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Nuclear Medicine Studies of the Prostate, Testes, and Bladder

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During the last decade, there has been a significant advancement in imaging of urologic diseases. Transrectal ultrasound (TRUS), computerized tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET) are still experiencing new developments in urology. Despite these many technological advances, the initial diagnostic procedure for a patient with suspected prostate cancer (PC) is multiple site blind prostate biopsies. There is a need for a noninvasive metabolic imaging modality to direct the site of biopsy to decrease the sampling error. MRS seems promising but as it is a costly and more time-consuming test, further studies are needed to evaluate its clinical utility. Currently, PET does not play any role to direct biopsy. Acetate and choline appear to be better tracers than FDG for the detection of a prostate lesion, however, further well-organized studies are needed before any of these agents can be used clinically. Incidental detection of intense focal uptake in the prostate during whole body PET scanning should be evaluated with prostate-specific antigen (PSA) and TRUS-guided biopsy. Although FDG is inferior to other tracers for primary staging, it may be useful in selected patients with suspected high-grade cancer. The role of ProstaScint scan is still controversial for detection of recurrent PC. This study may be helpful for evaluating nodal metastases when PSA is elevated and bone scan is negative. Bone scan remains the study of choice when bone metastases are suspected (PSA > 15-20 ng/mL ± bone pain). Acetate and choline provide better accuracy than FDG in the detection of local soft tissue disease, nodal involvement, and distant metastases. High FDG uptake may be indicative of more aggressive and possibly androgen-independent disease. PET/CT with any of the above PET tracers will most likely be preferred to the PET scan alone due to better localization of a hot lesion in PET/CT. Nuclear medicine studies also have been used to evaluate acute scrotum and testicular neoplasms. Scrotal scintigraphy has lost its popularity to Doppler ultrasound in the evaluation of the acute scrotum. In testicular tumors, FDG-PET appears to be superior to conventional imaging modalities in initial staging, detection of residual/recurrence, and monitoring treatment response. Tumor markers after treatment occasionally are elevated and cannot locate the site of recurrence, FDG-PET can play a very important role in this regard. Nuclear medicine studies also have been used to evaluate diseases of the urinary bladder. Radionuclide cystography is more sensitive and has less than 1/20 the radiation exposure of the conventional contrast enhanced micturating cystourethrogram (MCU). However, the utility of FDG-PET in the evaluation of bladder cancer seems to be limited to the evaluation of distant metastases. ^{11}C-Methionine and choline may be a better option for local and nodal disease due to their negligible excretion in the urine.
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Imaging of the prostate is important because of its involvement in many diseases of men. However, a number of problems have prevented success in this area. The size and location of the prostate contribute significantly to this problem. It is the size and shape of a large chestnut surrounding the first 1.25 inch of the male urethra proximal to the sphincter of the bladder.[1] The normal prostate weighs about 18 g.[2] Its composition is one-half glandular, one-fourth involuntary muscle, and one-fourth fibrous tissue.[1] Most of the clinically important prostate diseases, including prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer (PC), originate from the glandular component. Its small size and location deep in the pelvis interferes with the accurate detection of diseases with noninvasive imaging at an early stage. The

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other problem for nuclear imaging of the prostate is the proximity of the urinary bladder. Most radiopharmaceuticals are significantly excreted by the kidneys, resulting in bladder activity that significantly obscures the prostate.

Prostatitis syndrome is the most common urologic problem in men less than 50 years of age and about half of all men suffer from this syndrome at some time in their lives.[3] The prostate is also the site of two of the most common clinical problems faced by the elderly men: BPH and prostate cancer. BPH develops in virtually every male if he lives long enough, and, although few suffer significant morbidity, the majority of men over 60 will have some symptoms of BPH. Similarly, PC is now the most commonly diagnosed cancer in the United States, accounting for approximately one-third of all cancers diagnosed and it is the second most common cancer causing death from malignancy in American men.[4]

Prostatitis encompasses a heterogenous group of infectious and noninfectious disorders.[5,6] The prostatitis syndrome has been classified into acute bacterial prostatitis, chronic bacterial prostatitis, and chronic pelvic pain syndrome.[7] Patients with chronic prostatitis symptoms are more likely to have prostatic inflammation compared with asymptomatic controls, but in bacteriologic tests both groups may show similar results.[8] Moreover, at physical examination and in response to antimicrobial agents, patients with chronic bacterial prostatitis and chronic pelvic pain syndrome may have similar findings.[9] A culture for prostatic secretion frequently reveals a false-positive result due to microbial contamination or a false-negative one as the prostatic infection is a focal process and sampling errors are inevitable. Clinicians frequently use antibiotics empirically without definite evidence of infection[7,9,10] in suspected prostatitis. Chronic bacterial prostatitis requires prolonged antibiotic treatment, whereas nonbacterial prostatitis will not respond to antibiotic therapy. Considering the potential adverse effects of prolonged antibiotic treatment, accurate diagnosis of bacterial prostatitis is a major challenge for clinicians and microbiology laboratories. Conventional imaging such as ultrasound cannot differentiate bacterial from nonbacterial prostatitis.

^{111}Indium-labeled leukocyte scintigraphy is a well-established nuclear medicine imaging technique to evaluate acute infectious processes. This agent also has been used to assess the infected tissue of acute prostatitis and response to treatment.[11] However, as any inflammation can stimulate increased uptake of this agent, this study is not useful to differentiate bacterial versus nonbacterial chronic prostatitis. ^{99m}Tc-Ciprofloxacin imaging has been reported to be of value to differentiate bacterial infection from inflammation in various infectious conditions, such as osteomyelitis, soft tissue infection, lung abscess, pelvic inflammatory disease, and renal infection.[12-15] It has been shown that ^{99m}Tc-ciprofloxacin is taken up only by bacterial but not sterile abscesses and WBCs exhibit either no or negligible uptake.[12] Ryu and coworkers[16] conducted a study to investigate the value of ^{99m}Tc-ciprofloxacin imaging in the differential diagnosis of chronic bacterial prostatitis. This study included 4 normal subjects as the negative controls, 2 patients with acute prostatitis or cystourethritis as the positive controls, and 59 patients diagnosed as chronic bacterial prostatitis or chronic pelvic pain syndrome by traditional laboratory tests. SPECT images were obtained 3 hours after intravenous injection of ^{99m}Tc-ciprofloxacin. The results of the imaging were compared with laboratory tests. No uptake was observed in any normal subjects, while significant uptake, in the whole prostate of acute prostatitis patients and in the whole urethra of acute cystourethritis patients, was noted. In 13 (68%) of 19 patients categorized as chronic bacterial prostatitis by standard laboratory tests, increased uptake with less intensity than that of acute prostatitis was observed in the prostate area around the prostatic urethra. No uptake in the prostate was observed in 6 of 19 patients (32%) categorized as chronic bacterial prostatitis. Interestingly, uptake in the prostate was exhibited in 28 (70%) of the 40 patients categorized as chronic pelvic pain syndrome. This study also reported a significant excretion of the radioactivity via the urinary bladder. The investigators concluded that ^{99m}Tc-ciprofloxacin imaging is helpful in the differential diagnosis of prostatitis syndrome. However, its diagnostic accuracy, sensitivity, and specificity are not known. Further study is needed to validate this imaging method.

As mentioned previously prostate cancer is a significant health problem in elderly men. Nuclear medicine studies as well as other imaging modalities have been used for noninvasive detection of the primary lesion as well as evaluation of the extent of disease at different stages of the management of PC.

Diagnosis of Localized Primary

There are more than 200,000 new cases of PC diagnosed each year.[17,18] Apart from aging of the general population, an increased general awareness and improved diagnostic tools have raised the detection rate. Early diagnosis provides the best chance for cure and long-term survival. Prostate specific antigen (PSA) and direct rectal examination (DRE) provide the most cost-effective screening tests when used appropriately (American Cancer Society recommendations).[19] Suspicion of prostate cancer can be the consequence of a high PSA level or an abnormal DRE. The next step is histopathologic evaluation of tissue specimens obtained from prostate biopsy. Imaging modalities can play an important role in directing the site of biopsy to avoid sampling errors.

Transrectal ultrasound (TRUS) is the most commonly used imaging modality to evaluate the prostate gland. TRUS uses a high-frequency (5-7.5 MHz) endorectal transducer in close proximity to the prostate and produces high-resolution images (gray-scale imaging).[20] Prostate cancer most commonly appears hypoechoic (60-70%) compared with the normal peripheral zone, but up to 40% of lesions are isoechoic and are not detected.[20-22] Benign processes like prostatitis also frequently appear hypoechoic, therefore, hypoechogenicity is not specific for cancer. The positive predictive value of gray-scale is low (18-52%) and is not appropriate to make diagnosis of prostate cancer. Use of color Doppler, power Doppler, and contrast agents may increase the sensitivity and specificity. A positive predictive value as high as 77% has been reported.[20,22] Sonoelasticity imaging is another way to

increase the accuracy of the TRUS.[20] With the exception of gray-scale imaging, all other forms of TRUS are at an experimental stage. Currently, TRUS is not used during biopsy to guide the needle to any specific abnormal site; rather it is used to localize the usual sites for biopsy. Therefore, although it is called TRUS-guided prostate biopsy, it is basically blind, ie, irrespective of the presence of ultrasound abnormalities.[20,22] The yield from standard TRUS-mediated 6- to 12-zone prostate biopsy is found to be higher than biopsy only of lesions detected by TRUS.[20]

X-ray computed tomography (CT) lacks soft tissue contrast resolution for the detection of cancer within the prostate and offers no advantages over TRUS in biopsy guidance.[20]

Magnetic resonance imaging (MRI) using a combination of pelvic phased array and an endorectal coil provides the highest resolution images of the prostate and it is the best imaging modality for demonstrating normal zonal anatomy but it is of limited value in detecting primary prostate cancer.[20,22] Prostate cancer usually appears as abnormal areas of low signal intensity within the normal homogeneous high signal intensity background in T2-weighted images.[20] Cancer may not be detected if it does not demonstrate low signal intensity in T2, if it is located primarily within the central gland (does not demonstrate uniform high intensity like the peripheral zone), or if the peripheral zone does not possess a uniform high signal intensity. Low intensity in the peripheral zone is sensitive but not specific for cancer. Benign conditions including prostatitis, hemorrhage, or dystrophic changes related to radiation or androgen-deprivation therapy produce similar findings.[20,22] High cost and lack of a sufficiently high positive predictive value for cancer detection make MRI inappropriate for routine clinical detection of primary tumor.

Magnetic resonance spectroscopic (MRS) imaging provides metabolic information about the prostate gland in vivo.[20,22,23] Currently, it is possible to obtain a 3D metabolic map of the entire prostate with a resolution of 0.24 cm.[23,24] Normal prostate tissue is rich in citrate, and prostate cancer contains high levels of choline and often diminished citrate. This is due to conversion from citrate-producing to citrate-oxidating metabolism (low citrate) and a high phospholipid cell membrane turnover (high choline) in the cancer.[25,26] Therefore, prostate cancer is distinguished from the normal tissue by an increased (choline + creatine)/citrate ratio.[23] Though promising, the major limitations of MRS are cost, availability, and lack of supporting clinical data.

Among the currently available nuclear medicine studies only positron emission tomography (PET) has some potential (if any) to detect primary tumor in prostate cancer. The PET tracers used for clinical studies of prostate cancer are ^{18}F-FDG (fluorodeoxyglucose), ^{11}C-acetate, ^{18}F-acetate, ^{11}C-methionine, ^{11}C-choline, ^{18}F-choline, and ^{18}F-FDHT (16β-^{18}F-fluoro-5α-dihydrotestosterone).

^{18}F-FDG uptake in the cell is related to several glucose transporters in the cell membrane, which allow active ^{18}F-FDG passage across the membrane to the cytoplasm and trapping without further metabolization.[27] One of the biochemical characteristics of malignant cells is an enhanced rate of glucose metabolism due to increased numbers of these cell surface glucose transporter proteins and increased intracellular enzyme levels of hexokinase and phosphofructokinase, which promote glycolysis.[27-29] The most common glucose transport protein overexpressed on the tumor cell membranes is Glut-1, which is insulin independent.[30] In vitro studies have shown that FDG uptake is also determined by the number of viable tumor cells within a lesion (tumor-cell density).[29,30] Nontumoral tissue such as necrotic and fibrotic tissue may reduce tracer uptake.[29] Increased cell proliferation in tumors (assessed by the mitotic rate) results in increased glucose utilization.[30] Tumor hypoxia will also increase FDG uptake through hypoxia-inducible factor-1α, which upregulates Glut-1 receptors.[30] FDG accumulation within a tumor is likely related to a complex interaction between the cellular energy demand and the tumoral microenvironment.[31] Once inside the cell, FDG is phosphorylated by hexokinase into FDG-6-phosphate. FDG-6-phosphate is not metabolized and accumulates intracellularly.[28] Decreased levels of glucose-6-phosphatase (an enzyme that metabolizes FDG-6-phosphate back to FDG) within tumor cells compared with normal cells permits longer intracellular retention of FDG-6-phosphate.[32] The signal derived from tumors represents an average of the FDG uptake throughout the lesion.[29] Unfortunately, a large fraction of prostate cancer possess a relatively slow metabolic rate and express fewer Glut-1 binding sites, leading to lower FDG uptake compared with other cancers.

Acetate uptake in tumor cells is proportional to lipid synthesis.[33] Acetate is metabolized and incorporated into the cellular lipid pool, mostly phosphatidylecholine (a building block of cell membrane) and neutral lipids.[34] An increase in fatty acid synthesis and an overexpression of the key enzyme fatty acid synthase have been demonstrated in prostate cancer.[35] Acetate labeled with ^{11}C has been used in prostate cancer imaging. ^{11}C has a very short half-life of 20 minutes and an on-site cyclotrone is necessary at this time to use this tracer for clinical studies. Labeling of acetate with a longer-lived positron emitter such as ^{18}F has been investigated.[33] Methods for safe and efficient synthesis are still under investigation. Preliminary data from animal studies suggest that this agent might be useful for prostate cancer imaging.[33,36]

Table 1 provides a summary of agents used for prostate imaging and their potential role.

^{11}C-Choline (^{11}C-CHOL) is an agent that is incorporated into tumor cells by conversion into ^{11}C-phosphorlycholine, which is trapped inside the cell. This is followed by synthesis of ^{11}C-phosphatidylcholine, which constitutes a main component of cell membranes.[37] Because tumor cells duplicate very quickly, the biosynthesis of cell membranes also is very rapid and this is associated with increased uptake of choline and upregulation of the enzyme choline kinase.[37] The uptake of ^{11}C-CHOL in tumors represents the rate of tumor cell proliferation.[38] ^{11}C-CHOL is cleared very rapidly from the blood, and optimal tumor-to-background contrast is reached within 5 to 7 minutes.[37,39] ^{18}F-labeled choline compounds such as ^{18}F-fluoroethylecholine (FEC) and ^{18}F- fluoromethyl-dimethyl-2-hydroxyethylammonium (FCH) have been synthesized.[33,40,41]

Table 1 Radiopharmaceuticals Used in Prostate Cancer[20,22,23,33,73,103,109,158]

Radiopharmaceuticals	Potential Use
^{99m}Tc-Colloid lymphoscintigraphy[90]	To assess the laterality of lymphatic drainage of the prostate, before total prostatectomy with pelvic node dissection (requires further study)
^{99m}Tc-MDP bone scan	Evaluation of bone metastases (PSA > 15-20 ng/mL ± bone pain ± high alkaline phosphatase); not good for monitoring response due to "flare phenomenon"
^{111}In-Prostascint	To evaluate nodal recurrence (rising PSA) when bone scan is negative
^{18}F-FDG	So far, not very useful; possibly can be used to evaluate aggressiveness and androgen insensitivity; another use could be to identify progression of disease from "flare phenomenon" in bone scan
^{11}C-Acetate	Better than FDG to evaluate local disease, nodal metastases and distant metastases due to low urinary excretion; the major obstacle for routine use is short half-life of ^{11}C
^{18}F-Acetate	Limited data
^{11}C-Choline	Similar to acetate; not clear if it is better than acetate; requires head to head study with acetate
^{18}F-Choline	Better than FDG, less urinary excretion and longer half-life of ^{18}F compared to ^{11}C; can be used to evaluate local disease, nodal and distant metastases
^{11}C-Methionine	Limited data, useful for evaluating recurrent disease; half-life of ^{11}C is major limiting factor
^{18}F-Fluoride bone scan	Slightly more accurate than ^{99m}Tc-MDP bone scan particularly with CT in a PET/CT scanner; however, not cost effective
^{18}F-Fluoro-dihydrotestosterone[34,116]	Limited data; can be used to monitor treatment response and possibly with FDG to evaluate the androgen insensitivity

^{11}C-Methionine is proportional to the amino acid transport and to some extent protein synthesis.[33,42,43] In cancer, methionine uptake has been correlated with the amount of viable tumor tissue.[44]

Dihydrotestosterone (DHT) is the primary ligand of the androgen receptor and ^{18}F-FDHT is a radiolabeled analog of DHT. The androgen receptor plays an important role in the growth and proliferation of prostate cancer as well as modulation of androgen status. Anti-androgen is one of the most effective treatments in prostate cancer.[11] ^{18}F- FDHT may be useful in monitoring treatment response.

Several studies have been conducted using ^{18}F-FDG-PET in localized prostate cancer. Most of the results were disappointing.[33,45,46] Effert and coworkers[46] studied 48 prostate cancer patients and 16 patients with benign prostatic hyperplasia. They reported a low grade FDG uptake in 81% of these tumors and there was a significant overlap between benign prostatic hyperplasia and prostate cancer in uptake values. Hoffer and coworkers[45] reported similar findings.

In a study of 24 patients Liu and coworkers[47] found a sensitivity of 4% for FDG-PET in the diagnosis of primary PC. Melchior and coworkers [48] reported higher FDG accumulation in poorly differentiated PC than in low grade PC. Oyama and coworkers [49] examined 44 consecutive patients with histologically proven adenocarcinoma of the prostate. In visual analysis, 5 patients with BPH (control group) showed low FDG uptake. On the other hand, 28 of 44 (sensitivity 64%) patients with cancer were visually positive, showing intermediate and high FDG uptake. There was a trend for FDG uptake in PC to correlate Gleason scores.

The possible explanations for disappointing results as suggested by Schöder and Larson[33] include: (1) a relatively lower metabolic rate in the majority of prostate cancers with lower FDG uptake, (2) older image reconstruction techniques (ie, use of filtered back projection instead of iterative reconstruction), (3) location of the prostate adjacent to the urinary bladder, and (4) the lack of appropriate patient selection (FDG may be more useful in patients with clinical suspicion of a high-grade cancer).

Shreve and coworkers[50,51] suggested that the lack of urinary excretion and good tumor to background ratio makes ^{11}C-acetate a more suitable tracer for imaging prostate cancer. An in vitro study by Yoshimoto and coworkers[34] showed that tumor cell to nontumor cell ratios were higher for acetate than deoxyglucose. During the last several years this tracer has been used in prostate cancer.[52-54] Oyama and coworkers[55] studied 22 patients, among whom 18 also had an FDG scan. They reported ^{11}C-acetate uptake in all primary tumors with standard uptake values (SUVs) from 3.27 to 9.8, whereas FDG was positive only in 15/18 with SUVs from 1.97 to 6.34. In another study Kato and coworkers[56] found that there was an overlap of SUVs for patients with benign prostatic hyperplasia and those with cancer. They also noted that SUVs in normal subjects of below 50 years of age were significantly higher than that of above 50. Except for case reports[57] no significant data are available to evaluate the role of ^{18}F-acetate in prostate cancer.

^{11}C-Choline, ^{18}F-FEC, and ^{18}F-FCH have a rapid clearance from the blood pool and rapid uptake in prostate tissue.[40,41,58] Both ^{18}F-labeled compounds have some urinary excretion 3 to 5 min after injection. In contrast, ^{11}C-choline shows very little urinary excretion and the activity in the bladder is always lower than prostate cancer.[58] FEC concentration in the prostate reaches its highest activity at 55 min after injection (SUV 4.4 versus 2.8 at 5 min),[40] whereas FCH uptake shows a peak at approximately 3 min after injection

followed by a plateau.[41] Therefore, urinary excretion may interfere with FEC imaging. In vitro (cultured PC-3 human prostate cells) studies revealed that cellular uptake and phosphorylation by choline kinase is very similar for FCH and natural choline but is lower for FEC.[59] It seems that FCH may be a better tracer than FEC for prostate cancer imaging.

Tumor uptake of ^{11}C-methionine occurs rapidly (a peak at around 10 min followed by a plateau).[33,60] ^{11}C-Methionine undergoes rapid clearance from the blood pool and is primarily metabolized in liver and pancreas with no significant renal excretion, making it a better tracer than FDG.[60] Most of the reported studies have evaluated its role in metastatic prostate cancer and in recurrent disease. Insufficient data are available in primary prostate cancer.

Most of the primary prostate cancers express androgen receptors like normal prostate cells. Therefore, the main role of ^{18}F-FDHT may be to monitor response rather than in primary diagnosis.

Similar to FDG, methionine, acetate, and choline are not specific agents. Benign prostatic hyperplasia shows tracer uptake higher than normal but lower than that found in cancer; however, there are no discriminating SUVs to differentiate cancer from hyperplasia.[33,58] At this time, PET does not play a significant role in the primary diagnosis of prostate cancer. The reasons include a lack of appropriate image acquisition techniques such as zoom mode acquisition (the prostate is a small organ, therefore, zoom mode acquisition may provide better visualization of a small lesion), image fusion (combined PET/CT may provide more confidence to identify a hot area as abnormal in the prostate gland rather than in the prostatic urethra), longer acquisition time to increase sensitivity and possible dual time imaging (proven to be useful in lung lesions to discriminate cancer from an inflammatory lesion; this may help differentiate cancer from benign prostatic hyperplasia) (Fig. 1).

Despite technological advances, the initial diagnostic procedure for a patient with suspected prostate cancer is multiple site blind prostate biopsies (6 to 12 core biopsies) using TRUS to locate the zones of prostate gland. To diagnose one PC, 6 to 10 patients must undergo prostate biopsy. Unfortunately prostate biopsy suffers from a sampling error that is evidenced by the fact that a negative biopsy does not completely exclude PC. As many as 13 to 31% of patients with an initial negative biopsy will have PC on subsequent biopsy.[17,61] PSA, the most widely used blood test to screen PC, may be high in benign diseases like prostatitis and benign prostatic hyperplasia (BPH), which also are very common in the same age group as PC. In the early stage of PC there usually is no significant change in anatomy. Therefore it is difficult for conventional anatomical imaging modalities to be useful to direct the biopsy site. There is a need for a noninvasive metabolic imaging modality to direct the site of biopsy to decrease the sampling error. MRS seems promising but further studies are needed to evaluate its clinical utility. Currently, PET does not play a significant role in directing biopsy. Acetate and choline seem to be better tracers than FDG, however, further studies are needed to decide whether PET can have a significant role in the diagnosis of primary prostate cancer.

During routine whole body PET imaging, occasionally, focal intense uptake of tracer in the prostate has been reported during FDG (Fig. 2) and ^{11}C- choline imaging.[33] Further evaluation of these lesions in terms of PSA measurement and TRUS guided biopsy is important. Particularly, intense FDG uptake may indicate presence of a high-grade cancer.

Initial Staging and Predicting Grade

Staging of prostate cancer requires staging of tumor (T-stage), lymph nodes (N-stage), and distant metastases (M-stage). T-staging involves evaluation of the percentage of prostate occupied by the cancer (as well as unilateral versus bilateral), extracapsular extension (ECE), and seminal vesicle involvement (SVI). N-staging is based on detection of the groups of lymph nodes involved as well as laterally. In prostate cancer the most common and important organ for distant metastases is bone. Therefore, imaging is used primarily to evaluate local disease, nodal, and bone metastases.

Predicting Grade

PC is a remarkably heterogeneous disease.[17] Autopsy studies have shown that 30 to 46% of men older than age 50 have microscopic PC, yet less than 20% of men develop clinically significant PC during their lifetime.[17,61-63] It is evident that some of the PCs are small, well differentiated, and unlikely to cause clinically significant disease, whereas others are large, poorly differentiated, likely to metastasize, causing death.[61,63] The first group of patients may be pursued with watchful waiting or more conservative therapy compared with the second group of patients, who require urgent and more radical therapy. Radical treatment often is associated with a loss of urinary control, abnormal sexual function, and lesser quality of life, which are not acceptable to many young patients.[17,63,64] For these reasons, after the initial diagnosis it is very important to distinguish patients with aggressive cancer who need intensive therapy from those who can be pursued with watchful waiting. There are limitations of currently available tumor prognostic factors in differentiating indolent from aggressive disease.[61] There are several biologic markers under study for this purpose.[17,63,65,66] There is intense debate about the ability of any single currently available tumor prognostic marker to accurately assign patients to an appropriate risk stratum and treatment category.[17,61,63,65-67] Any imaging modality capable of identifying these groups of patients noninvasively will immensely help the treatment planning for PC patients.

Importance of Imaging for Staging

Accurate staging before treatment permits the appropriate selection of therapy and increases the likelihood of a favorable treatment outcome. Long-term cancer-free survival is determined both by the clinical extent of disease at the time of treatment and the type of treatment delivered.[22] Understaging can occur in 30 to 60% of patients who undergo surgery for clinically localized disease.[68] DRE alone is insufficient for detecting the presence or extent of cancer.[69] DRE has very

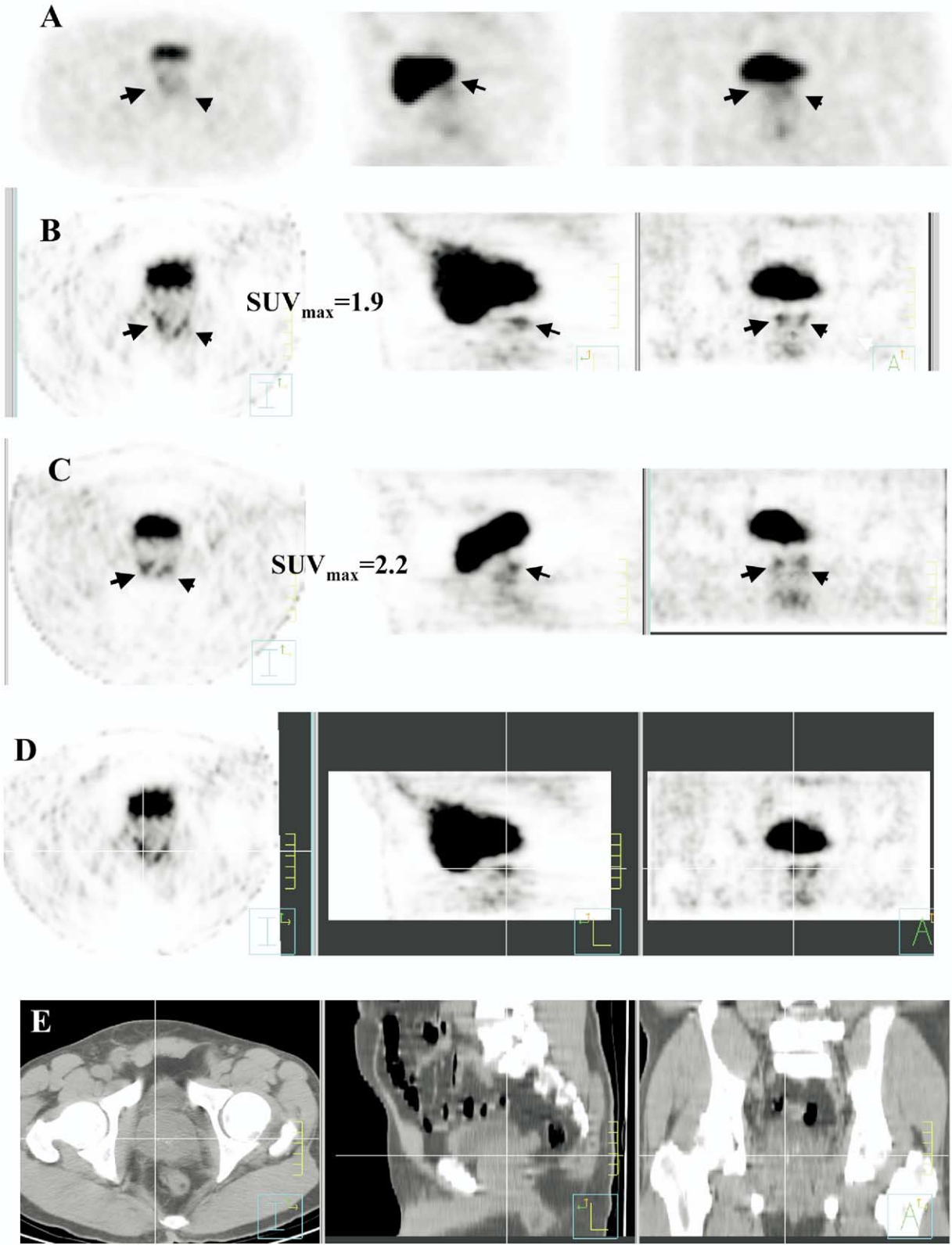

Figure 1 A 60-year-old African–American man underwent prostate biopsy in September 2001 due to a nodular prostate on rectal examination and an elevated PSA of 11.6. The biopsy showed focal glandula hyperplasia, basal cell hyperplasia, focal inflammation, and no evidence of cancer. In May 2004 the PSA increased to 14.2. Before repeat biopsy the patient underwent FDG-PET scan. A normally acquired PET scan displayed with magnification (A) showed mild asymmetric uptake (arrows) in the prostate, which was thought to be abnormal. The scan of the prostate was also acquired in zoomed mode at 60 min (B) and 120 min (C) after the FDG injection. There were discrete areas of FDG uptake in both images (B and C), which were clearly abnormal. These scans were performed on a PET/CT scanner. The SUV max of the prostate lesion was 1.9 from 60-min images (B) and was 2.2 from 120-min images (C). When PET images (D) were displayed with CT images (E) the focal uptakes were found to be located adjacent to the prostatic calcifications. The prostate biopsy was performed in the next week and the biopsy specimens were obtained from the calcified regions as suggested by PET/CT scan. The pathology was positive for adenocarcinoma (Gleason score 6/10 with minor foci of grade 5 adenocarcinoma).

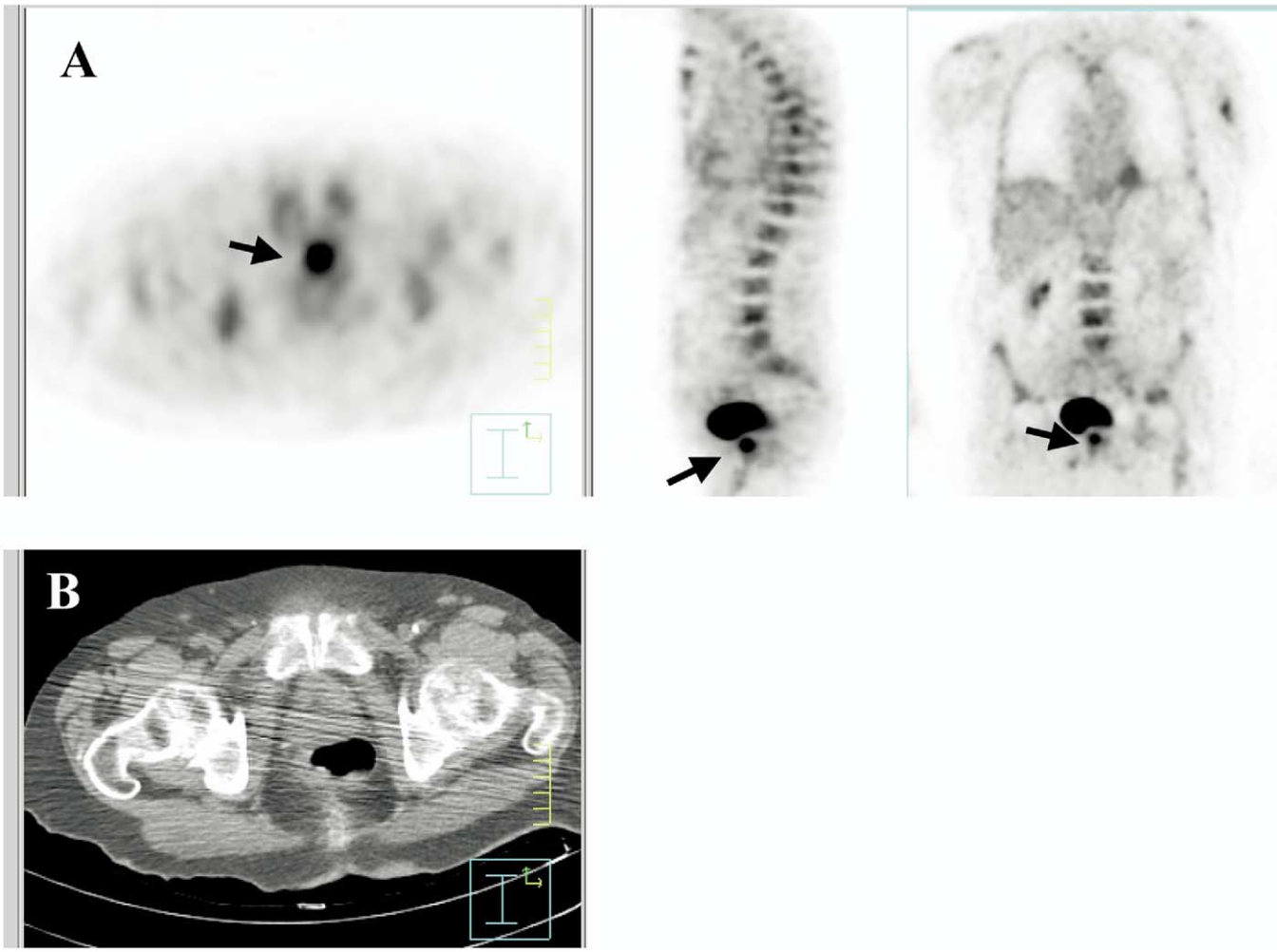

Figure 2 A 75-year-old man with history of metastatic lung cancer found to have intense uptake of FDG (arrow) in the prostate in the PET/CT scan (A and B). Prostate biopsy revealed adenocarcinoma of the prostate; Gleason score 8/10 (5 + 3).

low specificity due to the fact that about 50% of the palpable prostate nodules are benign.[70] More than 60% of prostate cancers staged by DRE alone are understaged.[71] Similarly, PSA alone also has poor sensitivity and specificity in predicting tumor stage when it is less than 20 ng/mL.[22] The accuracy of pretreatment staging does not improve significantly when DRE and PSA are combined.[72] In individual patients nomograms are used to predict the likely pathological stage of disease and probability of recurrence and metastases after curative treatment.[33] These nomograms combine information from PSA, Gleason score at biopsy, and clinical stage at presentation.[73]

The incidence of patients who present with organ-confined disease is more than 70%[33] due to increased awareness and more frequent use of PSA. PC is a remarkably heterogeneous disease and controversies result from the lack of firm data regarding the definitive treatment with either radical prostatectomy or radiation therapy. To resolve these controversies, many trials are under way comparing different screening and treatment methods.[74-76] However, the results of these trials will not be available earlier than a decade from now.

The most important goal of imaging is to identify patients with either organ-confined disease or limited extarcapsular extension (ECE) (who will receive radical prostatectomy, brachytherapy, or external beam radiation with curative intent) from those with more advanced disease, who will require palliative systemic therapy (antiadrogen alone or combined with chemotherapy).

Role of Conventional Imaging Studies

TRUS. The use of TRUS for local staging of prostate cancer remains controversial. TRUS alone has a relatively poor ability to detect palpable and nonpalpable prostate cancer and to predict disease outcome.[22,21,77] TRUS is operator dependent. In a multiinstitutional, prospective trial of 230 patients,[78] TRUS had a sensitivity of 66%, a specificity of 46%, a PPV of 63%, a NPV of 49% in predicting ECE, and sensitivities of 22 and 88% in predicting SVI. Bates and coworkers[79] found sensitivities of 23 and 33% in predicting ECE and SVI, re-

spectively. In another prospective, multiinstitutional study funded by the National Institutes of Health in 263 patients who had radical prostatectomy,[80] preoperative clinical staging by TRUS and DRE was compared with pathologic staging. TRUS was not significantly better than DRE in predicting ECE. Modifications to TRUS have been introduced in an attempt to increase its utility, including color Doppler, power Doppler, 3D Doppler, and new contrast agents.[22] Unfortunately, there are few data on the ability of these new modifications to stage localized disease. Preliminary data indicate that some of these modifications can potentially increase the sensitivity of TRUS.[22] Since neovascularization is a marker of a more aggressive cancer and Doppler can determine vascularity, Doppler studies could potentially predict prognosis. There are only limited data available at the present time in this regard.[20,22] TRUS is not useful for N or M staging.

Abdominopelvic CT scans. Abdominopelvic CT scans were found to be of little value in low-risk and intermediate-risk patients. Poor soft tissue contrast diminishes the ability to visualize the prostatic capsule and hinders accurate distinction of cancer from benign hypertropic nodules.[22] Studies[81-83] have found sensitivities ranging from 2.5 to 75% and specificities ranging from 60 to 92% in predicting ECE and sensitivities ranging from 5.8 to 33% and specificities ranging from 60 to 90% in predicting the presence of SVI. Even in higher risk patients, CT may have limited clinical utility in predicting nodal involvement.[83] Lervan and coworkers[84] showed that only 1.5% of 861 patients with a PSA of more than 20 ng/mL were noted to have suspicious lymph nodes on CT. CT scans may have little utility for preoperative staging in low-risk patients, but CT is used for pretreatment radiation dose planning[84] and CT-guided brachytherapy.[85]

MRI/MRS. MRI has been used to improve staging in low-grade to intermediate-grade tumors. The data on the ability of MRI alone to predict stage are variable.[78,86-88] Presti and coworkers[87] reported endorectal MRI to be 91 and 50% sensitive and 49 and 94% specific in predicting ECE and SVI, respectively. Rifkin and coworkers[78] presented similar data. Bartolozzi and coworkers[86] evaluated 73 patients who underwent endorectal MRI and radical prostatectomy. They found a sensitivity of 95% and a specificity of 82% for ECE. The combined anatomic and metabolic information provided by MRI and MRS may allow for a more accurate assessment of cancer location and stage than does MRI alone. Yu and coworkers[89] examined 53 patients who had undergone combined MRI/MRS before prostatectomy; combined MRI/MRS had a sensitivity of 46 to 54% and a specificity of 93 to 96% in predicting the ECE between observers. They also reported that MRS reduced the intraobserver variability. As experience among radiologists grows, it is likely that MRI will be used more often, but at this time there are limited data to suggest that it should be used routinely to assess prostate cancer. There is some evidence that early enhancement may signal more aggressive tumors, with poorly differentiated tumors showing the earliest and most rapid enhancement in MRI/MRS.[22] Abdominopelvic MRI does not have any significant advantage over CT in the evaluation of nodal staging following the size criteria and, although it is very sensitive in detecting early bone marrow metastases, it is not as cost effective or convenient as the bone scan.

Role of Nuclear Medicine Studies

Lymphoscintigraphy, ProstaScint scans, and PET have potential roles in prostate cancer. It is worth mentioning that nuclear medicine imaging modalities are useful for N and M staging mainly. At this time nuclear medicine studies do not play any significant role in T staging. The role of PET/CT for T staging is not clear.

Lymphoscintigraphy

Lymphoscintigraphy is a powerful tool for mapping the route of lymphatic drainage of a tumor. This technique currently plays a very important role in the nodal staging of breast cancer and melanoma. As mentioned above, current noninvasive methods of examination (US, CT, MRI) are limited in sensitivity and specificity; the definitive method of pelvic lymph node evaluation is bilateral pelvic lymphadenectomy, an extensive procedure with associated morbidity.[90] Unilateral in place of bilateral dissection could reduce operative complications.[91] Gardiner and coworkers[92,93] compared four routes of intraprostatic injection in human subjects and demonstrated superiority of transrectal injections over the transperitoneal, transurethral, and transabdominal approaches. Zuckier and coworkers[90] demonstrated contralateral lymphatic drainage after direct transrectal prostatic injection and thereby the possibility of contralateral lymph node metastases in patients with unilateral prostate cancer. However, further studies are needed to evaluate the full potential of this technique.

ProstaScint Scan

ProstaScint is a murine monoclonal antibody to an intracellular component of the prostate specific membrane antigen (PSMA) that is conjugated to ^{111}Indium.[22] This tracer has been approved by the Food and Drug Administration (FDA, USA) for use in the evaluation of patients before undergoing treatment for their primary disease and for detecting the site of recurrent disease in patients who have biochemical relapse after radical prostatectomy.[22] Three possible clinical uses have been summarized in an editorial by Lange:[94] the detection of lymph node metastases, the detection of the site of relapse in those with a detectable PSA after prostatectomy, and the detection of occult metastases before primary therapy. The sensitivity and specificity to predict nodal disease from studies before 2001 summarized in this editorial were 60 and 70%, respectively. The major drawback of ProstaScint is nonspecific binding and high blood pool activity causing a low target to background ratio; therefore, it requires a significant amount of expertise to interpret these scans. At this time, ProstaScint does not appear to be an important part of the initial assessment of most patients during primary staging.

Bone Scan

The bone scan is a very sensitive method to detect metastatic lesions in bone.[95] Previously bone scans were used routinely

for all patients with prostate cancer.[22] An analysis of patients in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry—a longitudinal database of men with various stages of cancer—revealed high utilization rates even among men at low (18.6%) and intermediate risk (50.9%).[96] Oesterling[97] found that less than 1% of men with a PSA level less than or equal to 20 ng/mL have positive bone scans. In a multivariate analysis of 631 men who had a bone scan and prostate biopsy, Lee and coworkers[98] found that bone scans were not useful as an initial staging tool but could assist in the determination of the existence of metastatic disease in men with a Gleason grade greater than 7, a PSA level of greater than 50 ng/mL, or clinical stage greater than T3 (tumor extends through prostate capsule) disease. Currently, bone scans are not recommended when the PSA is below 15 to 20 ng/mL unless there is unexplained high serum alkaline phosphatase or bone pain.

PET Scan

FDG. FDG was found to have a low accuracy in primary staging of prostate cancer. FDG is slightly better in detecting metastatic PC than that in primary lymph nodes.[99] Heicappell and coworkers[100] used FDG-PET for preoperative imaging of pelvic lymph nodes in 17 newly diagnosed prostate cancer patients and then compared the findings with postoperative histopathology. FDG was able to diagnose metastatic lymph nodes accurately in 4 of 6 affected patients. The 2 false-negative results were attributed to the small size of the lesions (less than 5 mm). There was no false-positive result in this study. Other small studies[101,102] report sensitivities ranging from 0 to 50% and specificities ranging from 72 to 90% for detection of nodal metastases. FDG uptake was noted in pelvic lymph nodes in patients with PET negative primary.[46,49] FDG-PET is variable in the detection of bone marrow metastases; however, the general belief is that it is more sensitive for the detection of bone metastases than local disease.[103] Shreve and coworkers[51] reported a sensitivity of 65% and PPV of 98% in 202 bone metastases. Yeh and coworkers[104] found that only 18% of bone lesions on the bone scan showed FDG uptake. Kao and coworkers[105] reported a high specificity of FDG-PET in detection of bone marrow metastases. Nunez and coworkers[60] found better detection of cervical spine metastases by FDG-PET than by bone scan. In another study Morris and coworkers[106] evaluated 154 bone lesions in 17 patients. Both FDG and the bone scan were positive in 71% lesions, 23% were seen only on bone scan, and 6% were seen only on PET scan. Schöder and Larson[33] suggested that FDG may selectively detect more aggressive tumors, which depend on higher glucose metabolism. In vitro studies in prostate cancer xenografts showed higher FDG uptake in tumors with higher Gleason scores,[107] and in clinical studies FDG uptake correlates with PSA level and PSA velocity as measure of tumor size and progression.[52,108,109] It seems that high FDG uptake most likely suggests a relatively high-grade tumor.

Acetate. ^{11}C-Acetate has been reported to be more sensitive than FDG-PET in the detection of regional lymph node metastases. Oyama and coworkers[55] found ^{11}C-acetate detected nodal metastases in five patients compared with FDG used in two patients. In the same study Oyama and coworkers[55] also found that six of seven bone metastases showed ^{11}C-acetate accumulation, whereas FDG was positive in only four patients. Fricke and coworkers[110] showed that FDG was superior to acetate for detection of bone metastases. Kotzerke and coworkers[111] compared ^{11}C- acetate and ^{11}C-choline in 12 patients for detection of metastases from prostate cancer. The relationship between intensity of acetate uptake in prostate cancer and PSA is unclear. At this time it is not clear whether acetate can predict the grade or aggressiveness of the cancer.

Choline. There is a small number of studies using choline available in the literature. Intense bowel uptake can be observed with all choline compounds and can pose a problem for accurate evaluation of pelvic and abdominal lymph nodes. Preliminary data suggest that choline can detect more metastatic lymph nodes and also bony metastatic lesions from prostate cancer than FDG[59,112] and that it has more intense uptake than FDG. Kotzerke and coworkers[101] and de Jong and coworkers[113] reported uptake in primary cancer, lymph nodes, and bone lesions. In another study de Jong and coworkers[114] reported sensitivity, specificity, and accuracy of 80, 96, and 93%, respectively, for staging lymph node disease. Although choline had higher SUVs than FDG on a lesion to lesion basis, there was no correlation between SUV of ^{11}C-choline and tumor grade or Gleason score.[58]

Methonine. Only limited number of studies report methionine use during primary staging of prostate cancer. Macapinlac and coworkers[115] and Nunez and coworkers[60] compared ^{11}C-methionine with FDG and demonstrated that methionine PET is superior to FDG in detecting primary and metastatic lesions in prostate cancer. These two studies also compared the biodistribution of methionine and FDG. Methionine is primarily metabolized in the liver and pancreas with no significant renal excretion and, therefore, provides better visualization of pelvic organs. Methionine uptake in cancer is correlated with the amount of viable tumor tissue,[44] however, data are lacking to correlate the SUV with tumor grade or Gleason score in prostate cancer.

FDHT. FDHT is a relatively new tracer and there are not enough data available at this time. No FDHT uptake with FDG uptake of a lesion could suggest androgen resistance (or androgen independence) of the lesion. Therefore, lack of uptake may be a bad prognostic factor. Its biodistribution and binding characteristics are currently under study.[33,116]

^{18}F-Fluoride. The ^{18}F-fluoride bone scan seems extremely promising for early detection of both sclerotic and lytic lesions, especially in combination with CT.[33,117,118] However, it should be used when a bone scan is indicated, ie, PSA is more than 15 to 20 ng/mL and suspicious for bone metastases. It is not likely to provide any more information than a conventional bone scan. A contrary view is presented in the article on bone scans in this issue.

Acetate, choline,[119] or methionine seem to be superior

tracers to FDG during primary staging due to their better biodistribution pattern (ie, low urinary excretion at the time of peak uptake in the lesions). Most of the studies have compared one of these tracers with FDG. Only one study compared choline and acetate head to head and found that they are similar. However, further comparative studies are needed to determine which of these tracers will provide the best result. Although FDG is inferior to other tracers for primary staging, it may be useful in selected patients with suspected high-grade cancer.

Recurrent Disease

The earliest and most common indication of recurrent prostate cancer after initial treatment with a curative intent is a rising serum PSA level.[23] There is no need for any imaging studies when the PSA is undetectable and there are no new clinical findings or symptoms. Once the PSA is elevated, the key clinical consideration is the differentiation between local and metastatic relapse.

Role of Imaging in Recurrent Disease

Clinical nomograms based on tumor stage and grade of tumor at the time of diagnosis and PSA doubling time are used to statistically predict whether a recurrence is local or metastatic.[73,120,121] According to this nomogram a distant recurrence is suggested by a short PSA doubling time (less than 10 months), in a patient with a high-grade cancer (Gleason score 8 to 10) or high pathologic stage (seminal vesicle invasion or nodal metastases). The reported incidence of PSA relapse following radical retropubic prostatectomy or radiation therapy with curative intent ranges from 15 to 53%.[23,73,122,123] In patients with a positive surgical margin, 60% will eventually recur, but recurrence is not always local.[123] The treatment of local recurrence is either surgery or radiotherapy, whereas distant recurrence is managed with systemic treatment.[23] While DRE is a useful screening tool for primary prostate cancer, it is unreliable after surgery or radiotherapy to detect local recurrence due to altered anatomy and consistency of the prostate bed.[23] Therefore, a noninvasive imaging modality is required to locate the source of the rising PSA so that appropriate treatment can be instituted.

Conventional Imaging Studies

Local recurrence appears as a hypoechoic mass in the surgical bed[23] with TRUS. However, up to 30% of recurrent tumors may be isoechoic and difficult to detect by TRUS.[124] The fibrosis after radiation distorts normal tissue planes and also makes it difficult to detect recurrence in this altered tissue.[23] The overall sensitivity of TRUS alone following radiation or surgery is less than 50%.[23,124,125] In these conditions sampling error is the major cause of false-negative results.[23,125] TRUS is not useful for detection of distant metastases.

CT has been used to assess metastatic disease in the prostate bed, nodes, bone, and visceral organs.[23] The role of CT in the detection of local recurrence is very limited particularly if the size of the recurrent tumor is smaller than 2 cm. CT detection rate of local recurrence was only 36% even in patients with the tumors larger than 2 cm in a study by Kramer and coworkers.[126] CT currently is the most frequently used imaging modality in the evaluation of nodal metastases. CT relies on the nodal size of >1 cm to discriminate metastases, therefore, the specificity is low; however, due to its easy accessibility and fast scanning, it is used most frequently. CT scans may be normal when the bone scan is positive for metastatic disease, therefore, the role of CT in the evaluation of bone metastases is limited and its routine use is not recommended.[23] However, CT can be used to characterize a focal uptake in a bone scan as benign or malignant.[127]

MRI/MRS

Endorectal MRI has been proven capable of detecting local recurrence in many patients with rising PSA particularly in patients with no palpable tumor in the prostatic fossa. Silverman and Krebs[128] reported both sensitivity and specificity as 100%. A high efficacy (95% sensitivity and 100% specificity) also has been reported by Sella and coworkers.[129] Although the most common site of local recurrence is the perianastomotic site, 30% can occur elsewhere in the pelvis. All of these sites of recurrence also can be seen and detected by MRI.[129] Endorectal MRI is still not in routine clinical use; however, it seems very promising. MRI has the potential to direct a transrectal biopsy to these sites and, when used in conjunction with pelvic phase array coil, it can evaluate pelvic lymph nodes and osseous structures, thus detecting all sites of pelvic relapse in a single examination. MRI is very good at evaluating bone marrow metastases; however, it is expensive, time consuming, and susceptible to motion artifacts, therefore, it is rarely used for evaluation of distant bone metastases.

Nuclear Medicine Studies

Nuclear medicine studies including ProstaScint, bone, and PET scans have been used to detect recurrence.

ProstaScint

Theoretically, ProstaScint should bind to prostate cancer cells with very high specificity; therefore, the scan should offer high specificity. However, nonspecific binding of the antibody to other structures and significant uptake in the bone marrow provide a very low target to back ground ratio. In the literature the sensitivity varies from 44 to 92% and the specificity varies from 36 to 86% for detection of local recurrence.[130] Smith-Jones and coworkers,[131] using biopsy as the gold standard, reported 10 to 20% false-negative cases of ProstaScint scans. The prevailing opinion is that ProstaScint imaging is not useful for the detection of local recurrence as a first test. However, it may have a role in identifying nodal metastases in patients with rising PSA but negative bone scan who might otherwise be a candidates for local salvage therapy.[23] There is a possibility that the ProstaScint scan in conjunction with CT in a SPECT/CT scanner will increase the accuracy of this tracer.[23]

Bone Scan

Currently PSA is used as a marker to assess the likelihood for osseous metastases from prostate cancer.[132] Bone involvement is unlikely when the PSA is below 2 ng/mL after pros-

tatectomy. A bone scan generally is not recommended following treatment unless there is a rising PSA and specific reproducible bone pain.[133] Bone scans play an important role in the management of patients with rising PSA. A negative bone scan in the face of a rising PSA may suggest local recurrence, which may be treated locally. On the other hand, a positive bone scan most likely requires systemic therapy. The other advantages associated with the bone scan are its easy availability, relatively low cost, and virtually no contraindication. Hence, in patients with rising PSA, bone scans are frequently used as the initial study. If the bone scan is positive, imaging assessment is essentially complete. However, bone scans are rarely positive before the PSA is 30 ng/mL or above.[134] Palmer and coworkers[135] suggested that bone scans could be more reliable to detect metastases than symptoms alone. In this study they found 34% asymptomatic bone metastases. They also found, among 1403 patients with prostate cancer, the bone scan was 28% more sensitive than plain radiographs.[134] SPECT imaging of the spine not only increases the sensitivity of the bone scan but also increases the specificity by locating the hot area in the parts of vertebra (ie, location in the facet joints is suggestive of degenerative diseases, whereas focal uptake inside the body or pedicle is highly suggestive of metastases).[136,137]

Role of PET Scan in Recurrent Prostate Cancer

FDG. Overall the results of imaging recurrent prostate cancer were not very successful with FDG.[23,33,103] Seltzer and coworkers[108] found a similar detection rate of 50% with FDG-PET and CT when the PSA was >4 ng/mL. Herrmann and coworkers[109] found a detection rate of 35% in recurrent prostate cancer. They concluded, due to the low yield of true-positive findings, FDG-PET is not useful in patients with PSA less than 2.4 ng/mL after prostatectomy. Other PET tracers, in particular acetate and choline, appear more promising in the detection of recurrent prostate cancer. Interestingly, Fricke and coworkers[110] reported that FDG was superior in the detection of distant metastases, whereas acetate was superior for detection of local disease recurrence and nodal metastases.

Acetate. ^{11}C-Acetate has been evaluated for the detection of recurrent prostate cancer in patients with elevated PSA. ^{18}F-Acetate has not been studied in an acceptable number of prostate cancer patients. Kotzerke and coworkers[54] studied the usefulness of this tracer in the detection of local recurrence at the prostate bed and adjacent tissues. The PSA value ranged from 0.9 to 151 ng/mL (mean $\pm$ SD = 15 $\pm$ 30) in total 31 patients. They reported a sensitivity of 83% in detecting local recurrence. In this study there were three false negatives but no false positive. All false-negative lesions were less than 1.5 cm in volume. In this study they also noted acetate uptake in distant metastastatic lesions (lymph node and bone) in five patients. In another study on 46 patients of rising PSA primary prostatectomy or radiotherapy, Oyama and coworkers,[53] compared ^{11}C-acetate and FDG (furosemide and catheter were used to decrease urinary bladder activity) to detect recurrent disease. Abnormal uptake was seen in 59% of acetate studies but in only 17% of FDG studies. In a similar study Fricke and coworkers[110] compared acetate with FDG in patients with rising PSA levels (0.4-400 ng/mL). In this study an SUV > 2 was used to identify disease. Overall, acetate detected 80% of the local recurrences or distant metastases and FDG detected only 66%. When the intensity of uptake in the detected lesions was compared, acetate also showed a higher SUV compared with FDG (median SUV 3.2 versus 1.4). FDG detected more of distant bony metastases compared with acetate (75 versus 50%). They concluded that acetate is a better tracer for detecting local and lymph node metastases, whereas FDG is superior for detecting bone metastases, suggesting that complete evaluation of prostate cancer may require more than one tracer.

Choline. Both ^{11}C-choline and ^{18}F-choline (FCH) have been used in human prostate cancer for detection of recurrence. Picchio and coworkers[138] compared ^{11}C-choline with FDG for detection of recurrent prostate cancer in 100 patients with rising PSA (0.14 to 171, mean = 6.5 ng/mL). They reported that more lesions suspicious for metastases were detected with choline than with FDG (47 versus 27%). They concluded that choline is more accurate than FDG for detecting all types of recurrence (local, nodal as well as distant). They also found that 80% of patients with a negative choline scan had a stable PSA after 1 year follow-up, therefore, a negative choline scan indicated a good prognosis. In a smaller group of 22 patients de Jong and coworkers[139] also reported a good negative predictive value of ^{11}C-choline. On the other hand, Price and coworkers,[112] studied ^{18}F-FCH (fluoro-choline) and ^{18}F-FDG in cell culture as well as in patients with androgen-dependent and androgen-independent prostate cancer. FCH uptake was 80 and 60% greater than FDG uptake in androgen-dependent and androgen-independent cell lines. In patient studies FCH detected more local as well as nodal recurrences than FDG. In the same study, the primary prostate cancer had a 2.8-fold greater uptake with FCH–PET than FDG.

Methionine. Only a very limited number of reports are available for the use of methionine. Nilsson and coworkers[140] reported ^{11}C-methionine uptake in most of the lesions in patients with androgen-independent prostate cancer. In another study Nunez and coworkers[60] compared the diagnostic yield of methionine and FDG in patients with rising PSA. They reported methionine not only detected more lesions than FDG but also the intensity of methionine uptake in these lesions was significantly higher than FDG. The sensitivity for detection of soft tissue and bony metastases was 70% for each with methionine compared with 48 and 34%, respectively, with FDG.

^{18}F-Fluoride PET. The bone scan with ^{18}F is reported to be more sensitive and specific than the conventional bone scan[33] to detect bony metastases, particularly if used in conjunction with CT in a PET/CT scanner. The indications to use this scan are the same as for a conventional bone scan. The major limitation of this test at this time seems to be the cost. A cost-effective study in comparison with conventional bone is

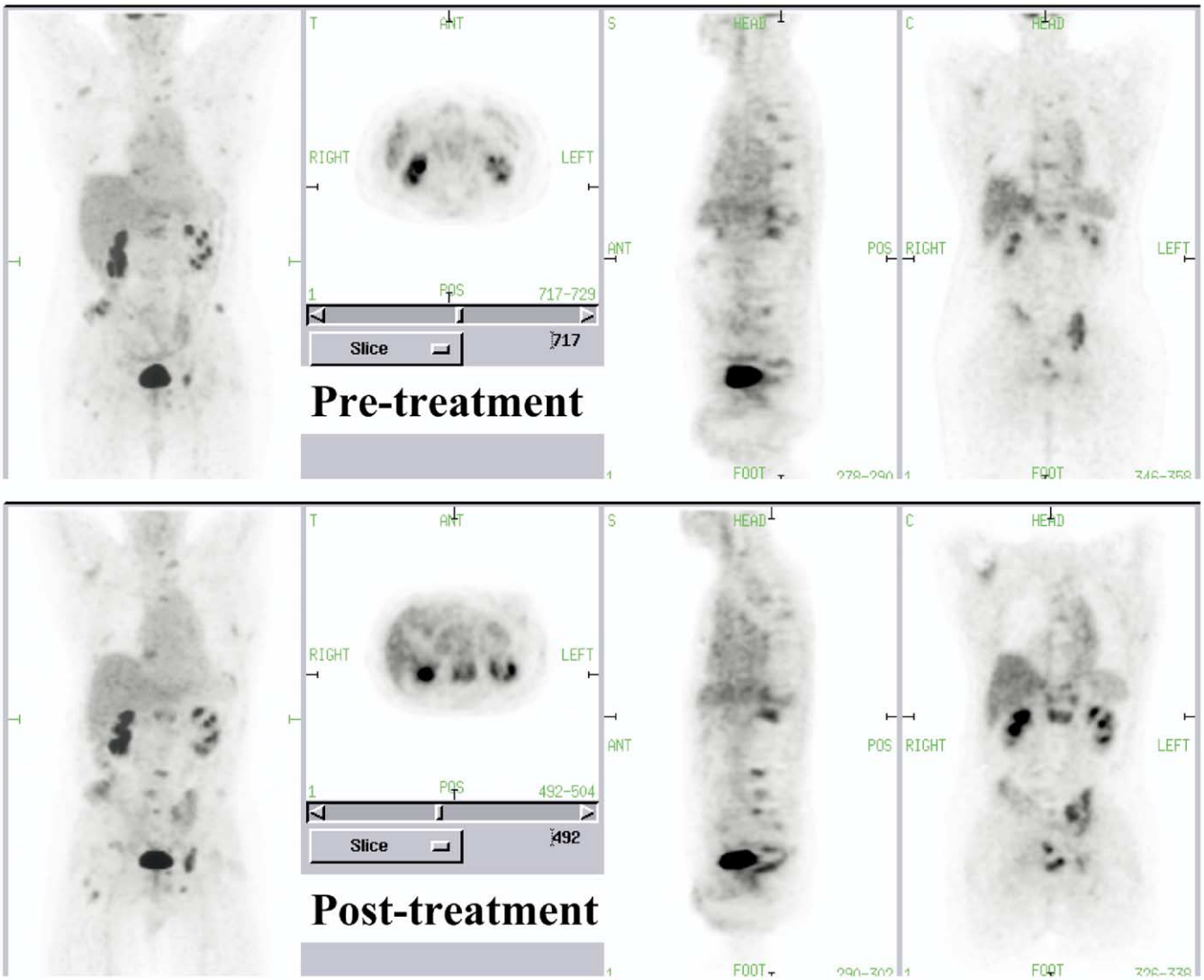

Figure 3 A 66-year-old man with a history of metastatic prostate cancer undergoing systemic hormonal and chemotherapy. Pretherapy whole body FDG-PET scans showed extensive metastatic disease. The posttherapy scans showed no response with further progression to the current treatment.

needed before this study can be used routinely for detection of bone metastases in prostate cancer.

PET/CT. This modality is slowly but steadily gaining popularity in oncology. Any of the above-mentioned tracers can be imaged in this device. This can increase the confidence of the interpreter in identifying a hot spot as physiological versus pathological compared with any of the above PET tracers used alone. Preliminary data suggest that this modality may be helpful in the detection of recurrence in the local soft tissue, nodal, or even bone metastases.[33,57,117,119]

Monitoring Treatment Response

FDG-PET has been shown to play a significant role monitoring treatment response in oncology (Fig. 3).[141] Due to its overall low sensitivity in imaging prostate cancer only a few studies have been conducted using FDG in monitoring treatment response in prostate cancer. Oyama and coworkers[142] reported a decrease in FDG uptake in all FDG-positive lesions at the primary and metastatic sites in 10 patients. Similarly, Morris and coworkers[106] reported a parallel change in mean SUV and PSA after treatment in 75% of (9/12) patients studies. In another study, Kurdziel and coworkers[143] reported a parallel decrease in SUV and PSA during antiangiogenic therapy in patients with androgen-independent prostate cancer. FDG-PET so far has been shown to detect fewer bony metastases from prostate cancer than either the bone scan or CT.[33,104,144] However, bone scans are not useful for monitoring treatment response and may show more intense uptake after treatment due to the "flare phenomenon."[141] FDG-PET may reflect the response to therapy more accurately in this group of patients.[33,145] The only tracer other than FDG studied in this regard is ^{18}F-choline. DeGrado and coworkers[41] found, although the lesions were still visualized on the follow-up scans after the androgen withdrawal in metastatic prostate cancer patients, there was a 60% decline in SUV from baseline.

Testes

Each hemiscrotum contains a testicle measuring approximately 4 to 5 cm in length and 2 to 3 cm in thickness, covered by a dense white fibrous capsule, the tunica albuginea.[146] Nuclear medicine studies have been used to evaluate the acute scrotum (testicular torsion versus epididymoorchitis) and testicular tumors.

Evaluation of Acute Painful Scrotum

The role of scintigraphy in patients with a painful scrotum centers on excluding torsion of the testicle, a condition requiring immediate surgical exploration if testicular viability is to be preserved.[146] Nadel and coworkers[147] introduced scrotal scintigraphy in 1973 as a means to differentiate acute testicular torsion from epididymoorchitis. Both dynamic flow images and static blood pool images are evaluated. Effective use of scrotal scintigraphy is dependent on adequate history and physical examination, accurate positioning and marking of the patient, reliable acquisition of data, and proper interpretation.[146] In this scan interpretation depends on the relative amount of radioactivity present in the affected side compared with the other side. Therefore, it is prudent to determine and record the symptomatic side unequivocally by clinical history and physical examination.[148] Most authors advocate the use of 550 to 750 MBq of ^{99m}Tc-perecthnetate.[146] ^{99m}Tc-Sestamibi has been used in an experimental model to detect changes in testicular blood flow; however, there are not enough clinical data to suggest any significant advantage over ^{99m}Tc-pertachnetate.[146,149,150] Immediate static (blood pool) images comprise the core of the examination and consist of a relatively high-count ($0.3\text{-}1 \times 10^6$/cps) anterior view of the scrotum.[146,148] Either hot or cold linear markers should be placed along the median raphe of the scrotum to delineate the position of the left and right testicles. This is invaluable when asymmetric swelling of the scrotum is present.[146] Blood pool images clearly display a decrease on the affected side in testicular torsion whereas there is an increase in epididymoorchitis.[146,148] A metaanalysis of approximately 1200 patients included in several large series performed before 1990 suggested that the sensitivity of the examination is 96%.[146,151] However, due to easy availability of color Doppler and power Doppler ultrasound in the emergency department, there currently is a trend toward a lesser use of scrotal scintigraphy. At our institution, this has declined to almost zero.

Sonography

Duplex and color Doppler ultrasound have been developed as successful methods for evaluating testicular perfusion in suspected cases of torsion.[146] Power Doppler, a newer technique that encodes the integrated energy of the reflected Doppler signal, has improved the sensitivity in the evaluation of intratesticular blood flow.[146,152,153] The additional benefit of ultrasound is the detection of incidental findings such as hydroceles, varicoceles, cysts, and abscesses.[146,154] The major disadvantage of ultrasound is its intraobserver variability and significantly lower sensitivity in the hands of an inexperienced interpreter.[146,155] However, easy availability, rapid diagnosis, and identification of incidental findings make it the first choice for evaluating acute painful scrotum in the emergency room.

Testicular Cancer

Testicular cancer is the most common cancer of men in the age group between 15 and 35 years except in African–Americans.[156] Primary testicular cancer, or germ cell tumor, occurs in approximately 7000 men and causes 300 deaths per year in the United States.[156] The most common presentation is a painless, hard, testicular lump. Histologically, the testicular tumor can be of germ cell origin or nongerm cell origin. Germ cell tumors include seminoma, embryonal cell carcinoma, teratoma, and choriocarcinoma. About 40% are mixed, ie, contain more than one cell type. Choriocarcinoma is the most aggressive testicular cancer, with a propensity for rapid growth and early hematogenous spread. On the other hand nongerm cell tumors are rare and usually benign. Nongerm cell tumors include interstitial cell (Lydig's cell) tumors and Sertoli's cell tumors. This discussion is restricted to the malignant tumors. Although there are several types of germ cell tumors histologically (as mentioned above), for treatment purposes these are divided into two major groups, seminoma and nonseminoa.[156] Seminomas, which represent approximately 50% of all germ cell tumors, are very radiosensitive. The cure rate for patients with seminoma (all stages combined) exceeds 90%. Nonseminomas tend to metastasize early to the retroperitoneal lymph nodes and lung parenchyma. Tumors with histologic mixtures of seminoma and nonseminoma components are treated as nonseminomas. Increased levels of α-fetoprotein (AFP) in the blood are suggestive of nonseminoma and the tumor should be treated as nonseminoma irrespective of the histology. On the other hand the β-subunit of human chorionic gonadotropin (β-HCG) may be elevated in both and is used routinely as serum tumor marker in conjunction with AFP and lactate dehydrogenase.[157] Testicular cancer spreads via the peritoneal lymphatic system. The scrotal skin drains into the inguinal nodes.[156] Transscrotal needle biopsy or orchiectomy is contraindicated because these procedures can potentially lead to nonperitoneal lymphatic dissemination of the tumor cells. Therefore, imaging plays a very important role in the management of testicular tumors.

Scrotal ultrasound is an excellent imaging modality for the assessment of testicular masses.[156] Testicular microcalcifications are associated with a high propensity for developing seminomas, and patients should be screened by ultrasound.[156] Suspected testicular tumors should be explored via an inguinal incision with early control of the spermatic cord to prevent vascular or lymphatic dissemination of tumor cells.[156] TNM staging is conventionally used for testicular cancer. Accurate staging in the early phases of disease is very important to classify patients into low- or high-risk groups because management differs between the two.[156] In stages II and III, the prognosis depends on the extent of the disease and tumor markers. Currently, initial staging is based on

clinical examination, tumor markers, and CT scan.[103,156] Staging of testicular cancer using conventional imaging modalities has limited accuracy.[158] False-negative rates of 30 to 59% and false-positive rates as high as 25% have been reported using CT for evaluating early stages of testicular cancer.[159,160] After treatment there could be a residual mass on CT. CT is unable to differentiate between residual tumor, fibrosis, necrosis, and teratoma, which diminishes its role in guiding therapy. Ultrasound is even less accurate for initial staging as well as evaluating treatment response. False-negative rates may be as high as 70% with ultrasound.[158,159] To overcome the limitations of conventional imaging modalities, FDG-PET has been investigated as an alternative.

Among nuclear medicine studies FDG-PET and gallium have been used in the evaluation of testicular cancer. FDG-PET in particular has shown promising results for initial staging, detection of recurrent/residual disease, and monitoring treatment response in testicular cancers.

Gallium

Several studies[161] support the utility of gallium scintigraphy in the staging of lymph node metastases from seminoma and embryonal cell carcinoma, while it has poor sensitivity in the evaluation of metastases from teratoma or teratocarcinoma.[162-165] Extraabdominal sites of uptake, such as pleura, bone, lung, and mediastinum, also have been accurately identified.[166] Although residual masses remain on CT, gallium scans often revert to normal after effective radiotherapy or chemotherapy.[165] There has been some initial interest in using gallium to evaluate response to tumor therapy;[165] however, while a positive gallium scan remains highly suggestive of recurrence, a negative scan does not seem to conclusively rule it out.[163,167] The failure of gallium uptake to predict which posttherapy patients will recur[167] severely limits utility of this potential application. The major limitations of gallium are (1) excretion of gallium in the gut limits its ability to evaluate metastases in the abdomen and pelvic lymph nodes, (2) most of the patients undergo surgery as a treatment for testicular cancer, and prior surgery may limit the value of gallium scan, and (3) any inflammatory process such as infection, epididymoorchitis, or sarcoidosis can cause false-positive results. Similar to lymphoma, FDG-PET has now replaced gallium in the evaluation of testicular cancer[141] due to the better quality of scan, better resolution, and superior ability to evaluate abdominal and pelvic lymph nodes. However, gallium may be used when FDG-PET is not available.

PET

Initial Staging. Albers and coworkers[168] in 37 patients with stage I and II found FDG-PET is 70% sensitive and 100% specific, whereas similar values for CT were 40 and 78%, respectively. In this study the 3 false-negative PET results were in 2 small (<0.5 cm) nodal metastases and a mature teratoma. High sensitivity, specificity, PPV, and NPV of 87, 94, 94, and 94% were reported by Cremerius and coworkers.[169] Hain and coworkers[170] found similar results in the initial staging of seminoma and nonseminoma. PET also identified additional unsuspected visceral and bone metastases. Most of the studies suggested that PET is superior to CT.[103] However, in a small number (12 patients) of patients with stage I and II nonseminoma, Spermon and coworkers[171] reported equivalent results for PET and CT.

Residual/Recurrent Disease

Most patients with bulky nodal disease have residual mass after treatment. In this situation viable tumor cells inside the mass require further treatment, whereas fibrosis or necrosis requires watchful follow-up. Unnecessary radiotherapy or chemotherapy can potentially increase the short-term as well as long-term toxicities. Considering the fact that these individuals are young and most of them will live more than 15 to 20 years when cured, they are more likely to experience the long-term toxicities. Although tumor markers are very useful in this regard, occasionally they may be misleading and not helpful to locate the site of recurrence/residual.[156] Imaging plays a significant role in locating the residual/recurrent disease noninvasively. Conventional imaging modalities including CT cannot confirm the presence of viable tumor cells in a residual mass. FDG being a metabolic imaging modality has better results.[103] Stephen and coworkers[172] and Sugawara and coworkers[173] reported that FDG-PET was able to differentiate viable tumor from fibrosis in the posttreatment residual masses. However, the major limitation of PET is mature teratoma, which is usually negative in the FDG-PET scan but can cause a false-positive result if there are any inflammatory changes associated with it. In a series of 70 patients, Hain and coworkers[174] reported sensitivity, specificity, PPV, and NPV of 88, 95, 96, and 90%, respectively, for FDG in differentiating viable tumor from fibrosis or necrosis or mature teratoma. Sanchez and coworkers[175] found that FDG-PET can detect relapse earlier than CT. Several other studies.[103,171,172,174,176-178] conducted in patients with seminomas or nonseminomas have shown that FDG-PET is superior to CT in this regard.

Monitoring Treatment Response

FDG-PET has been shown to predict response to chemotherapy, similar to high-grade lymphomas (Fig. 4). Bokemeyer and coworkers[179] reported that FDG-PET accurately predicts the outcome of high-dose chemotherapy in 91%; in comparison CT accurately predicted outcome in 59% cases and tumor markers predicted the correct response in only 48% of cases.

Urinary Bladder

The clinically important disorders of urinary bladder are cystitis, vesicoureteral reflux disease, disorders related to voiding,[180] and carcinoma of the urinary bladder.

Cystitis

Inflammation of urinary bladder may be infectious or noninfections in etiology. The most common cause of infectious cystitis is *Escherichia coli* bacteria. Symptoms, signs, and urinanalysis are sufficient for diagnosis. Imaging mo-

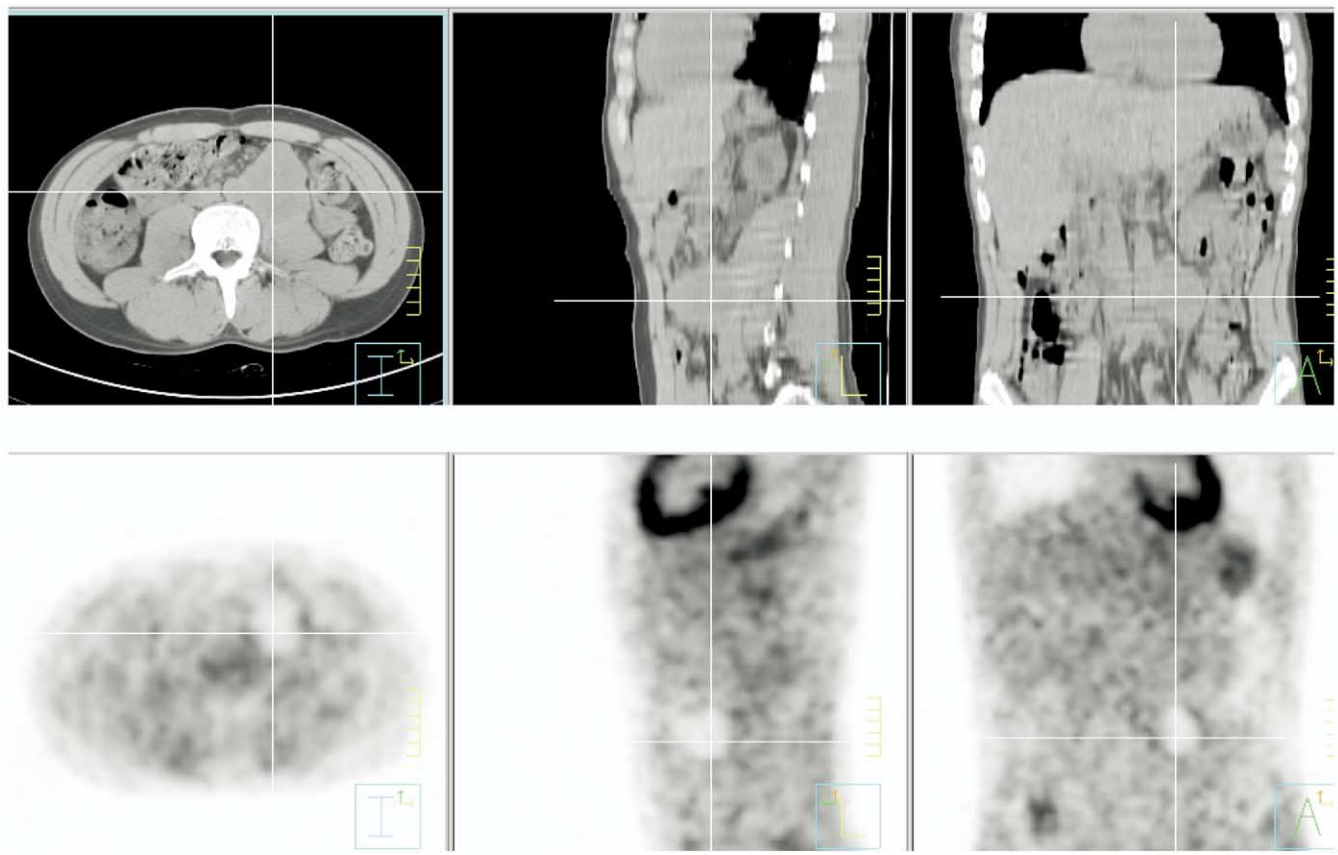

Figure 4 A 24-year-old man with a history of testicular cancer [mixture of teratoma (80%) and germ cell tumor], status postsurgical resection and chemotherapy. PET/CT was performed 4 weeks after chemotherapy; CT continues to show a large paraaortic mass; however, FDG-PET showed a photopenic lesion with very mild uptake at the periphery of the lesion. Subsequent excision biopsy of the lesion showed only necrotic tissue with surrounding inflammation; no tumor cells were found in the specimen.

dalities do not play any significant role. However, a more serious infection involving the kidneys requires more aggressive management and occasionally presents with similar findings in the history, physical examination, and urinanalysis. In this case imaging is indicated. The gallium scan has been shown to differentiate pyelonephritis from cystitis. Janson and Robert[181] found unique patterns to differentiate cystitis, ureteritis, pyelonephritis, and renal or perirenal abscesses. In this study they used a combination of antibody-coated urinary bacteria by measured immunofluorescence, ^{131}I-hippuran, and ^{67}Ga-citrate. Hurwitz and coworkers[182] reported that gallium is 86% accurate in differentiating pyelonephritis from cystitis. Traisman and coworkers[183] used ^{99m}Tc-labeled glucoheptonate and compared it with gallium to localize urinary tract infection. They found gallium and glucoheptonate can detect 86% of cases accurately, whereas renal ultrasound or intravenous pyelogram were able to detect only 24%. All of these studies localized the disease by identifying the pyelonephritis not cystitis. More recently Lin and coworkers[184] reported ^{67}Ga uptake in the bladder wall in lupus cystitis and Palestro and coworkers[185] used ^{111}In-labeled WBC to image chemical cystitis. Renal imaging in infection is reviewed in more detail in the article on pediatric renal studies.

Vesicoureteric Reflux

Untreated vesicoureteric reflux (VUR) and urinary tract infection are associated with subsequent renal damage, hypertension, and chronic renal failure. Gleeson and Gordon[186] found, in children over 1 year of age, the group with a renal scar had a higher frequency of VUR than those without scars. VUR by itself is not harmful. Sterile reflux does not appear to cause renal damage unless it is severe. Reflux of infected urine is responsible for the subsequent renal damage. The goal of therapy is to prevent infection of the kidney until reflux resolves spontaneously. VUR is a common disease in children. Normally, as a child grows, the ureter grows in length more than diameter, resulting in decreased incidence of reflux and eventually resolution of VUR in 80% of cases. If the high-grade VUR does not resolve with age or is present in adults with recurrent urinary tract infection, a surgical correction of the vesicoureteral junction is required. After diagnosis, these children need serial follow-up imaging to evaluate the progress of the VUR. Therefore, it is important that an

imaging modality not only should be sensitive but also should provide the least amount of radiation. The two imaging modalities that provide adequate diagnostic ability to be used are the conventional contrast-enhanced micturating cystourethrogram (MCU) and radionuclide cystography. The radionuclide method is reported to be more sensitive than conventional MCU for detection of VUR and the overall radiation dose is approximately 1/20 that used for MCU.[187,188] There is 1/50 to 1/200 the radiation to the gonads with the radionuclide method compared with the MCU.[189] ^{99m}Tc-sulfurcolloid is the most commonly used radiotracer for this purpose; however, ^{99m}Tc-MAG3 and DTPA also have been used. The test was first described with pertechnetate.[189] Any radioactivity above the bladder activity is considered abnormal. Generally, reflux is considered minimal when confined to the ureter, mild to moderate when it reaches the pelvicocalyceal system, and severe when a distended collecting system and /or redundant ureters are noted. One of the advantages of nuclear medicine studies is the ability to quantify the amount of reflux, which is not possible with MCU.[190] The radionuclide technique permits detection of reflux volumes on the order of 1.0 mL. Two forms of commonly used radionuclide cystography are direct and indirect. The indirect method is performed as part of routine dynamic renal scan with DTPA or MAG3. The child is asked not to void until the bladder is maximally filled and at that time a prevoid image of the urinary bladder is obtained. Dynamic images are then acquired continuously during voiding and subsequently a postvoid image is also obtained. Although this is a noninvasive procedure compared with the direct method, the disadvantages associated with this method are upper urinary track stasis that often poses a problem for interpretation. Good renal function is necessary, and this method can miss up to 20% of VUR, which occurs during filling phase only. The sensitivity and specificity of the indirect method using DTPA were reported to be 74 and 90%, respectively.[191-193] The direct method requires catheterization of the urinary bladder. It usually is performed as a three-phase procedure, with continuous monitoring during filling of the bladder, during voiding, and after voiding. One of the greatest advantages of this method is the possibility of combining with pressure measurements so that a full urodynamic assessment of the bladder can be made.[194]

Disorders of Voiding

Storage of urine and voiding has to be accomplished within a pressure limit to protect the upper urinary tract and kidneys. Any disease involving either the bladder or the urethra can affect voiding, leading to change in intravesical pressure, flow rate, or both. The common diseases, which involve the voiding function of the urinary bladder, are incontinence, neurogenic bladder, sphincter–detrusor dissynergy, and urethral stricture or posterior urethral valve. Proper diagnosis of these disorders requires the study of voiding function. The study of true voiding function involves concurrent recording of pressure and flow. When flow rate is low, it is difficult to distinguish between outflow tract obstruction and inadequate detrusor contraction unless the intravesical pressure is measured. Similarly, normal flow can be achieved despite increased sphincter activity or lack of complete relaxation if detrusor contraction is increased to overcome the outlet resistance. Conventionally, a urodynamic study deals with all of the functions of the lower urinary tract. It constitutes urine flow studies (uroflowmetry), cystometry, urethrometry, and electromyography of the sphincter. Nuclear medicine studies have attempted to derive the parameters of uroflowmetry and cystometry. During radionuclide cystography (described above), if the voided urine volume and activity are measured and correction factors are applied for decay and attenuation, then full and residual bladder volumes, and maximum urine flow rate, can be quantified.[190] The other parameters usually obtained from a conventional uroflowmetric study, ie, delay time, voided volume, voiding time, average flow rate, and time to maximum flow rate, can be obtained also from a radionuclide cystrographic study. In comparison to conventional cystometry, radionuclide cystography normally does not provide any intravesical pressure calculation, one of the most important parameters. However, there have been attempts to estimate the pressure–flow relationship through mathematical modeling. Backman and coworkers[195] proposed a relationship between pressure and flow considering the urethra as a round, straight, uniform, rigid tube. In practice, the urethra is not a round, straight, rigid tube. Subsequently, Jana and coworkers[180,196] attempted a mathematical model to derive intravesical pressure from uroflowmertic parameters obtained from radionuclide cystography. In this model, the urethra was considered as an elastic, nonuniform tube and the flow of urine inside the urethra was considered as turbulent in nature. However, the full potential of these models has never been validated by any well-defined clinical studies. Therefore, conventional cystometry/urodynamic study is still the modality of choice to evaluate a pressure–flow relationship of the urinary bladder.

Bladder Cancer

In the United States, bladder cancer is the fourth most common malignancy in men.[197] Most of the newly diagnosed bladder cancers are low grade and noninvasive.[33] There is a high grade cancer also, which is characterized by rapid progression with local invasion, extension to the adjacent organs, and development of regional and distant metastases.[33] The invasive disease confined to the pelvis is treated with radical cystectomy and pelvic lymphadenectomy. The cure rate of organ-confined bladder cancer is more than 70%.[198-200] On the other hand the presence of lymph node metastases increases the chance of recurrence and distant disease, and this group has a 5-year survival of only 20 to 25%.[198-201] Preoperative diagnosis of local extension would help to select appropriate bladder-sparing

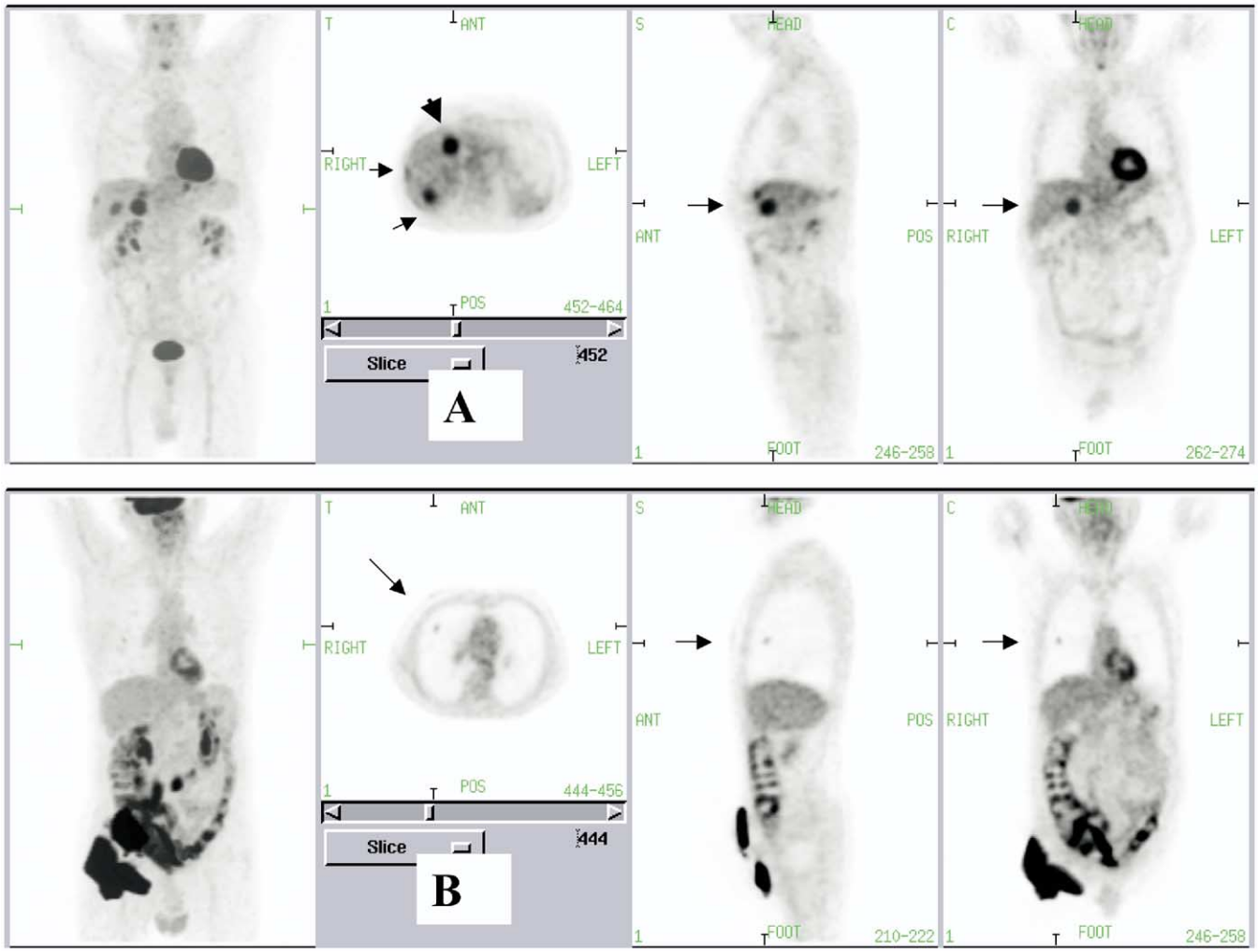

Figure 5 (A) A 70-year-old man with a history of bladder cancer, status post surgical resection of the bladder cancer; recent CT scan showed liver lesions. FDG-PET scan showed multiple areas of intense focal uptake (arrows) suggestive of liver metastases. (B) A 74-year-old man with a history of bladder cancer, status post radical cystectomy and found to have lung nodule in CT. FDG-PET showed intense FDG uptake in the right lung nodule (arrow) suggestive of metastases.

surgery, nerve- or vaginal-sparing operations, or pelvic exenteration. Historically, the staging of bladder cancer with various imaging modalities has been limited. CT scanning can detect only gross tumor extension beyond the bladder wall with an accuracy of 64 to 92%.[202] The accuracy of CT in detecting lymph node metastases ranges from 70 to 90% with false-negative rates as high as 40%.[203] Similarly, MRI has been disappointing with regard to staging, with accuracies ranging from 60 to 75%.[204] The major limitation of these imaging modalities is the dependence on nodal size and anatomical changes to make a diagnosis of cancer. Given the ability of PET to detect differential metabolic activity, investigators have begun exploring the use of PET to stage bladder cancer.

The role of FDG-PET in the detection of localized bladder cancer is limited because of the difficulty in differentiating radiotracer activity excreted into the urine from tumor activity in the bladder or adjacent lymph nodes. However, FDG-PET has demonstrated some utility in identifying distant lymph node involvement and distant disease (Fig. 5). Kosuda and coworkers[205] reported that PET imaging identified 17 of 17 patients with metastatic disease (lung, bone, and remote lymph nodes) as well as 2 of 3 patients (67%) with localized lymph node involvement. Similarly, Heicappell and coworkers reported a 67% detection rate for local nodal disease.[100] Investigators have attempted to improve the sensitivity of PET by using tracers that are not excreted in the urine. Ahlstrom and coworkers[206] found ^{11}C-methionine is superior to FDG, however, tumor was identified with a sensitivity of 78% (18/23) only with methionine PET. They also reported that tracer uptake was proportional to tumor stage. ^{11}C-Choline, another tracer minimally excreted in the urine, was studied by de Jong and coworkers[207] in 18 patients with bladder cancer before cystectomy and 5 volunteers. Normal bladder showed little uptake. The primary tumor was visualized in 10 patients with residual invasive diseases in the cystectomy specimen (mean SUV, 4.7 ± 3.6,

Table 2 Role of PET in Prostate, Bladder, and Testicular Cancer[20,22,23,33,73,103,109,158]

Cancer Agents	Localized Primary	Tumor (T) Staging	Nodal (N) Staging	Metastases (M) Staging	Assessment of Aggressiveness (Prognosis)	Monitoring Treatment Response
Prostate						
FDG	Not useful	Not useful	Not useful	Somewhat useful	Useful	Useful
Acetate	Probably useful	Not useful	Useful	Useful	Not useful	Limited data
Choline	Probably useful	Not useful	Useful	Useful	Not useful	Limited data
Methionine	Not useful	Not useful	Not useful	Useful	Not useful	Useful
FDHT	Not useful	Not useful	Not useful	Not useful	May be useful	Limited data
Bladder						
FDG	Not useful	Not useful	Not useful	Useful	Limited data	Useful
Choline	May be useful	Not useful	May be useful	May be useful	Not useful	Limited data
Methionine	May be useful	Not useful	May be useful	May be useful	Limited data	Limited data
Testes						
FDG	May be useful	Not useful	Good	Good	May be useful	Excellent

FDG, fluorodeoxyglucose; FDHT, fluoro-dihydrotestosterone.

range, 1.5-13.0). Utility of FDG-PET in the evaluation of bladder cancer seems to be limited to the evolution of distant metastases. Table 2 summaries the role of PET scans in prostate, bladder, and testicular cancer.

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