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PET in the management of urologic malignancies

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The ability of PET to study various biologic processes has opened up new possibilities in both fundamental research and the day-to-day practice of medicine. At present, 2-deoxy-2-[^{18}F]-fluoro-D-glucose ([^{18}F]-FDG) is most commonly used for PET imaging throughout the world. ([^{18}F]-FDG is a radiolabeled analogue of glucose and as such it is able to detect altered glucose metabolism in both physiologic and pathologic states. Frequently, there is a significant increase in glucose metabolism in cancer cells compared with that in the surrounding tissues. The role of FDG-PET in the initial staging, monitoring response to the therapy, and management of many types of cancer has been well documented [1]. There are relatively few FDG-PET reports describing its role in assessing primary urologic tumors at their sites of origin due to the potential problem of tracer excretion through the kidneys. The usefulness of FDG-PET has been documented in the detection of distant metastasis from these malignancies [2,3]. In recent years, however, with the introduction of other PET radiotracers, such as C11-choline and C11-acetate, the role of this technique in patients with urologic cancer and especially in those with prostate cancer has been enhanced [4]. This article focuses on the role of PET imaging in prostate, renal, bladder, and testicular cancer.

Prostate cancer

Carcinoma of the prostate is the second most common cause of death from cancer among men in America. The incidence of disease is likely to increase with improved detection and public awareness. Optimal treatment of this cancer depends on the accurate staging of the disease at the time of presentation. Localized primary or recurrent prostate cancer can be treated with radical prostatectomy [5]. Chemotherapy, immunotherapy, or hormonal therapies are the most frequent choices of treatment of metastatic tumors with variable success. Prostate-specific antigen (PSA) has been shown to detect prostate cancer earlier than rectal examination alone, but it has low specificity [6]. Conventional imaging techniques like CT, transrectal ultrasonography, and MR imaging show excellent anatomic details and sensitivity in detecting cancer in the prostate, but have certain limitations in distinguishing benign from malignant tissues and in identifying metastatic disease in small lymph nodes. In addition, CT cannot differentiate postsurgical or radiotherapy-induced changes from recurrence. PET as a functional imaging modality is being evaluated for improving sensitivity and specificity of other diagnostic procedures for better management of this disease. Because FDG-PET has shown low sensitivity in patients with prostate cancer, other positron labeled tracers, such as methionine, choline, and more recently, acetate, have been investigated in a limited number of patients to determine their efficacy in this population. This article discusses the potential role of PET techniques in the diagnosis, distribution of metastases or re-

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currence, and assessing treatment response in prostate cancer.

Diagnosis and initial staging

Fluorodeoxyglucose-PET

Many investigators have studied the use of FDG-PET in localized prostate cancer and reported conflicting results. Effert et al [7] studied 48 patients with untreated prostate cancer and 16 patients with benign prostatic hyperplasia with FDG-PET. Low FDG uptake was noted in 81% of these tumors and there was no correlation between FDG uptake and the tumor grade or stage of the disease. The authors also noted a significant overlap in uptake values between benign prostatic hyperplasia and prostate cancer. Hofer et al [3] reported a similar experience with FDG-PET. Lui et al [8] performed FDG-PET scans on 24 patients with clinically confined prostate cancer and reported false-negative results in 23 cases. Oyama et al [9] also found a lower sensitivity of 64% in 44 patients with FDG-PET. In contrast to previous reports, however, they found a good correlation between FDG uptake and the Gleason grade of the tumor. In a recent study, Sung et al [10] reported the detection of 60% (8 of 13) in locally advanced untreated or hormone-resistant prostate cancers.

C11-acetate PET

FDG-PET for the diagnosis of primary prostate cancer is somewhat ineffective, primarily because most prostate cancers have low glycolytic rates and show low FDG uptake. In addition, there is considerable overlap between cancer and benign conditions

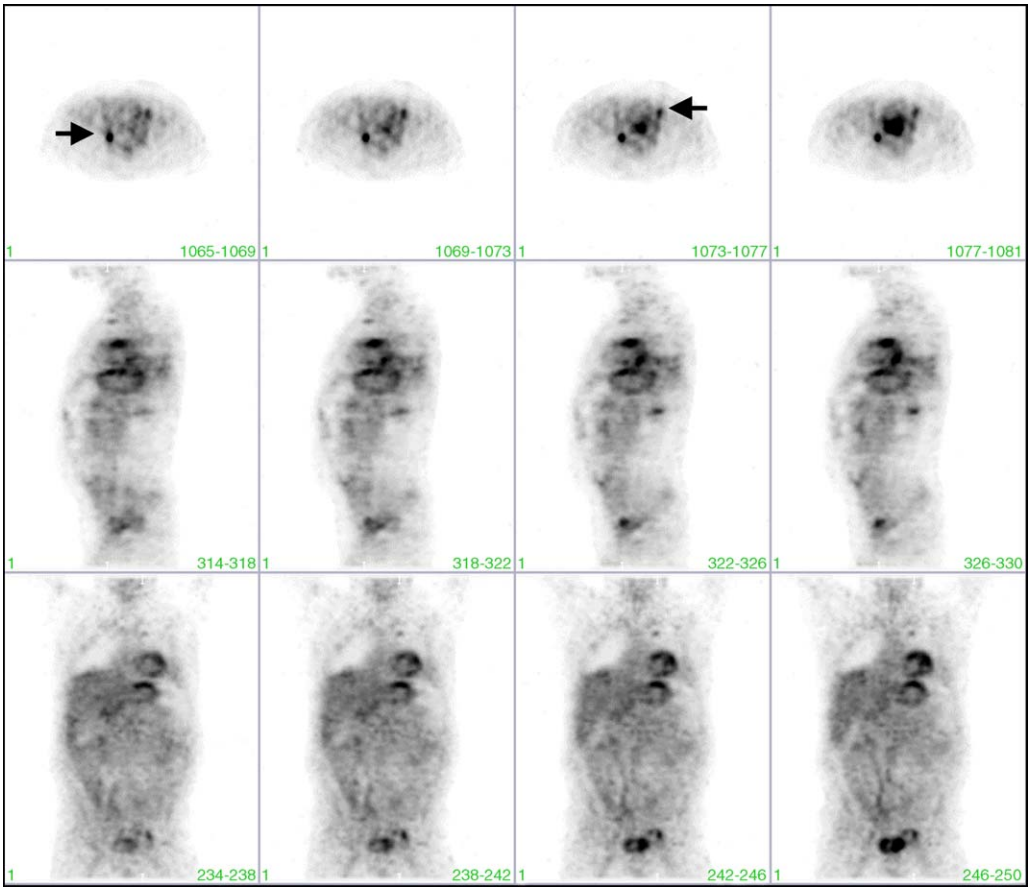

Fig. 1. Transverse, sagittal, and coronal views of FDG-PET study show two focal areas of intense FDG uptake in the pelvis (*arrows*), suggestive of lymph node metastases.

of prostate. C11-acetate has been proposed for imaging of prostate cancer. C11-acetate is incorporated into the lipid pool in cancer tissue with low oxidative and high lipid metabolism. Shreve et al [11] used C11-acetate for the first time in 18 patients with renal diseases and found differences in the clearance of tracer for malignant and nonmalignant renal tissues. Oyama et al [12] investigated C11-acetate in 22 patients with prostate cancer. Eighteen of 22 patients also had FDG-PET scans. The authors reported C11-acetate uptake in all primary tumors with standardized uptake values ranging from 3.27 to 9.87, whereas FDG-PET was positive only in 15 of 18 tumors with standardized uptake values ranging from 1.97 to 6.34. C11-acetate also showed more pelvic lymph node metastasis as compared with FDG-PET (five versus two). Kato et al [13] studied 30 normal subjects using C-11 acetate, 9 patients with benign prostatic hyperplasia, and 6 patients with prostate cancer. There was an overlap of standardized uptake values for patients with benign prostatic hyperplasia and those with cancer. The authors also noted that standardized uptake values in normal subjects less than 50 years of age were significantly higher than the subjects more than 50 years of age. The results of two studies were not consistent because of different acquisition protocols (dynamic versus static).

Metastatic disease

Fluorodeoxyglucose-PET

FDG-PET has shown some promise in the preoperative assessment of lymph nodes and distant metastases. FDG uptake was noted in pelvic lymph nodes in patients with PET-negative primary [7,9]. The possible explanation for this discrepancy is an increased proliferative activity in metastatic sites. Heicappell et al [14] studied 17 patients with FDG-PET preoperatively and compared the scan findings with those of postoperative histopathologic result. PET detected lymph node metastases in four of six patients (Fig. 1). The two false-negative results were attributed to the size of the lesions. There were no false-positive results in this study. Seltzer et al [2] found a similar detection rate of 50% with FDG-PET and CT. Other studies with small numbers of patients demonstrated lower sensitivities and specificities with FDG-PET for nodal metastases [15]. Chang et al [16] evaluated 24 patients with rising serum PSA levels for lymph node detection (Fig. 2). The authors reported a sensitivity, specificity, accuracy, positive

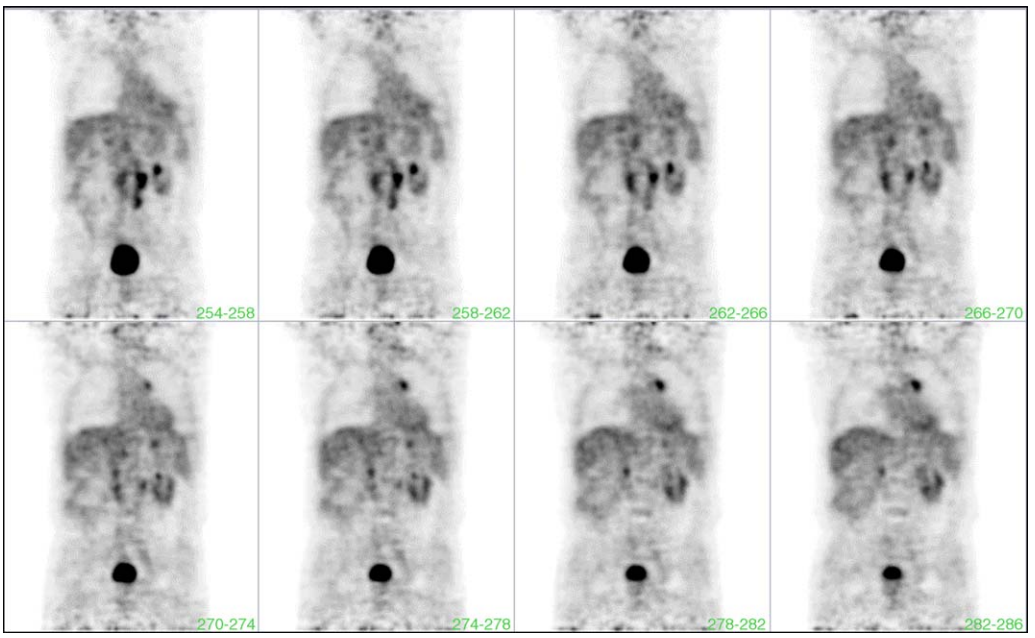

Fig. 2. Coronal views of FDG-PET study show intense FDG uptake in the abdomen suggestive of metastatic lymphadenopathy from prostate cancer.

predictive value (PPV), and negative predictive value (NPV) of 75%, 100%, 83%, 100%, and 68%, respectively. In a recent study, Fricke et al [17] showed FDG uptakes in 3 of 10 nodes.

FDG-PET has better sensitivity for the detection of bone marrow metastases than local disease [7,11], but FDG-PET showed large variability when compared with bone scintigraphy [18,19]. Shreve et al [11] reported a sensitivity of 65% and PPV of 98% in 202 bone metastases. Yeh et al [19] demonstrated that only 18% of bone marrow lesions on the bone scan showed FDG uptake. Kao et al [18] reported high specificity of FDG-PET in detecting bone marrow metastases. FDG-PET was positive in 11 patients with bone marrow metastases and negative in all 20 patients with positron scan because of benign pathology (Fig. 3). Nunez et al [20] demonstrated better detection of cervical spine metastases by FDG-PET than by bone scan. Morris et al [21] evaluated 154 lesions in 17 patients; 134 bone lesions were evident on PET or bone scan. Both FDG-PET and bone scan were positive in 71% lesions, 23% were seen only on bone scan, and 6% were seen only on PET scan.

C11-acetate PET

C11-acetate has been reported to be more sensitive than FDG-PET in the detection of regional lymph node metastases. Oyama et al [12] demonstrated detection of lymph node metastases using C11-acetate in five patients as compared with two patients with FDG-PET. Kotzerke et al [22] compared C11-acetate and C11-choline in 12 patients for detection of metastases of prostate cancer. The author concluded that both tracers have similar sensitivity for detection of metastases. In a study by Oyama et al [12] six of seven bone metastases showed C11-acetate accumulation, whereas FDG-PET was positive in only four patients. Fricke et al [17] showed that FDG-PET was superior to C11-acetate for the detection of bone metastases.

Recurrent disease

Fluorodeoxyglucose-PET

FDG-PET can differentiate fibrosis from recurrent tumors after treatment in patients with lymphoma, testicular tumors, and many other cancers. Results of studies in prostate cancer, however, are variable. In a study by Hofer et al [3], FDG-PET was unable to distinguish postoperative fibrosis from local recurrence after radical prostatectomy. Sanz et al [15] studied 10 patients with rising PSA level and accurately detected recurrent disease in two patients. Salminen et al [23] demonstrated accuracy of 72% with FDG-PET for staging and restaging of prostate cancer.

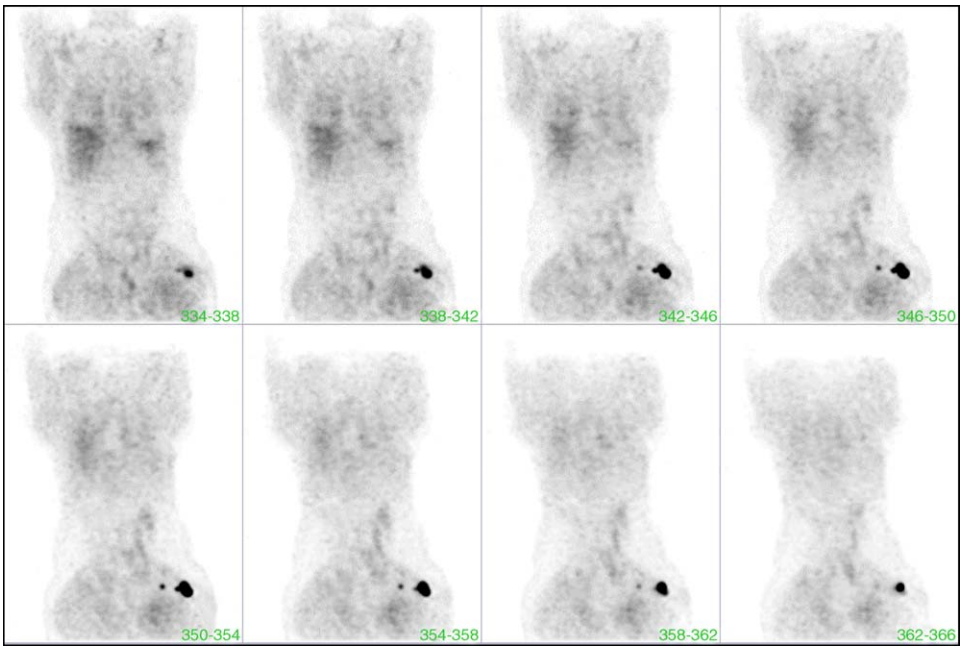

Fig. 3. Coronal views of FDG-PET study show two focal areas of intense FDG uptake in the right iliac bone suggestive of bone metastases.

C11-acetate PET

Kotzerke et al [24] demonstrated a high sensitivity and specificity in 31 patients with suspected local recurrence. The studies were compared with biopsy results. C11-acetatate PET was true-positive in 15 of 18 patients and true-negative in all 13 patients. Fricke et al [17] evaluated efficacy of C11-acetate PET and FDG-PET during follow-up with suspected relapse in 20 patients. C11-acetate accumulated in 70% (14 of 20) of patients, whereas FDG uptake was seen in 43% (6 of 14) of patients. Recently, Oyama et al [4] studied the effectiveness of C11-acetate PET in 36 patients with rising PSA after radical prostatectomy or radiation therapy. C11-acetate PET was positive in 27 (59%) of 46 patients, whereas FDG-PET had only 8 (17%) positive results.

Monitoring treatment response

FDG-PET has a well-established role in the evaluation of treatment response, especially in patients with lymphoma. Because the sensitivity of FDG-PET is low for the primary, metastatic, and local recurrent lesions in prostate cancer, however, few studies have been performed to determine its role in this regard. Oyama et al [25] investigated the effect of androgen ablation. Eight of 10 patients had FDG uptake at the primary and metastatic sites. The authors reported a decrease in FDG uptake in all positive lesions after initiating the hormonal treatment. Morris et al [21] compared changes in mean standardized uptake values with PSA levels in response to treatment. Parallel changes in standardized uptake values and PSA were noted in 9 (75%) of 12 patients. Recently, Kurdziel et al [26] reported a decrease in standardized uptake values during antiangiogenic therapy and correlated well with the changes in PSA ($r = 0.94$, $P < .01$) in patients with androgen-independent prostate cancer.

Other PET tracers

C11-choline

Hara et al [27] introduced C11-choline PET for imaging prostate cancer. The choline is taken up by tumor cells and is retained because of phosphorylation by the enzyme choline kinase. In contrast to FDG there is little urinary excretion of this radiotracer. Kotzerke et al [28] and de Jong et al [29] showed uptake in primary cancer and lymph nodes and bone marrow metastases. Recently, de Jong et al [30] demonstrated a sensitivity, specificity, and accuracy of 80%, 96%, and 93%, respectively, for staging lymph node disease. Kotzerke et al [22], by comparing C11-choline with C11-acetate, noted that both tracers had identical sensitivities in detecting primary prostate cancer and its metastases. C11-choline PET showed superior results when compared with FDG-PET for restaging in 100 patients with prostate cancer [31]. C11-choline PET has also been used to evaluate the treatment response. The site of recurrence was detected correctly in 78% of the patients after radiation therapy and in 38% of the patients after radical prostatectomy [32].

C11-methionine

C11-methionine has been used to image a variety of tumors. The uptake of C11-methionine is attributed to increased amino acid transport and metabolism. Nilsson et al [33] reported C11-methionine uptake in most lesions in patients with androgen-resistant prostate cancer. Macapinlac et al [34] and Nunez et al [20] compared C11-methionine-PET with FDG-PET and reported that C11-methonine PET is superior to FDG-PET in detecting primary and metastatic lesions of prostate cancer.

Testicular cancer

Testicular cancer is the most common tumor of young men and its incidence is increasing [35]. Seminoma and nonseminoma germ cell tumors (NSGCTs) have different biologic behaviors. Most patients with minimal metastatic disease can be cured with chemotherapy. NSGCTs with stage I disease does not require chemotherapy and can be followed-up clinically for progression.

Initial staging

Accurate early staging in the early phases of disease is very important to classify patients into low- and high-risk groups because management differs between the two. In stage II and III, the prognosis depends on the extent of the disease and tumor marker. At present, initial staging is based on clinical examination, tumor marker measurement, and CT scan. Of the patients classified as having stage I, 20% to 30% were found to have involvement of the retroperitoneal nodes. Based on conventional techniques, up to 50% of patients are understaged and about 25% are overstaged [36]. CT is most commonly performed for staging purposes, but it has a false-negative rate up to 59% and a false-positive rate up to 40% [37,38].

FDG-PET has been investigated for the staging of testicular tumors. Albers et al [39] studied 37 patients

with stage I and II testicular tumors using FDG-PET and CT. PET was found to have sensitivity of 70% and specificity of 100%, whereas similar values for CT were 40% and 78%, respectively. Three false-negative results were found in two small (<0.5 cm) metastatic nodes and one mature teratoma. Cremerius et al [40] investigated FDG-PET for staging in 50 patients and demonstrated sensitivity, specificity, PPV, and NPV of 87%, 94%, 94%, and 94%, respectively. The authors also compared PET findings with the levels of tumor marker and found a high specificity and PPV of 100%; however, sensitivity and NPV were 67% and 88%, respectively. Both CT and PET missed small retroperitoneal nodes. Hain et al [41] reported a specificity of 100%, PPV of 100%, sensitivity of 83%, and NPV of 90% for initial staging in seminoma and NSGST. PET identified unsuspected visceral and bone metastases in all patients, but overall changes in stage was noted in a small number of cases. Spermon et al [42] studied 12 patients with stage I and II NSGCTs and reported that FDG-PET staging results were equivalent to those of the CT. Recently, Lassen et al [43] studied 46 patients who had normal CT and normal tumor marker levels. The sensitivity, specificity, and accuracy of PET were 70%, 100%, and 93%, respectively, whereas the NPV of conventional staging procedures was 78%.

Many studies have confirmed the superiority of FDG-PET over CT. The limitation of FDG-PET is its inability to detect disease in very small nodes because of its limits on spatial resolution. It is difficult, however, to detect microscopic disease by any gross imaging modality.

Recurrent and residual disease

Most of the patients with metastatic disease have residual masses after treatment. Often these masses contain a mixture of necrotic and fibrotic tissues and may not need further treatment. Some patients may have residual tumor in these masses, however, which requires immediate aggressive treatment. It is very important to know if the residual masses contain viable tumor or fibrosis or necrosis. CT and other conventional imaging modalities are unable to differentiate between the two possibilities.

FDG-PET has been used to determine viable tumor in residual masses after treatment. Stephens et al [44] studied 30 patients with NSGCT with postchemotherapy residual masses and reported that PET was able to differentiate viable tumor from fibrosis. Sugawara et al [45] confirmed these results. In contrast to the study by Stephens et al, the authors were also able to differentiate mature teratoma differentiated from fibrosis or necrosis by using kinetic rate constants. In a large series of 70 patients, Hain et al [46] demonstrated a sensitivity of 88%, specificity of 95%, PPV of 96%, and NPV of 90% for differentiating tumor from fibrosis or necrosis or mature teratoma differentiated. Sanchez et al [47] reported 25 FDG-PET studies in 15 patients diagnosed with NSGCT. The authors concluded that FDG-PET detects relapse earlier than CT. Spermon et al [42] studied 28 patients with NSGCT after completion of chemotherapy and histology results were obtained in 20 patients. FDG-PET was true-negative in all 11 patients without teratoma component in their primary tumors. FDG-PET was false-positive, however, in 4 of 12 patients with mature teratoma having some inflammation components.

In patients with seminoma, the differentiation of fibrosis and necrosis from viable tumor is even more important, because the treatment of patients with residual disease is difficult. Cremerius et al [48] reviewed 42 FDG-PET scans in patients with seminoma after treatment and reported an accuracy of 90% in determining the presence of active disease. Other investigators confirmed these findings of high accuracy of FDG-PET [46,49]. De Santis et al [49] investigated 23 patients with seminoma and residual masses of less than 1 cm in size and reported a sensitivity, specificity, PPV, and NPV of 89%, 100%, 100%, and 97%, respectively. Ganjoo et al [50] studied 29 patients of seminoma and reported true-negative PET results in 19 patients after initial chemotherapy. In 10 patients after salvage chemotherapy, however, five patients were true-negative and five were false-negative. False-negative results occurred in patients with tumors that were small in size and harbored malignant cells during the relapse [46,50].

Tumor markers are important in the follow-up of patients with testicular tumor and elevated tumor markers, which may be the first indicator of relapse [51]. Tumor markers, however, are less sensitive and are less specific for recurrent disease. Cremerius et al [48] demonstrated an improvement in sensitivity and NPV if the results of FDG-PET were added to the information, but adding marker values to PET added no further information. Hain et al [46] found the residual disease in all patients (12 of 12) who had elevated marker levels and no residual masses. PET was positive in all patients except one (15 of 16) who had raised marker and residual masses (Fig. 4). Elevated marker levels and negative scan findings can be caused by microscopic disease, and in such patients follow-up examination with PET is warranted.

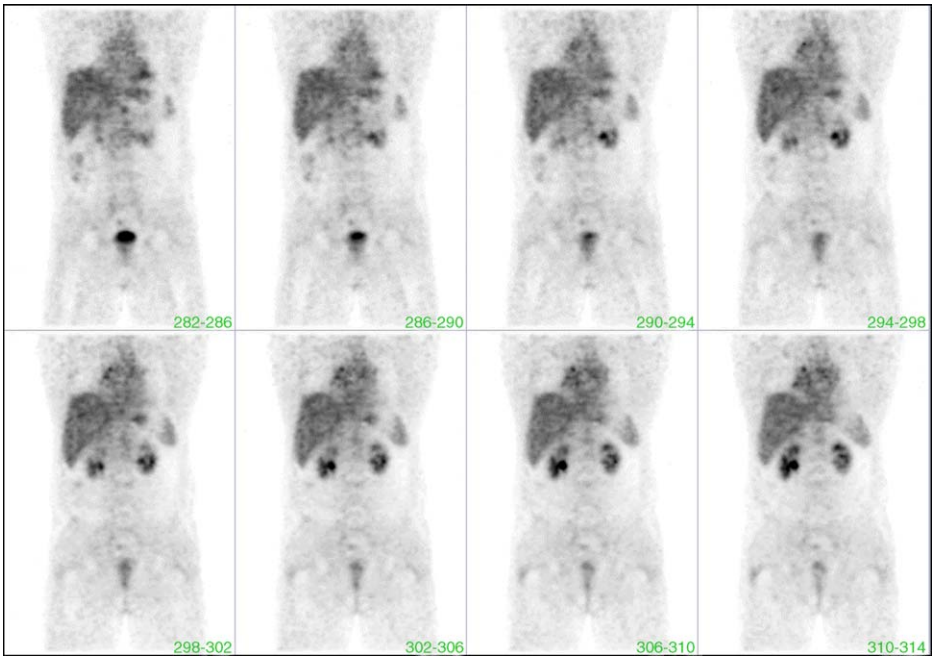

Fig. 4. Patient with a diagnosis of germ cell tumor presented with rising CA125. Coronal views of FDG-PET study show two focal areas of increased FDG uptake in the mediastinum suggestive of lymph node metastases.

Response to treatment

FDG-PET has been shown to predict responses to chemotherapy in several tumors. Bokemeyer et al [52] evaluated treatment response to high-dose salvage chemotherapy in patients with relapsed germ cell cancer using FDG-PET. PET accurately predicted the outcome of high-dose chemotherapy in 91% as compared with CT and tumor marker in 59% and 48% of these lesions, respectively (Fig. 5).

Renal cancer

Diagnosis and staging

Despite significant uptake and excretion through the kidneys, FDG has been used in the diagnosis and management of renal cell carcinoma (RCC). Bachor et al [53] studied 29 patients with solid renal masses and found that PET was positive in 20 (77%) of 26 patients of RCC. PET was false-negative in the remaining six patients; and it was false-positive in an angiomyolipoma, a pericytoma, and a pheochromocytoma. Ramdave et al [54] evaluated the accuracy of FDG-PET for staging and management of 17 patients with known or suspected RCC. PET identified the tumor in 16 of 17 patients with primary tumor (Fig. 6). PET and CT had an accuracy of 94%. In addition, PET detected pulmonary metastases in two patients. FDG-PET altered the management in 35% of patients. Miyakita et al [55] compared biologic characteristics of RCC with FDG and concluded that PET-positive tumors had higher tumor grade and increased GLUT-1. PET has been reported to evaluate renal masses and distinguish tumors from cysts [56]. Goldberg et al [56] reported that a positive lesion on FDG-PET can obviate the need for biopsy.

The detection of lymph node metastases has important implications in the management of RCC. Ramdave et al [54] found two patients with regional lymph node involvement using FDG-PET, whereas CT was negative in both patients.

Recurrent and distant disease

Ramdave et al [54] evaluated eight patients with local recurrence or metastatic disease. PET was found to have an accuracy of 100% in detecting local recurrence and metastases as compared with 88%

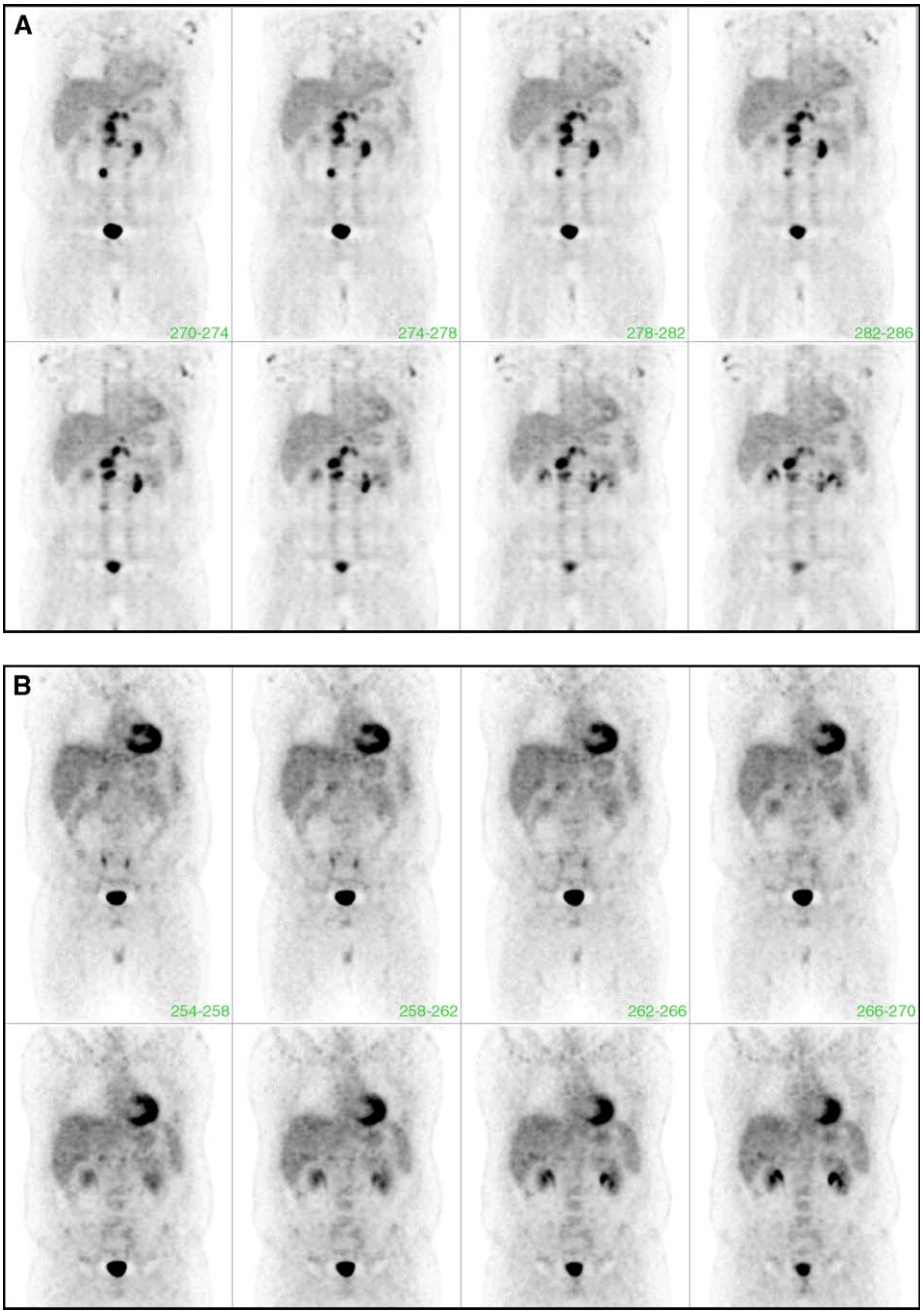

Fig. 5. (*A*) Serial FDG-PET scans showing treatment response during and after the completion of chemotherapy. Coronal views of FDG-PET study show multiple focal areas of intense FDG uptake in the abdominal lymph nodes suggestive of metastatic involvement. (*B*) Follow-up FDG-PET study obtained 6 weeks after completion of chemotherapy shows no FDG uptake suggestive of good response to chemotherapy.

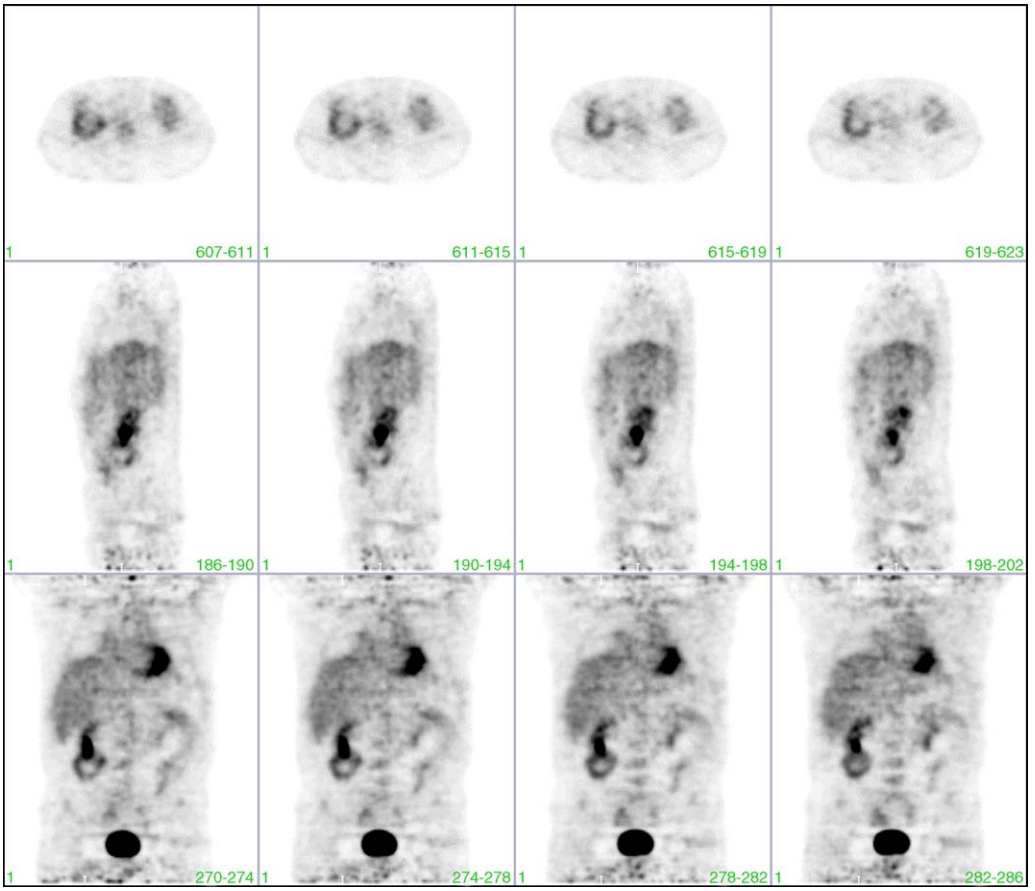

Fig. 6. Coronal views of FDG-PET study show a rim lesion at the lower pole of right kidney suggestive of primary renal cell carcinoma with central necrosis.

with CT. Safaei et al [57] demonstrated usefulness of FDG-PET for restaging in 36 patients with advanced RCC. FDG-PET classified clinical staging correctly in 32 of 36 patients (sensitivity 87%, specificity 75%). The authors also evaluated the accuracy of PET for 25 lesions, which had undergone biopsies for definitive diagnosis. PET correctly classified 21 of 25 (84%) biopsied lesions (sensitivity 88%, specificity 75%). Wu et al [58] compared FDG-PET and bone scans for the detection of bone metastases in 52 bone lesions. The authors reported a high sensitivity and accuracy of 100% for FDG-PET as compared with 77.5% and 60%, respectively, for bone scans. Recently, Majhail et al [59] evaluated FDG-PET in the detection of distant metastases in 24 patients with RCC. FDG-PET results were compared with those abstracted with biopsy in 33 lesions (Fig. 7). Overall sensitivity, specificity, and PPV of FDG-PET were 64%, 100%, and 100%, respectively.

Bladder cancer

Physiologic excretion of FDG in urine results in much difficulty in detecting lesions in the bladder and adjacent lymph nodes. FDG-PET has a limited use in diagnosis and management of bladder cancer. Kosuda et al [60] studied 12 patients with FDG-PET for the evaluation of recurrent or residual disease. PET identified 100% (17 of 17) of distant metastases (lung, bones, and remote lymph nodes) and 67% (2 of 3) of local lymph nodes. Heicappell et al [14] also had similar detection rate of 67% for local lymph node involvements. Ahlstrom et al [61] attempted to improve the accuracy of PET by using C11-methio-

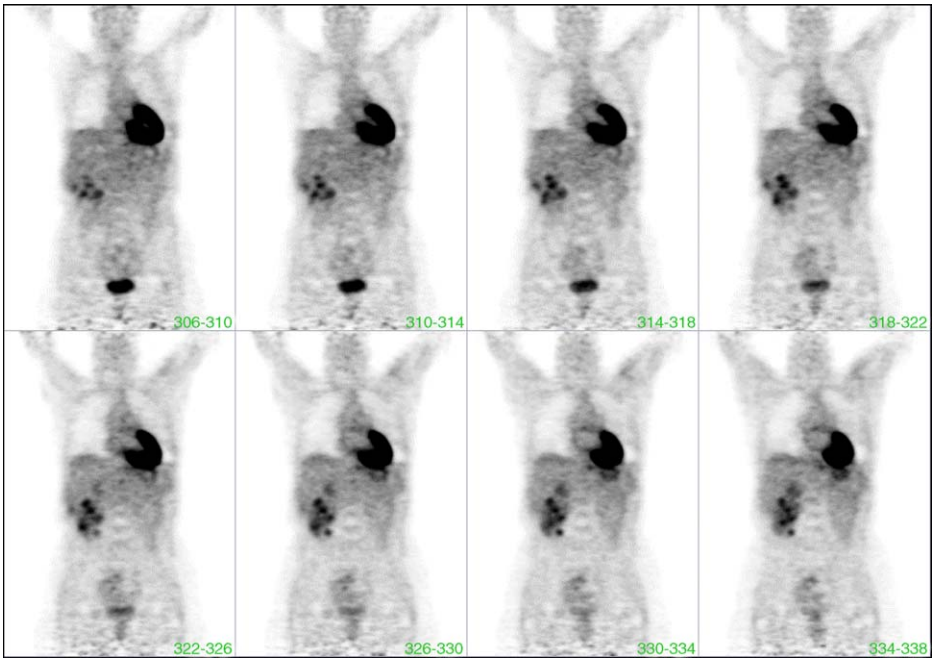

Fig. 7. Coronal views of FDG-PET show no multiple focal areas of increased FDG uptake in the right lobe of liver and perirenal region suggestive of metastases.

nine, which has no urinary excretion. The authors reported a sensitivity of 78% (18 of 23) and there was good correlation of tracer uptake and tumor stage.

Summary

FDG-PET has a limited role in the diagnosis of prostate cancer mainly because of the low uptake of FDG in the tumor and normal excretion of FDG through urine. FDG-PET has shown some promise in the assessment of lymph nodes and bone metastases. There is a large degree of variability when FDG-PET is compared with bone scintigraphy. New C11-labeled radiotracers (acetate, choline, and methionine) have shown promising initial results but further studies are required to determine their role in such settings. These radiotracers provide a unique opportunity for dynamic, multitracer, and quantitive studies, which improve the sensitivity and specificity of PET in this population. Short half-lives of C-11, however, with the limits to their use requires an on-site cyclotron. Recent synthesis schemes with [^{18}F]-labeling, however, may overcome this limitation. FDG-PET has a significant potential to assist with the diagnosis and management of testicular cancer. PET has been most useful in defining the presence or absence of disease in patients with residual masses. PET has shown promising results for the initial diagnosis of this cancer, but further studies are required to determine its role in the management of this malignancy. PET can be used in conjunction with conventional imaging techniques to diagnose retroperitoneal masses in patients with primary testicular cancer. FDG-PET has shown very encouraging results in a limited number of studies, and has also demonstrated a good sensitivity for initial staging. FDG-PET seems to be superior to conventional imaging modalities for detecting local disease and recurrence, and distant metastases.

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