues of choline for positron emission tomography (PET) scans in patients who have biochemical recurrence and that sequentially incremental Fluorocholine (FCH) uptake tends to be associated with malignancy and that on the other hand decreasing tracer activity would tend to indicate benign aetiology; nevertheless, the aforementioned pattern of tracer activity had not been fully validated and no standardized (18)F-Fluorocholine ((18)F-FCH) has so far been put in place, Tong et al. [22] undertook a study in order to better define the role of dual-phase (18)F-FCH PET/computed tomography (CT) imaging with the use of retrospective masked reading focussing on the detection of loco-regional recurrence/metastasis in patients who had biochemical recurrence of disease pursuant to definitive local primary treatment of the tumour. Tong et al. [22] enrolled a total of 32 subjects between April 2010 and May 2014 who had histologically proven carcinoma of the prostate gland and who did undergo primary treatment of curative intent and who subsequently developed biochemical recurrence of disease. The early scans and delayed images of the pelvis were graded separately by blinded readers. The final evaluation was undertaken by using a combination of information obtained from dual-phase studies as "summative scan". The maximum standardized uptake value was computed by using regions of interest that had been constructed over areas of focal hyperactivity. The calculations were undertaken by using Statistical Product and Service Solutions Version 20 for Windows. A composite reference which had consisted of histopathology, correlation with other imaging, or serum prostate-specific antigen (PSA) trend with clinical follow-up of at least 6 months was utilized to determine the true disease status of the patient. With regard to the results, Tong et al. [22] reported that early phase pelvis phase imaging sensitivity and specificity were computed to be 73.1% and 90.9% respectively and the late-phase pelvis imaging sensitivity and specificity were computed to be 80.8% and 100% respectively. The summation scan sensitivity and specificity were computed to be 76.9% and 100% respectively. The odds ratio of developing recurrent disease with an uptrend of SUV-max on dual-phase imaging was computed to be 33.3%. The optimal cut-off value of serum PSA was computed to be 1.85 ng/mL with 80% sensitivity and 62.5% specificity. Tong et al. [22] made the ensuing conclusions:

- Single-phase FCH PET/CT imaging is a reliable scanning modality which is capable of detecting sites of disease at low levels of serum PSA which still fulfill the criteria of biochemical recurrence.
- This would enable clinicians to identify sites which should be considered for potential biopsy or sites to be considered for loco-regional treatment.

Apolo et al. [23] undertook a prospective study which evaluated the capability of Na(18)F PET/CT scan to detect as well as monitor bone metastases over time including its correlation with clinical outcomes and survival in advanced carcinoma of the prostate gland. Apolo et al. [23] reported that sixty patients who had carcinoma of the prostate gland including 30 patients who had confirmed bone metastases and 30 patients who did not have any bone metastases based upon conventional imaging, who had undergone Na(18)F PET/CT scan at baseline, at 6-months and at 12-months follow-up. Positive lesions had been verified

on subsequent follow-up scans. Changes in SUVs and the number of lesion number(s) were correlated with the serum prostate-specific antigen (PSA) change, clinical impression and the overall survival. With regard to the results, Apolo et al. [23] reported that they did find significant associations which included the ensuing: SUV and prostate-specific antigen (PSA) percentage change at 6 months (P = 0.014) and 12 months (P = 0.005); SUV maximal percentage change from base-line and clinical impression at 6 months (P = 0.0147), and 6 to 12 months (P = 0.053); SUV change at 6 months and overall survival (P = 0.018); number of lesions on Na(18)F PET/CT scan and clinical impression at base-line (P < 0.0001), 6 months (P = 0.0078), and at 12 months (P = 0.0029); and number of lesions on Na(18)F PET/CT per patient at base-line and overall survival (P = 0.017). Apolo et al. [23] stated that with regard to paired-exploratory analysis, paired (99m) Tc-methylene diphosphonate bone scans ((99m)Tc-BS were available for 35 patients at base-line, 19 patients at 6 months, and 14 patients at 12 months (68 scans). Malignant lesions on Na(18)F PET/CT scans (total number 57) were classified on (99m) Tc-BS as malignant 65% of the time, indeterminate 25% of time, and negative 10% of the time. Furthermore, 69% of paired scans did show more lesions on Na(18)F PET/CT scans in comparison with on (99m) Tc-BS. Apolo et al. [23] made the ensuing conclusions:

- The base-line number of malignant lesions and changes in SUV on follow-up Na (18) F PET/CT scans did significantly correlate with clinical impression and overall survival.

- Na (18) F PET/CT scans, tend to detect more bone metastases earlier in comparison with (99m) Tc-BS and tends to enhance the detection of new bone disease in high-risk patients.

Lavalaye et al. [24] reported a 75-year-old man who was diagnosed as having Gleason 9 adenocarcinoma of the prostate gland. His serum prostate-specific antigen (PSA) was noted to be 5.04 ng / m L. He had a routine isotope bone scan which was negative in that it did not show any evidence of bone metastasis. (a) In view of the high histological grading of his tumour and the relatively high level of his serum PSA, (68)Ga-PSMA PET/CT scan was requested in order to confirm or exclude distant metastasis. The (68)Ga-PSMA PET/CT scan did show several skeletal lesions which had high tracer accumulation as a sign of diffuse bone metastases. (b) On low-dose CT scan there was no evidence of sclerosis. (c) The (68)Ga-PMSA PET/CT scan also did show high uptake in the prostate gland, and in the para-aortic lymph nodes, as well as in the para-iliac lymph nodes, without any evidence of any lymph node enlargement. Lavalaye et al. [24] stated that unfortunately biopsy of the bone was not undertaken in order to confirm histologically presence of metastases from carcinoma of the prostate gland. In view of the PET/CT scan findings the patients treatment plan was changed to systemic therapy rather than the local therapy which was originally planned. It would be argued from the findings of this case report that in some cases of bone metastasis in the early stage of bone metastasis from carcinoma of the prostate gland (68)Ga-PSMA PET/CT scan could show evidence of bone metastasis which isotope bone scan may not be able to pick despite the fact that bone biopsy was not undertaken to prove for certainty that the metastases were from adenocarcinoma of the prostate gland.

Graziani et al. [25] evaluated the use of (11)C-choline PET/CT scan as a diagnostic tool for the re-staging of carcinoma of the prostate gland in a large homogeneous and clinically relevant population of patients who had biochemical recurrence of carcinoma of the prostate gland pursuant to undergoing primary treatment for carcinoma of the prostate gland. Graziani et al. [25] also assessed the best timing for the performance of (11) C-choline PET/CT scan during the period of biochemical recurrence. Graziani et al. [25] retrospectively analysed 9,632 (11)C-choline PET/CT scans which had been performed in their institution for the re-staging carcinoma of the prostate gland from January 2007 to June 2015. The inclusion criteria for the study were: (1) Proven case of carcinoma of the prostate gland which had been treated by means of radical prostatectomy or by means of external beam radiotherapy; (2) Serum prostate-specific antigen (PSA) level results of the patient must be available; (3) There must be evidence of proven biochemical recurrence (BCR) (PSA > 0.2 ng/mL pursuant to radical prostatectomy or serum PSA > 2.0 ng/mL above the nadir pursuant to primary external beam radiotherapy with rising serum PSA levels). In the end 3,203 patients who had recurrent carcinoma of the prostate gland that matched the study inclusion criteria had been retrospectively enrolled into the study and all together 4,426 scans were analysed. With regard to the results, Graziani et al. [25] reported that on the whole 52.8% of the (11) Choline

PET/CT scan (2,337/4,426) and 54.8% of the patients (1,755/3203) were positive. With regard to 29.4% of the scans, at least one distant metastasis was identified. The median and mean serum PSA levels were respectively recorded as 4.9 ng/mL and 2.1 ng/mL at the time of the PET/CT scan and the serum PSA levels had ranged between 0.2 ng/mL and 50.0 ng/mL. Graziani et al. [25] also reported that in their study, 995 PET/CT scans had been performed in patients whose serum PSA levels had ranged between 1 ng/mL and 2 ng/mL. Graziani et al. [25] further reported the following:

- In their subpopulation of patients studied, the positivity rate of the 995 PET/CT scans was 44.7%, with a documented incidence of distant findings in 19% of patients, as well as an incidence of oligometastatic disease (one to three lesions) in 37.7% of cases.
- The absolute value of the serum PSA at the time of the PET/CT scan and the on-going androgen deprivation therapy had been associated with an increased probability of a positive (11) Choline PET/CT scan result ($p < 0.001$).
- The ROC analysis did reveal that a serum PSA value of 1.16 ng/mL had been the optimal cut-off value.
- With regard to patients who had serum PSA value less than 1.16 ng/mL, 26.8% of 1,426 (11) choline PET/CT had been positive with oligometastatic disease in 84.7% of the positive scans.

Graziani et al. [25] made the ensuing conclusions:

- The results of their study of a large cohort of patients had confirmed the feasibility of (11) Choline PET/CT scan for the detection of sites of metastatic disease in patients with carcinoma of the prostate gland who have developed biochemical recurrence
- The serum PSA level had been identified as the main predictor of a positive (11) choline PET/CT positive scan with 1.16 ng/mL as the optimal cut-off value.
- In the majority of positive (11) Choline PET/CT scans oligometastatic disease which is potentially treatable by salvage therapies had been observed.

Paone et al. [26] reported the incidental detection of Hurtle cell adenoma by using 18—choline PET/CT scan in a patient with prostate cancer which although anecdotal would indicate that 18-cholne PET/CT scan has the capability of detecting malignant lesions as well as non-malignant lesions at times hence histological examination would be required to confirm a definite diagnosis of lesions that are picked up by this form of PET/CT scan; however, with regard to adenocarcinoma of prostate gland which had been originally treated by means of radical radiotherapy, if there is an associated benign lesion in the prostate, a CT scan undertaken in the planning of the radiotherapy of the prostate with an associated benign lesion of the prostate, would have picked up the benign lesion earlier, therefore in the follow-up PET/CT scanning in the case of biochemical failure the problem of finding a de novo benign lesion would be avoided. The article published by Paone et al. [26] was published in Spanish and the details are not available to the author.

Oprea-Lager et al. [27] reported 12 patients (mean age ± SD; 64 years ± 8 years) who had metastasized carcinoma of the prostate gland who had undergone two sets of (18)F-fluoromethylcholine PET/CT scans, on consecutive days. Each seat of the PET/CT scan did consist of a thirty minutes dynamic PET/CT scan of the thorax pursuant to intravenous administration of 200 MBq of (18)F-fluoromethylcholine, which was ensued by a whole body PET/CT scan at 40 minutes. The dynamic scan was utilized to derive the area under the blood activity concentration curve. The lesion uptake was derived from the whole body PET/CT scan by using a variety of types of volumes of interest: maximum, peak, and mean. Each of the aforementioned parameters was normalized to injected activity per body weight, area under the blood activity concentration curve, and blood concentration itself at 40 minutes, which did result in a number of types of SUVs including: SUV, SUVAUC, and SUVTBR. The test-retest repeatability of the aforementioned metrics and the metabolic tumour volume (MTV), as well as total uptake of choline within the lesion, had been studied. The level of agreement between the test-retest data and reliability was evaluated by using Bland-Altman plots, repeatability coefficients, and intra-class correlation coefficients (ICCs). With regard to the results, Oprea-Lager et al. [27] reported that they had identified a total of 67 choline-avid metastatic lesions which included 44 bone lesions, and 23 lymph node lesions. With regard to the SUVmax, the repeatability coefficient for SUV, SUVAUC, and SUVTBR were recorded as 26% (ICC, 0.95), 31% (ICC 0.95), and 46% (ICC 0.89), respectively. Oprea-Lager et al. [27] also reported that they had obtained similar values for SUVpeak, and SUVmean and furthermore, the repeatability of SUVAUC had been comparable to that of SUVmax,

SUVpeak, as well as SUVmean. Oprea-Lager et al. [27] additionally found that the tissue type and localization of the tumour did not in any way affect the repeatability. Oprea-Lager et al. [27] made the ensuing additional findings: An MTV of less than 4.2 cubic centimetres did have larger variability in comparison with larger volumes (with repeatability coefficient of 45%, versus 29%; P=0.048). The repeatability coefficient was found not to be significantly different between lesions that had SUVpeak above or below the median value of 8.3 (19% versus 28%; P = 0.264). Oprea-Lager et al. [27] made the following conclusions: The repeatability of SUVAUC had been comparable with that of standard SUV. The repeatability of a variety of semi-quantitative (18)F-fluoro-methyl-choline parameters (SUV, MTV, and total uptake within the lesion) had been about 35%. Larger differences could likely be related to treatment effects. The findings of Oprea-Lager et al. [27] would indicate the repeatability of quantitative 18F-Fluromethylcholine PET/CT scan studies in carcinoma of the prostate gland as well as its potential of being used to localize or detect metastatic carcinoma of prostate in the nodes as well as distant sites.

Conclusions

Recent reports related to the use of Positron Emission Tomography (PET)/computed tomography CT scan in the investigation of patients who had developed biochemical (PSA) recurrence pursuant to treatment of carcinoma of the prostate gland with curative intent (radical prostatectomy or radical external beam radiotherapy or brachytherapy) have highlighted the effectiveness and capability of various types of modern PET/CT scans in detecting localized lesions as well as distant recurrent lesions that are responsible for the biochemical recurrence. Even though anecdotal there is recent evidence that PET/CT scan can detect recurrent lesions in the bones as well as in soft tissues recurrent lesions when conventional isotope bone scan and computed tomography scans have failed to demonstrate the lesions in some cases of biochemical failure. Early use of PET/CT scan when the serum PSA is marginally raised would most likely lead to the detection of recurrent lesions of small sizes that would be amenable to salvage lymph adenectomy or salvage radiotherapy treatment which would hopefully constitute a second-line treatment of curative intent whilst leaving hormonal treatment, chemotherapy and other ancillary treatments for 3rd line use in the event of another subsequent biochemical recurrence; however, there is the chance that some patients who undergo second-line treatment with curative intent may not develop biochemical recurrence again. Clinicians and Oncologists should be encouraged to undertake early PET/CT scans on their patients to detect small lesions.

Conflict of Interest: None

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