

Review

Recent Advances in Prostate Cancer (PCa) Diagnostics

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Abstract: Prostate cancer (PCa), which is among the most prevalent types of cancer in men, is a prominent topic in imaging research. The primary aim of PCa imaging is to acquire more accurate characterizations of the disease. More precise imaging of the local stage progression, early discovery of metastatic cancers, reliable diagnosis of oligometastatic cancer, and optimum treatment response evaluation are areas in which contemporary imaging is quickly improving and developing. Imaging techniques, such as magnetic resonance imaging (MRI) for the whole body and molecular imaging with combined positron emission tomography (PET), computed tomography (CT), and MRI, enable imaging to support and enhance treatment lines in patients with local and advanced PCa. With the availability of multiple imaging modalities for the management of PCa, we aim in this review to offer a multidisciplinary viewpoint on the appropriate function of contemporary imaging in the identification of PCa.

Keywords: prostate cancer; diagnostic tests; imaging techniques

1. Introduction

PCa is a heterogeneous disease with a longer natural history than other solid tumors and a wide range of behavioral and biological activity ranging from inactive to aggressive behavior [1,2]. According to the American Cancer Society, there were 248,530 new cases of PCa and more than 3.1 million survivors in the United States in 2021. Prostate cancer was considered the second leading cause of cancer-related death among men in the United States in 2021, after lung cancer [3]. Additionally, males of African ancestry have a greater risk of PCa than those of European ancestry [4]. Despite the early diagnosis of PCa, the risk/benefit ratio of the treatment remains uncertain and is one of the most challenging and disputed areas of medicine because of the significant morbidity associated with the therapy [5,6].

Historically, imaging had a minimal role in diagnosing locally advanced PCa. Transrectal ultrasound (TRUS) was the only modality that was successfully employed during diagnosis and was primarily used to guide biopsies [6]. The bone scan (BS) and computed tomography (CT) are typically used in patients who are at an increased risk of developing advanced disease. However, PET/CT scanning with tracers, high-field endorectal coil MRI,

and contrast-enhanced TRUS improve the detection of locally progressed PCa [7]. Each imaging method has its own set of pros and cons and a subset of indications for best uses within the setting of PCa [8]. In our review, we try to summarize each imaging modality's role and its impact on the management of PCa.

2. Localized PCa Diagnosis

2.1. Digital Rectal Examination (DRE)

DRE is one of the most frequently used methods for the early identification of PCa. The DRE is a low-cost test that evaluates the prostate's size, consistency, mobility, and form abnormalities. However, we cannot rely on size alone as a PCa risk indicator, and there is no correlation between DRE-estimated prostate volume and TRUS-measured volume [9,10]. Furthermore, similar indurations may be caused by calculi or benign prostatic hypertrophy (BPH), whereas carcinomas are felt as hard irregular nodules. This implies that when any induration is felt the provider must request more tests, such as TRUS, and repeat the DRE regularly to identify any changes or advancement [11]. Additionally, the DRE requires technical proficiency. Not all examiners can palpate the prostate's whole posterior surface [12,13].

There is considerable doubt that early detection approaches such as the digital rectal examination (DRE) and serum PSA testing contributed significantly to the decades-long decline in PCa stage progression [14]. Since 1988, the rate of metastatic disease detected through standard physical examinations has decreased considerably [15]. At the time of diagnosis, 70% to 80% of PCa are organ-confined, pathologically. Recent studies show that PSA screening of early-stage prostate cancer patients is more often prostate-confined than those found only through DRE [14,16].

The value of DRE may be questioned due to conflicting findings regarding the effectiveness of PCa screening in reducing morbidity and mortality. Nonetheless, due to the disease's prevalence and the potential to detect it while it is curable, many patients and clinicians opt for screening [13]. A recent meta-analysis showed that the pooled sensitivity and specificity of DRE conducted by primary care practitioners to detect PCa were 0.51 and 0.59, respectively. The aggregated positive predictive value (PPV) was 0.41, and the aggregated negative predictive value (NPV) was 0.64 [10]. As determined by Grades of Recommendation Assessment, Development, and Evaluation (GRADE), the quality of evidence was inferior.

Additionally, when DRE is performed to screen males over the age of 50 for PCa, the cancer detection rate is 3.2%, with a 21% PPV, a sensitivity of 21%, and a specificity of 86% [17]. Thus, DRE should be used in combination with a prostate-specific antigen (PSA) test in PCa screening to increase the overall sensitivity. Whereas DRE detected PCa at a rate of 3.2%, PSA detected it at a rate of 4.6%, and the two procedures together detected it at a rate of 5.8%. Notably, the two tests' detection rates separately are slightly close, and when combined, they identify a higher number of instances with PCa [13,18].

2.2. Transrectal Ultrasound (TRUS)

Holm and Gammelgaard established TRUS-guided biopsies as the gold standard technique for prostate cancer diagnosis [19]. Due to its widespread availability and low cost, TRUS is the most often utilized clinical imaging modality for PCa. TRUS is primarily used to determine the prostate's volume, guide biopsy placement, and implant brachytherapy seeds. However, it is deemed insufficient for detecting or staging prostate cancer. Of note, contrast agents and computer-assisted methods have been examined as ways to enhance TRUS diagnostic performance.

While gray-scale TRUS is ineffective in detecting prostate cancer consistently and therefore cannot be used in place of systematic biopsies, it has established itself as the gold standard for prostate biopsy guidance. Since PCa can present with different intensities such as hypo-, iso-, or hyperechoic [20], the sensitivity (46–91%) and specificity (18–96%) are relatively varied [21]. The increasing number of patients with elevated PSA but normal

DRE highlights the critical need to develop more accurate TRUS-based procedures to improve the diagnostic equipment predictive values, specificity, and sensitivity [22,23].

Due to increased tumor vascularity, contrast-enhanced TRUS utilizing intravenously administered microbubble contrast agents has been demonstrated to improve PCa detection [24]. The bulk of modern ultrasound machines are equipped with ultrasonic technology capable of scanning microbubble contrast agents. In addition, because cancers are often associated with increased blood flow, targeted prostate biopsies may be conducted [25]. A study of 1776 males scheduled for their first or subsequent biopsy showed that collecting five targeted biopsy cores from hypervascular areas in the peripheral zone resulted in a slightly better detection rate (26.8%) than doing ten systematic core biopsies (23.1%) [26]. However, the specificity of this approach is hampered by benign prostatic hyperplasia and prostatitis hypervascularity, which might provide false-positive findings [27].

However, Taverner et al. randomly assigned 300 patients with a negative DRE and a PSA level less than 10 ng/mL to one of three groups: systematic biopsy guided by TRUS, color Doppler ultrasound-guided biopsy, or color Doppler ultrasound-guided biopsy prior to and during contrast agent injection. According to the authors, there was no statistically significant variance in the frequency of PCa detection between the three methods [28].

In another study, Loch et al. created a computer-based TRUS signal analysis (C-TRUS) approach for collecting signal information from serial static TRUS pictures independent of the ocular gray scale, hence improving PCa diagnostic imaging [29]. Further technological advancements resulted in the development of a network-compatible module that enables remote users to input photographs, which are then re-transmitted as tagged images through the internet after analysis [24,30]. C-TRUS offers the benefit of requiring no extra equipment aside from a storage system for digital ultrasound pictures. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 83%, 64%, 80%, and 68%, respectively, when preoperative C-TRUS pictures were compared to tumor localization in 28 patients having radical prostatectomies [31]. Combining multiparametric MRI with C-TRUS appeared to improve PCa detection in a study of twenty individuals suspected of having the disease. In this analysis, PCa was detected in 58% of instances, which is comparable to the results of large-scale C-TRUS investigations [32].

Furthermore, ultrasonography was combined with real-time elastography, which is a technique that uses physical compression and relaxation to detect changes in tissue compliance. The sensitivity, specificity, PPV, and NPV of this approach were previously reported to be 50%, 72%, 76%, and 44%, respectively [21]. Another study employed elastography and contrast-enhanced ultrasound (CEUS). Elastography indicated a sensitivity of 49% and a specificity of 74% in 86 PCa patients. The percentage of false positives was lowered from 34.9% to 10.3% when elastography was combined with CEUS, while the PPV for cancer diagnosis increased from 65.1% to 89.7% [33]. However, the findings show that elastography is less effective when the gland volume is larger and the lesions are located anteriorly. Additionally, it has been demonstrated that elastography is more sensitive to identifying PCa lesions with a higher Gleason score, a diameter greater than 5 mm, and extracapsular extension [34,35].

2.3. Magnetic Resonance Imaging (MRI)

MRI plays a critical role in detecting PCa [36]. Regarding traditional (T2W) MRI, Hambrock et al. [37] found that 59% of prostate cancer patients with a minimum of two prior negative biopsy sessions could be identified using a 3-Tesla scanner and an average of just four sample cores. However, it is crucial to stress that the majority of these tumors (57%) were detected in the ventral transitional zone and the anterior horns of the peripheral zone (11%), suggesting a carefully selected group of participants. Before the biopsy, conducting an MRI resulted in a 41.2% PPV and an 83.0% sensitivity [38].

Multiparametric MRI has made dramatic inroads into the management of localized PCa over the last five years. International rules are steadily promoting the use of MRI

before the biopsy. This presents a widespread shift in the management of localized PCa, which has traditionally been guided by biopsy histology rather than imaging [39].

The current findings indicate that including prebiopsy MRI into the diagnostic tool kit for clinically suspected PCa enhances the detection of clinically relevant illness, lowers biopsy-related complications, and may even eliminate unnecessary biopsies in some patients [40]. New guidelines for PCa analysis and management from the United Kingdom National Institute for Health and Care Excellence (NICE) recommend that all persons with suspected clinically localized PCa undergo multiparametric MRI as a first-line investigation [41]. However, the American Urological Association (AUA) guidance suggests that there is a lack of sufficient evidence to support routine MRI use in each biopsy-naïve subject and confined its utility to males whose clinical examinations for biopsy are undefined (normal PSA with abnormal DRE, minimal PSA elevated, or very young or old subjects) [42].

Multiparametric MRI gives biopsy target data and can serve as guidance for conducting a focused prostate biopsy [43,44]. In this situation, an MRI-guided biopsy of the prostate will detect clinically significant cancer in 34% to 41% of males with a previous negative biopsies. In addition, numerous meta-analyses have reported that targeted biopsies have resulted in increasing identification rates of clinically relevant PCa compared to systemic biopsies in a repeat biopsy context [45–47].

In a recent systematic review, MRI had a pooled sensitivity of 72% and a pooled specificity of 96% compared to a template-guided biopsy. In contrast, the pooled sensitivity for systematic biopsy was 62%, and the specificity was 100% [47]. With time, we anticipate that advancements in MRI will make further contributions to PCa diagnosis.

2.4. Computed Tomography (CT)

CT has a minor role in the identification of PCa and is not advised for reasons such as low prostate soft-tissue resolution and poorly defined gland margins. However, CT is sometimes used for nodal staging of PCa [48]. A recent study showed that CT, in conjunction with deep learning, has the potential to perform comparably to diagnostic pipelines based on MRI [49], suggesting enhancements in the diagnostic capability of CT are potentially forthcoming.

3. Advanced PCa Diagnosis

3.1. Positron Emission Tomography (PET)

PET has displayed significant superiority in the recognition of extra-prostatic disease (Figure 1) [50]. Multiple PET tracers are available for PCa detection. The clinically available tracers include 18F-sodium fluoride (18F-NaF), fludeoxyglucose (FDG), 18F-choline, 11C-choline, 68Ga-prostate-specific membrane antigen (PSMA), and 18F-fluciclovine, a tracer newly approved by the U.S. Food and Drug Administration (FDA) [51].

Despite its poor sensitivity of 33% for detecting primary lesions, FDG caught nodal or bone metastatic disease in six out of nine participants [52]. Notably, FDG is more sensitive in detecting metastatic lesions than primary lesions, which might be explained by the increased metabolic activity of metastatic lesions [53].

In a study involving 24 patients who had a biochemical relapse and underwent FDG PET before the dissection of pelvic lymph nodes, the authors found that specificity, sensitivity, PPV, and NPP were 100%, 75.0%, 100%, and 67.7%, respectively, for nodal detection [54]. However, in a prospective study involving 37 patients with a biochemical relapse but negative findings on imaging, the investigators noticed a superior detection rate using NaF PET/CT compared to FDG PET/CT, which has limited efficacy in detecting metastases [55].

Concerning choline PET/CT, two large meta-analyses examining its utility in the staging of nodal disease showed high specificity with variable sensitivity; however, sensitivity increased in higher-risk cases with nodal disease [56,57]. In one meta-analysis of 609 patients, choline PET/CT demonstrated a pooled specificity of 92% and a sensitivity

of 62% in assessing pelvic nodal disease at staging [56]. In another study of 1270 cases, C-11-choline PET/CT showed a pooled assessment rate of 62%, specificity of 89%, and sensitivity of 89% in detecting any relapsed disease [58].

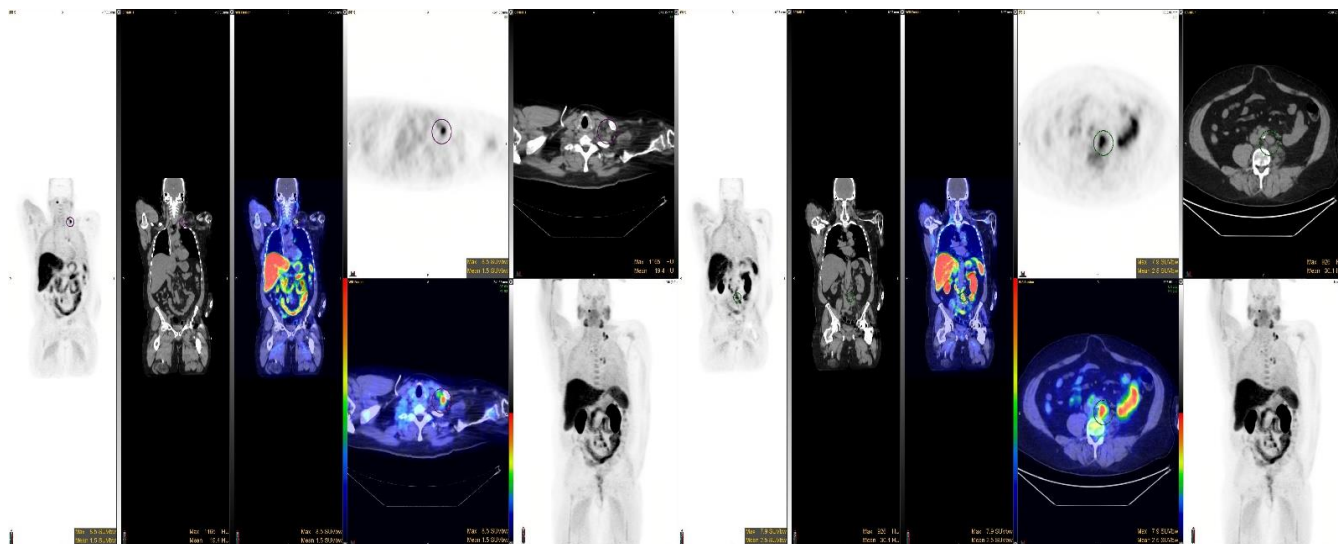


Figure 1. Choline PET/CT shows the extra-prostatic extension of PCa with involvement of left supraclavicular and retroperitoneal lymph nodes.

Although 16 trials using ^{18}F -choline with or without ^{11}C -choline demonstrated a satisfactory pooled sensitivity of 75.4% and a specificity of 82%, additional studies have shown that MRI remains the preferable approach in detecting local recurrence [59].

The PSA levels influence the disease detection with choline PET/CT in biochemical relapse. A study of C11-choline PET/CT in 4426 cases showed that a PSA level greater than 1.16 ng/mL was a positive predictor of the scan. The positive ^{11}C -choline scan rate increased with high PSA levels in 358 cases with biochemical relapse. With PSA levels between 0.2 and 1 ng/mL, the detection rate of the ^{11}C -choline scan was 19%, and for PSA levels between 1 and 3 ng/mL, 46% of scans were positive. Finally, with a PSA level >3 ng/mL, 82% of scans were positive [60].

Another imaging modality is prostate-specific membrane antigen (PSMA) PET/CT scan, which is a surface protein found on prostate cells expressed differently than in other tissues. PSMA overexpression is reported in PCa cells and can be detected using gallium-68-labeled PSMA ligands via PET/CT imaging (PSMA-PET/CT) [61]. The PSMA-PET/CT lymph node (LN) staging sensitivity and specificity were 65.9% and 98.9%, respectively, according to a retrospective study of 130 intermediate- to high-risk PCa patients who also underwent radical prostatectomy (RP) with pelvic LN dissection [62]. According to a meta-analysis, the PSMA-PET/CT sensitivity and specificity were recently reported to be 71% and 95%, respectively, in pelvic LN metastasis detection [63]. PSMA-PET scan is considered a promising mode of imaging for diagnosing positive lymph nodes.

Hybrid PSMA PET/mp-MRI improves the diagnosis of suspicious lesions on MRI and may also assist in better fusion biopsy guidance in patients who have previously had negative biopsies and had intratumoral bleeding, as intratumoral bleeding would impact mp-MRI results. Notably, PSMA has a higher sensitivity than choline or acetate PET in detecting nodal and distant metastasis [64].

The combination of mp-MRI and PSMA PET also has the potential to serve as a single comprehensive staging modality in intermediate- to high-risk PCa. However, PSMA PET has mainly been investigated in the context of detecting disease recurrence [65]. In a study of 248 patients who underwent RP and experienced biochemical recurrence, Eiber et al. observed an 89.5% detection rate using ^{68}Ga -PSMA PET. Faster PSA velocity and levels

of more than 2 ng/mL correlated with the highest detection rate [66]. In both post-RP and post-RT patients, ^{68}Ga -PSMA PET had higher detection rates than choline PET in detecting local and distant recurrence [66,67]. This was especially evident during the early stages of PSA rise (0.5–1 ng/mL) when choline PET was only shown to be positive in a few cases [2,65].

^{18}F -DCFPyL is another PSMA-based PET ligand with exceptional staging performance in clinical trials (Figure 2). For example, in a study of over 400 patients with PC of all Gleason grades, ^{18}F -DCFPyL demonstrated a detection rate of over 90% in patients with a PSA of 0.5 ng/mL and approximately 50% for PSA levels <0.5 ng/mL [68]. One of the drawbacks of PSMA is its uptake in a diverse range of nonmalignant conditions such as bone-related conditions, inflammatory and infectious processes, and benign tumors; however, many factors should be considered to decrease the bias in reporting, such as topography, distribution, and PSMA uptake intensity [68,69].

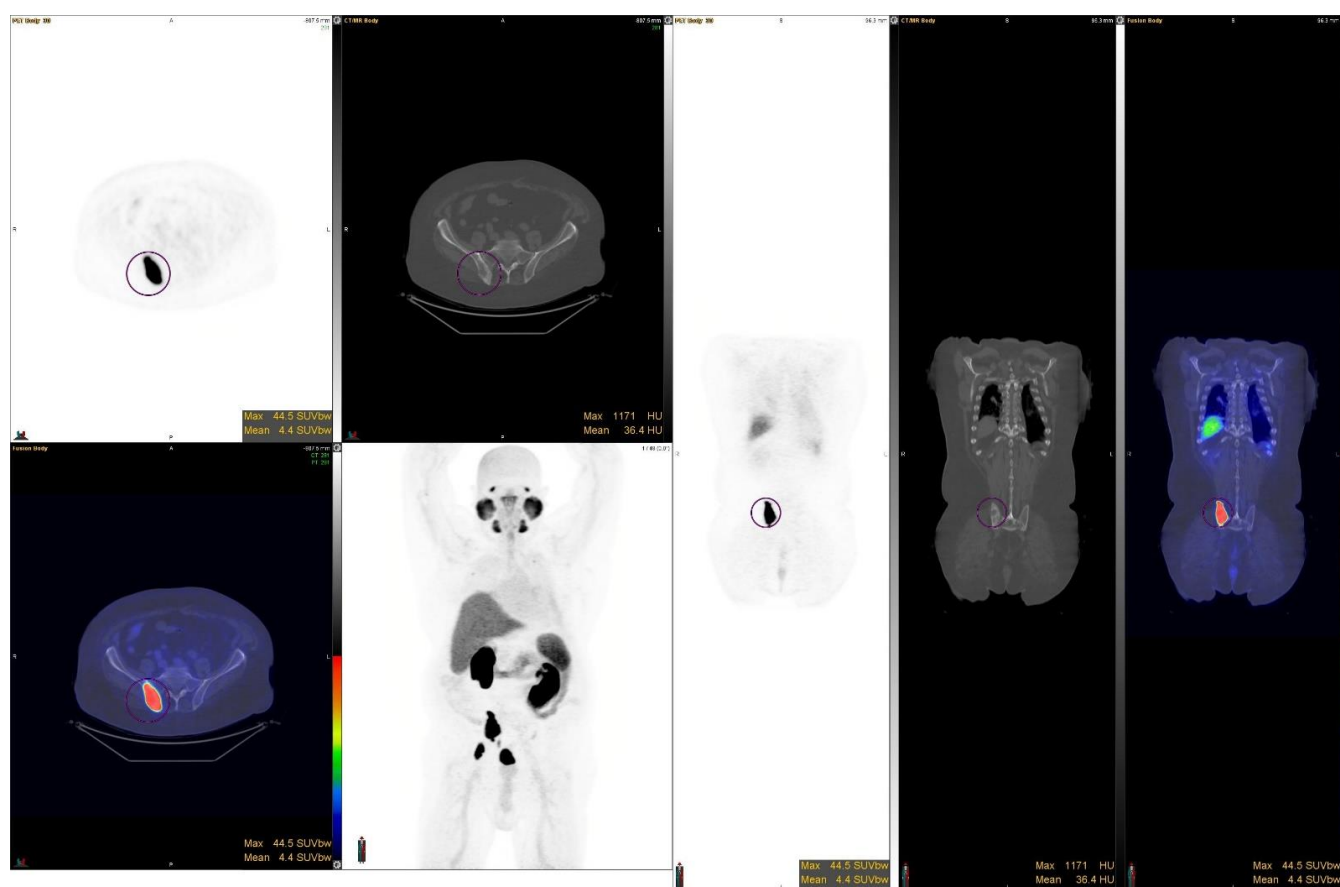


Figure 2. F-18 Pyl PSMA PET/CT demonstrates the distribution of PCa metastasis at pelvic bones.

Another PSMA-based PET ligand is ^{64}Cu -PSMA PET/CT. A prospective cohort of 23 individuals with intermediate- to high-risk prostate cancer who had radical prostatectomy with extensive pelvic LN dissection was studied. The researchers discovered that ^{64}Cu -PSMA PET/CT had a sensitivity of 87.5 percent, specificity of 100%, PPV of 100%, and NPV of 93.7% in identifying LN metastasis [70].

3.2. Bone Scan (BS)

A meta-analysis that included 12 articles investigating the BS revealed a pooled sensitivity of 0.79 and a specificity of 0.82 for bone metastases diagnosis [71]. However, the sensitivity and specificity were enhanced when combined with a minimal CT dose or single-photon emission computed tomography (SPECT) with CT. The combination of

SPECT-CT with BS raised the sensitivity from 70% to 87–92% [72]. Of note, metastases are not directly imaged by BS, but instead, this modality detects the osteoblastic response to the presence of tumor cells. However, a bone scan only detects bone metastases in <1% of cases with PSA < 20 ng/mL (Figure 3) [73,74]. Notably, the detection rate of bone scans rises in concordance with increased PSA levels. Specifically, the detection rates for the metastases were 2.3% in cases with a PSA level of ≤ 10 ng/mL, 5.3% in cases with a PSA level of 10.1–19.9 ng/mL, and 16.2% in cases with a PSA level of 20.0–49.9 ng/mL [75].

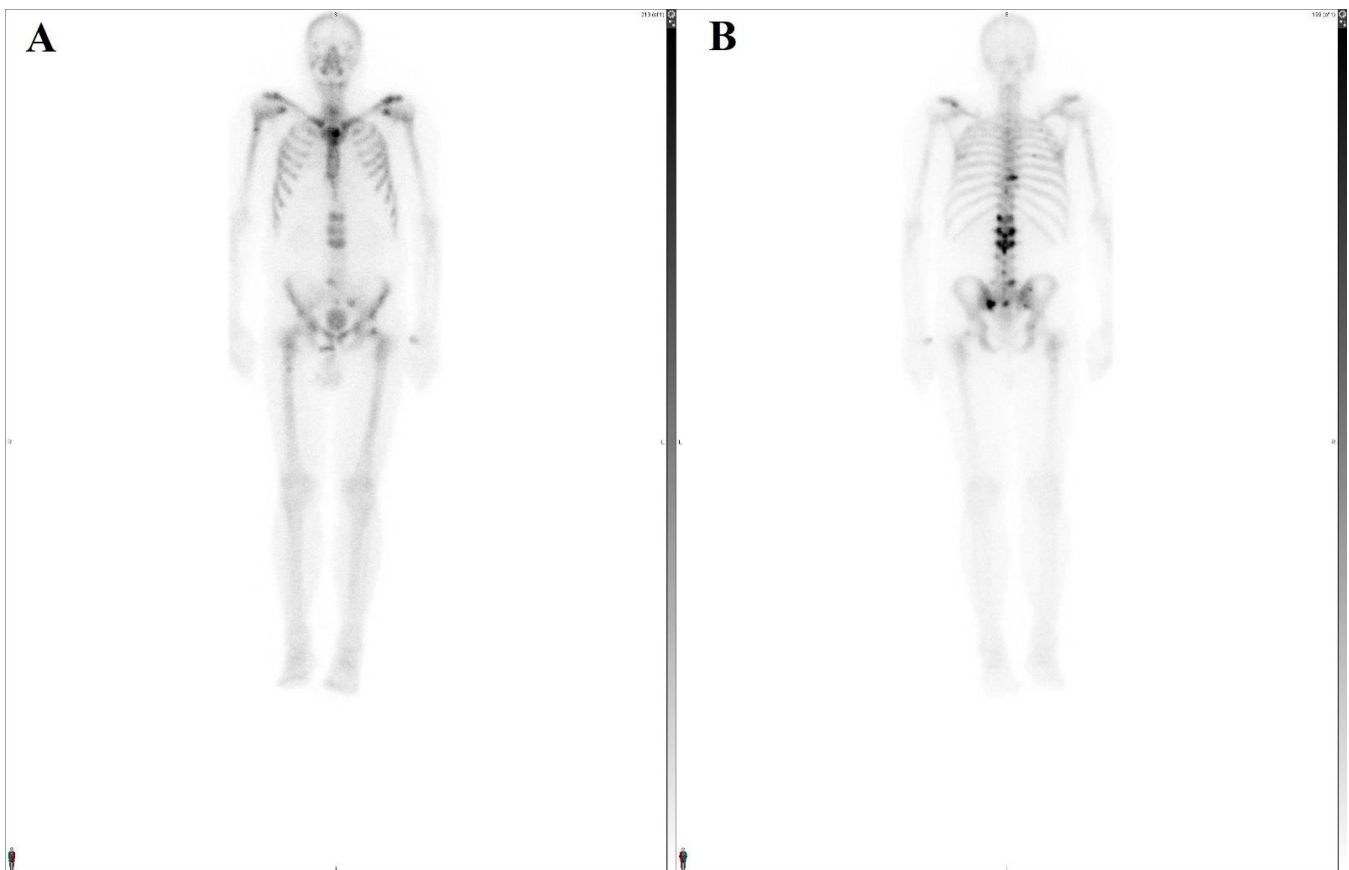


Figure 3. Anterior (A) and posterior (B) planar views of a whole-body bone scan show multiple radiotracer avid bone metastases at both axial and appendicular skeleton, most located at the spine.

3.3. Conventional CT Imaging

Conventional CT has a poor performance in detecting lymph node involvement due to the similarities in the size of benign reactive versus metastatic nodes [48]. In addition, CT diagnostic sensitivity and standard anatomic T1- or T2-weighted MRI sequences are less than 40% sensitive in identifying nodal metastases (0.5–2 cm on a shorter axis) in patients with PCa due to the common occurrence of micrometastases [76]. As a result, clinical nomography has played a vital role in deciding whether or not to perform lymph node dissection (LND) during primary PCa surgery.

The most frequently used technique for detecting and evaluating bone metastases in patients with prostate cancer is technetium 99 m (99 mTc) diphosphonate BS. Nonetheless, early metastases located in the bone marrow may lack tracer absorption, making disease detection more complex [77]. The SPECT to planar imaging inclusion can increase diagnostic accuracy, particularly when employing hybrid SPECT/CT cameras. On a per-patient basis, a meta-analysis of 1102 PCa patients across 12 studies using 99 mTc planar BS and 3 studies using SPECT found that the sensitivity and specificity of PCa diagnosis using planar BS

were 59% and 75% per lesion, respectively, compared to 90% and 85%, respectively, by adding SPECT [71].

3.4. MRI

Multiparametric MRI shows usefulness in differentiating between residual local disease and distant metastases. In addition, MRI is utilized for detecting seminal vesicle invasion and extraprostatic extension in patient candidates for salvage prostatectomy based on high-risk features. MRI studies after radiotherapy to the prostate seem effective in cases with suspected clinical local recurrence based on elevated PSA. However, MRI is not suggested for monitoring therapeutic responses until clinical evidence of disease recurrence exists [78,79].

Diffusion-weighted (DW) MRI detects changes in water mobility between tissues and allows the apparent diffusion coefficient (ADC) to be calculated. However, in malignant lymph nodes, it has been shown that ADC values did not differ significantly from benign nodes [80]. According to a meta-analysis, DW MRI accompanied with ultrasmall superparamagnetic iron oxide (USPIO) demonstrated higher sensitivity in terms of the diagnosis of lymph node metastasis in PCa than utilizing USPIO-MRI alone. The use of DW MRI combined with a USPIO enhanced both the diagnostic sensitivity, with a range of 65–75%, and the specificity, with a range of 93–96%, compared with USPIO-MRI alone (sensitivity ranged from 55–65% and specificity ranged from 71–91%) [81]. Furthermore, in a study of 2993 normal-sized lymph nodes in patients with prostate or bladder cancer, combined USPIO-DW-MRI had sensitivity and specificity ranges of 65–75% and 93–96%, respectively, and was found to be superior to MRI with a USPIO alone (sensitivity ranged from 55–65%, and specificity ranged from 71–91%) [82].

In bone metastasis detection, whole-body MRI was more sensitive than BS and choline PET/CT; however, choline PET/CT exhibited better specificity [71]. The addition of DW MRI to modern whole-body MRI increases bone metastasis diagnosis by including morphologic sequences (e.g., T1- or T2-weighted sequences, short inversion time inversion-recovery sequence). In a study involving 30 patients, the whole-body DW MRI demonstrated a higher sensitivity (100%) and specificity (100%) in detecting bone or node metastases compared with the combination of BS and CT, which demonstrated a sensitivity and specificity of 85% and 88%, respectively [83]. A whole-body MRI approach, which incorporates both conventional and diffusion-weighted imaging, offers a high detection sensitivity in bone and visceral metastases [84,85].

4. Conclusions

While various novel imaging techniques have been developed in recent years, an unmet need exists for improved PCa diagnosis and staging. Concerning diagnosis, advancements in imaging technology have the potential to enable us to abandon spontaneous biopsies in favor of targeted biopsies in the future. Combining several imaging modalities may be one approach to enhance our current standards in diagnosing PCa.

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References

1. Rawla, P. Epidemiology of Prostate Cancer. *World J. Oncol.* **2019**, *10*, 63–89. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/31068988> (accessed on 11 April 2022). [CrossRef]
2. Jadvar, H.; Alavi, A. Role of Imaging in Prostate Cancer. *PET Clin.* **2009**, *4*, 135–138. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/20161047> (accessed on 11 April 2022). [CrossRef]
3. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. *CA Cancer J. Clin.* **2021**, *71*, 7–33. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/33433946>. (accessed on 11 April 2022). [CrossRef]
4. Giri, V.N.; Morgan, T.M.; Morris, D.S.; Berchuck, J.E.; Hyatt, C.; Taplin, M.-E. Genetic testing in prostate cancer management: Considerations informing primary care. *CA Cancer J. Clin.* **2022**, online ahead of print. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/35201622> (accessed on 11 April 2022). [CrossRef]
5. Desai, M.M.; Cacciamani, G.E.; Gill, K.; Zhang, J.; Liu, L.; Abreu, A.; Gill, I.S. Trends in Incidence of Metastatic Prostate Cancer in the US. *JAMA Netw. Open* **2022**, *5*, e222246. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/35285916> (accessed on 11 April 2022). [CrossRef]
6. Cuzick, J.; Thorat, M.A.; Andriole, G.; Brawley, O.W.; Brown, P.H.; Culig, Z.; Eeles, R.A.; Ford, L.G.; Hamdy, F.C.; Holmberg, L.; et al. Prevention and early detection of prostate cancer. *Lancet Oncol.* **2014**, *15*, e484–92. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/25281467> (accessed on 11 April 2022). [CrossRef]
7. Turkbey, B.; Albert, P.S.; Kurdziel, K.; Choyke, P.L. Imaging localized prostate cancer: Current approaches and new developments. *AJR. Am. J. Roentgenol.* **2009**, *192*, 1471–1480. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/19457807> (accessed on 11 April 2022). [CrossRef]
8. Ghafoor, S.; Burger, I.A.; Vargas, A.H. Multimodality Imaging of Prostate Cancer. *J. Nucl. Med.* **2019**, *60*, 1350–1358. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/31481573> (accessed on 11 April 2022). [CrossRef]
9. Soares, S.C.M.; de Camargo Cancela, M.; Migowski, A.; de Souza, D.L.B. Digital rectal examination and its associated factors in the early detection of prostate cancer: A cross-sectional population-based study. *BMC Public Health* **2019**, *19*, 1573. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/31775710> (accessed on 11 April 2022). [CrossRef]
10. Naji, L.; Randhawa, H.; Sohani, Z.; Dennis, B.; Lautenbach, D.; Kavanagh, O.; Bawor, M.; Banfield, L.; Profetto, J. Digital Rectal Examination for Prostate Cancer Screening in Primary Care: A Systematic Review and Meta-Analysis. *Ann. Fam. Med.* **2018**, *16*, 149–154. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/29531107> (accessed on 11 April 2022). [CrossRef]
11. Izawa, J.I.; Klotz, L.; Siemens, D.R.; Kassouf, W.; So, A.; Jordan, J.; Chetner, M.; Iansavichene, A.E. Prostate cancer screening: Canadian guidelines 2011. *Can. Urol. Assoc. J.* **2011**, *5*, 235–240. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/21801679> (accessed on 11 April 2022). [CrossRef]
12. Koulikov, D.; Mamber, A.; Fridmans, A.; Abu Arafeh, W.; Shenfeld, O.Z. Why I cannot find the prostate? Behind the subjectivity of rectal exam. *ISRN Urol.* **2012**, *2012*, 456821. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/22530153> (accessed on 11 April 2022). [CrossRef]
13. Zhang, A.; Fear, T.; Ahmed, H. Digital rectal examination in prostate cancer screening. *Univ. West. Ont. Med. J.* **2013**, *82*, 10–11. Available online: <https://ojs.lib.uwo.ca/index.php/uwomj/article/view/4626> (accessed on 11 April 2022). [CrossRef]
14. Kawachi, M.H.; Bahnson, R.R.; Barry, M.; Busby, J.E.; Carroll, P.R.; Carter, H.B.; Catalona, W.J.; Cookson, M.S.; Epstein, J.I.; Etzioni, R.B.; et al. NCCN clinical practice guidelines in oncology: Prostate cancer early detection. *J. Natl. Compr. Cancer Netw.* **2010**, *8*, 240–262. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/20141680> (accessed on 11 April 2022). [CrossRef]
15. Adhyam, M.; Gupta, A.K. A Review on the Clinical Utility of PSA in Cancer Prostate. *Indian J. Surg. Oncol.* **2012**, *3*, 120–129. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/23730101> (accessed on 11 April 2022). [CrossRef]
16. Miller, D.C.; Hafez, K.S.; Stewart, A.; Montie, J.E.; Wei, J.T. Prostate carcinoma presentation, diagnosis, and staging: An update from the National Cancer Data Base. *Cancer* **2003**, *98*, 1169–1178. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/12973840> (accessed on 11 April 2022). [CrossRef]
17. Richie, J.P.; Catalona, W.J.; Ahmann, F.R.; Hudson, M.A.; Scardino, P.T.; Flanigan, R.C.; DeKernion, J.B.; Ratliff, T.L.; Kavoussi, L.R.; Dalkin, B.L.; et al. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. *Urology* **1993**, *42*, 365–374. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/7692657> (accessed on 11 April 2022). [CrossRef]
18. Catalona, W.J.; Richie, J.P.; Ahmann, F.R.; Hudson, M.A.; Scardino, P.T.; Flanigan, R.C.; DeKernion, J.B.; Ratliff, T.L.; Kavoussi, L.R.; Dalkin, B.L.; et al. Comparison of Digital Rectal Examination and Serum Prostate Specific Antigen in the Early Detection of Prostate Cancer: Results of a Multicenter Clinical Trial of 6630 Men. *J. Urol.* **2017**, *197*, S200–S207. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/28012755> (accessed on 11 April 2022). [CrossRef]
19. Anastasi, G.; Subba, E.; Pappalardo, R.; Macchione, L.; Ricotta, G.; Muscarà, G.; Lembo, F.; Magno, C. Transrectal ultrasound (TRUS) guided prostate biopsy: Three different types of local anesthesia. *Arch. Ital. Urol. Androl.* **2016**, *88*, 308–310. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/28073199> (accessed on 11 April 2022). [CrossRef]
20. Dähnert, W.F.; Hamper, U.M.; Eggleston, J.C.; Walsh, P.C.; Sanders, R.C. Prostatic evaluation by transrectal sonography with histopathologic correlation: The echopenic appearance of early carcinoma. *Radiology* **1986**, *158*, 97–102. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/3510032> (accessed on 11 April 2022). [CrossRef]

21. Brock, M.; von Bodman, C.; Sommerer, F.; Löttenberg, B.; Klein, T.; Deix, T.; Palisaar, J.R.; Noldus, J.; Eggert, T. Comparison of real-time elastography with grey-scale ultrasonography for detection of organ-confined prostate cancer and extra capsular extension: A prospective analysis using whole mount sections after radical prostatectomy. *BJU Int.* **2011**, *108* Pt 2, E217–E222. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/21819532> (accessed on 11 April 2022). [CrossRef]
22. Trevethan, R. Sensitivity, Specificity, and Predictive Values: Foundations, Plabilities, and Pitfalls in Research and Practice. *Front. Public Health* **2017**, *5*, 307. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/29209603> (accessed on 11 April 2022). [CrossRef]
23. Pummer, K.; Rieken, M.; Augustin, H.; Gutsch, T.; Shariat, S.F. Innovations in diagnostic imaging of localized prostate cancer. *World J. Urol.* **2014**, *32*, 881–890. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/24078105> (accessed on 11 April 2022). [CrossRef]
24. Wildeboer, R.R.; Postema, A.W.; Demi, L.; Kuenen, M.P.J.; Wijkstra, H.; Mischi, M. Multiparametric dynamic contrast-enhanced ultrasound imaging of prostate cancer. *Eur. Radiol.* **2017**, *27*, 3226–3234. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/28004162> (accessed on 11 April 2022). [CrossRef]
25. Carpagnano, F.A.; Eusebi, L.; Carriero, S.; Giannubilo, W.; Bartelli, F.; Guglielmi, G. Prostate Cancer Ultrasound: Is Still a Valid Tool? *Curr. Radiol. Rep.* **2021**, *9*, 7. Available online: <https://link.springer.com/10.1007/s40134-021-00382-6> (accessed on 11 April 2022). [CrossRef]
26. Mitterberger, M.J.; Aigner, F.; Horninger, W.; Ulmer, H.; Cavuto, S.; Halpern, E.J.; Frauscher, F. Comparative efficiency of contrast-enhanced colour Doppler ultrasound targeted versus systematic biopsy for prostate cancer detection. *Eur. Radiol.* **2010**, *20*, 2791–2796. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/20571801> (accessed on 11 April 2022). [CrossRef]
27. Halpern, E.J. Contrast-enhanced ultrasound imaging of prostate cancer. *Rev. Urol.* **2006**, *8* (Suppl. 1), S29–S37. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/17021624> (accessed on 11 April 2022).
28. Taverna, G.; Morandi, G.; Seveso, M.; Giusti, G.; Benetti, A.; Colombo, P.; Minuti, F.; Grizzi, F.; Graziotti, P. Colour Doppler and microbubble contrast agent ultrasonography do not improve cancer detection rate in transrectal systematic prostate biopsy sampling. *BJU Int.* **2011**, *108*, 1723–1727. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/21756276> (accessed on 11 April 2022). [CrossRef]
29. Loch, T. Computerized transrectal ultrasound (C-TRUS) of the prostate: Detection of cancer in patients with multiple negative systematic random biopsies. *World J. Urol.* **2007**, *25*, 375–380. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/17694312> (accessed on 11 April 2022). [CrossRef]
30. van der Aa, A.A.M.A.; Mannaerts, C.K.; Gayet, M.C.W.; van der Linden, J.C.; Schrier, B.P.; Sedelaar, J.P.M.; Mischi, M.; Beerlage, H.P.; Wijkstra, H. Three-dimensional greyscale transrectal ultrasound-guidance and biopsy core preembedding for detection of prostate cancer: Dutch clinical cohort study. *BMC Urol.* **2019**, *19*, 23. Available online: <https://bmculol.biomedcentral.com/articles/10.1186/s12894-019-0455-7> (accessed on 11 April 2022). [CrossRef]
31. Walz, J.; Loch, T.; Salomon, G.; Wijkstra, H. Imaging of the prostate. *Die Urol.* **2013**, *52*, 490–496. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/23494334> (accessed on 11 April 2022).
32. Strunk, T.; Decker, G.; Willinek, W.; Mueller, S.C.; Rogenhofer, S. Combination of C-TRUS with multiparametric MRI: Potential for improving detection of prostate cancer. *World J. Urol.* **2014**, *32*, 335–339. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/22885659> (accessed on 11 April 2022). [CrossRef]
33. Brock, M.; Eggert, T.; Palisaar, R.J.; Roghmann, F.; Braun, K.; Löttenberg, B.; Sommerer, F.; Noldus, J.; von Bodman, C. Multiparametric ultrasound of the prostate: Adding contrast enhanced ultrasound to real-time elastography to detect histopathologically confirmed cancer. *J. Urol.* **2013**, *189*, 93–98. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/23164379> (accessed on 11 April 2022). [CrossRef]
34. Sigrist, R.M.S.; Liau, J.; El Kaffas, A.; Chammass, M.C.; Willmann, J.K. Ultrasound Elastography: Review of Techniques and Clinical Applications. *Theranostics* **2017**, *7*, 1303–1329. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/28435467> (accessed on 11 April 2022). [CrossRef] [PubMed]
35. Zhu, Y.; Chen, Y.; Qi, T.; Jiang, J.; Qi, J.; Yu, Y.; Yao, X.; Guan, W. Prostate cancer detection with real-time elastography using a bi-plane transducer: Comparison with step section radical prostatectomy pathology. *World J. Urol.* **2014**, *32*, 329–333. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/22885658> (accessed on 11 April 2022). [CrossRef]
36. Yuan, J.; Poon, D.M.C.; Lo, G.; Wong, O.L.; Cheung, K.Y.; Yu, S.K. A narrative review of MRI acquisition for MR-guided-radiotherapy in prostate cancer. *Quant. Imaging Med. Surg.* **2022**, *12*, 1585–1607. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/35111651> (accessed on 11 April 2022). [CrossRef]
37. Hambrock, T.; Somford, D.M.; Hoeks, C.; Bouwense, S.A.W.; Huisman, H.; Yakar, D.; van Oort, I.M.; Witjes, J.A.; Fütterer, J.J.; Barentsz, J.O. Magnetic resonance imaging guided prostate biopsy in men with repeat negative biopsies and increased prostate specific antigen. *J. Urol.* **2010**, *183*, 520–527. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/20006859> (accessed on 11 April 2022). [CrossRef]
38. Choi, M.S.; Choi, Y.S.; Yoon, B.I.; Kim, S.J.; Cho, H.J.; Hong, S.H.; Lee, J.Y.; Hwang, T.-K.; Kim, S.W. The Clinical Value of Performing an MRI before Prostate Biopsy. *Korean J. Urol.* **2011**, *52*, 572–577. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/21927706> (accessed on 11 April 2022). [CrossRef]
39. Laurence Klotz, C.M. Can high resolution micro-ultrasound replace MRI in the diagnosis of prostate cancer? *Eur. Urol. Focus* **2020**, *6*, 419–423. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/31771935> (accessed on 11 April 2022). [CrossRef]

40. Schoots, I.G.; Padhani, A.R. Delivering Clinical impacts of the MRI diagnostic pathway in prostate cancer diagnosis. *Abdom. Radiol. (N. Y.)* **2020**, *45*, 4012–4022. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/32356003> (accessed on 11 April 2022). [CrossRef]
41. Available online: <https://www.ncbi.nlm.nih.gov/books/NBK544759/?report=reader> (accessed on 11 April 2022).
42. Bjurlin, M.A.; Carroll, P.R.; Eggener, S.; Fulgham, P.F.; Margolis, D.J.; Pinto, P.A.; Rosenkrantz, A.B.; Rubenstein, J.N.; Rukstalis, D.B.; Taneja, S.S.; et al. Update of the Standard Operating Procedure on the Use of Multiparametric Magnetic Resonance Imaging for the Diagnosis, Staging and Management of Prostate Cancer. *J. Urol.* **2020**, *203*, 706–712. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/31642740> (accessed on 11 April 2022). [CrossRef] [PubMed]
43. Siddiqui, M.M.; Rais-Bahrami, S.; Turkbey, B.; George, A.K.; Rothwax, J.; Shakir, N.; Okoro, C.; Raskolnikov, D.; Parnes, H.L.; Linehan, W.M.; et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA* **2015**, *313*, 390–397. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/25626035> (accessed on 11 April 2022). [CrossRef] [PubMed]
44. Penzkofer, T.; Tuncali, K.; Fedorov, A.; Song, S.-E.; Tokuda, J.; Fennessy, F.M.; Vangel, M.G.; Kibel, A.S.; Mulkern, R.V.; Wells, W.M.; et al. Transperineal in-bore 3-T MR imaging-guided prostate biopsy: A prospective clinical observational study. *Radiology* **2015**, *274*, 170–180. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/25222067> (accessed on 11 April 2022). [CrossRef] [PubMed]
45. Moore, C.M.; Robertson, N.L.; Arsanious, N.; Middleton, T.; Villers, A.; Klotz, L.; Taneja, S.S.; Emberton, M. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: A systematic review. *Eur. Urol.* **2013**, *63*, 125–140. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/22743165> (accessed on 16 April 2022). [CrossRef] [PubMed]
46. Wegelin, O.; van Melick, H.H.E.; Hooft, L.; Bosch, J.L.H.R.; Reitsma, H.B.; Barentsz, J.O.; Somford, D.M. Comparing Three Different Techniques for Magnetic Resonance Imaging-targeted Prostate Biopsies: A Systematic Review of In-bore versus Magnetic Resonance Imaging-transrectal Ultrasound fusion versus Cognitive Registration. Is There a Preferred Technique? *Eur. Urol.* **2017**, *71*, 517–531. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/27568655> (accessed on 16 April 2022). [CrossRef]
47. Drost, F.-J.H.; Osses, D.F.; Nieboer, D.; Steyerberg, E.W.; Bangma, C.H.; Roobol, M.J.; Schoots, I.G. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochrane Database Syst. Rev.* **2019**, *4*, CD012663. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/31022301> (accessed on 16 April 2022). [CrossRef]
48. Hövels, A.M.; Heesakkers, R.A.M.; Adang, E.M.; Jager, G.J.; Strum, S.; Hoogeveen, Y.L.; Severens, J.L.; Barentsz, J.O. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: A meta-analysis. *Clin. Radiol.* **2008**, *63*, 387–395. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/18325358> (accessed on 16 April 2022). [CrossRef]
49. Korevaar, S.; Tennakoon, R.; Page, M.; Brothie, P.; Thangarajah, J.; Florescu, C.; Sutherland, T.; Kam, N.M.; Bab-Hadiashar, A. Incidental detection of prostate cancer with computed tomography scans. *Sci. Rep.* **2021**, *11*, 7956. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/33846450> (accessed on 16 April 2022). [CrossRef]
50. Rowe, S.P.; Gorin, M.A.; Allaf, M.E.; Pienta, K.J.; Tran, P.T.; Pomper, M.G.; Ross, A.E.; Cho, S.Y. PET imaging of prostate-specific membrane antigen in prostate cancer: Current state of the art and future challenges. *Prostate Cancer Prostatic Dis.* **2016**, *19*, 223–230. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/27136743> (accessed on 16 April 2022). [CrossRef]
51. Wang, R.; Shen, G.; Huang, M.; Tian, R. The Diagnostic Role of 18F-Choline, 18F-Fluciclovine and 18F-PSMA PET/CT in the Detection of Prostate Cancer With Biochemical Recurrence: A Meta-Analysis. *Front. Oncol.* **2021**, *11*, 684629. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/34222008> (accessed on 16 April 2022). [CrossRef]
52. Liu, Y. Diagnostic role of fluorodeoxyglucose positron emission tomography-computed tomography in prostate cancer. *Oncol. Lett.* **2014**, *7*, 2013–2018. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/24932281> (accessed on 16 April 2022). [CrossRef] [PubMed]
53. Wallitt, K.L.; Khan, S.R.; Dubash, S.; Tam, H.H.; Khan, S.; Barwick, T.D. Clinical PET Imaging in Prostate Cancer. *Radiographics* **2017**, *37*, 1512–1536. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/28800286> (accessed on 16 April 2022). [CrossRef]
54. Chang, C.-H.; Wu, H.-C.; Tsai, J.J.P.; Shen, Y.-Y.; Changlai, S.-P.; Kao, A. Detecting metastatic pelvic lymph nodes by 18F-2-deoxyglucose positron emission tomography in patients with prostate-specific antigen relapse after treatment for localized prostate cancer. *Urol. Int.* **2003**, *70*, 311–315. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/12740497> (accessed on 16 April 2022). [CrossRef]
55. Jadvar, H.; Desai, B.; Ji, L.; Conti, P.S.; Dorff, T.B.; Groshen, S.G.; Gross, M.E.; Pinski, J.K.; Quinn, D.I. Prospective evaluation of 18F-NaF and 18F-FDG PET/CT in detection of occult metastatic disease in biochemical recurrence of prostate cancer. *Clin. Nucl. Med.* **2012**, *37*, 637–643. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/22691503> (accessed on 16 April 2022). [CrossRef] [PubMed]
56. von Eyben, F.E.; Kairemo, K. Meta-analysis of (11)C-choline and (18)F-choline PET/CT for management of patients with prostate cancer. *Nucl. Med. Commun.* **2014**, *35*, 221–230. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/24240194> (accessed on 16 April 2022). [CrossRef] [PubMed]
57. Evangelista, L.; Guttilla, A.; Zattoni, F.; Muzzio, P.C.; Zattoni, F. Utility of choline positron emission tomography/computed tomography for lymph node involvement identification in intermediate- to high-risk prostate cancer: A systematic literature review and meta-analysis. *Eur. Urol.* **2013**, *63*, 1040–1048. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/23036576> (accessed on 16 April 2022). [CrossRef] [PubMed]

58. Fanti, S.; Minozzi, S.; Castellucci, P.; Balduzzi, S.; Herrmann, K.; Krause, B.J.; Oyen, W.; Chiti, A. PET/CT with (11)C-choline for evaluation of prostate cancer patients with biochemical recurrence: Meta-analysis and critical review of available data. *Eur. J. Nucl. Med. Mol. Imaging* **2016**, *43*, 55–69. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/26450693> (accessed on 16 April 2022). [CrossRef]
59. Evangelista, L.; Zattoni, F.; Guttilla, A.; Saladini, G.; Zattoni, F.; Colletti, P.M.; Rubello, D. Choline PET or PET/CT and biochemical relapse of prostate cancer: A systematic review and meta-analysis. *Clin. Nucl. Med.* **2013**, *38*, 305–314. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/23486334> (accessed on 16 April 2022). [CrossRef]
60. Graziani, T.; Ceci, F.; Castellucci, P.; Polverari, G.; Lima, G.M.; Lodi, F.; Morganti, A.G.; Ardizzoni, A.; Schiavina, R.; Fanti, S. (11)C-Choline PET/CT for restaging prostate cancer. Results from 4426 scans in a single-centre patient series. *Eur. J. Nucl. Med. Mol. Imaging* **2016**, *43*, 1971–1979. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/27277279> (accessed on 16 April 2022). [CrossRef]
61. Jones, W.; Griffiths, K.; Barata, P.C.; Paller, C.J. PSMA Theranostics: Review of the Current Status of PSMA-Targeted Imaging and Radioligand Therapy. *Cancers* **2020**, *12*, 1367. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/32466595> (accessed on 16 April 2022). [CrossRef]
62. Ferraro, D.A.; Garcia Schöler, H.I.; Muehlematter, U.J.; Eberli, D.; Müller, J.; Müller, A.; Gablinger, R.; Kranzbühler, H.; Omlin, A.; Kaufmann, P.A.; et al. Impact of 68Ga-PSMA-11 PET staging on clinical decision-making in patients with intermediate or high-risk prostate cancer. *Eur. J. Nucl. Med. Mol. Imaging* **2020**, *47*, 652–664. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/31802175> (accessed on 16 April 2022). [CrossRef]
63. Luiting, H.B.; van Leeuwen, P.J.; Busstra, M.B.; Brabander, T.; van der Poel, H.G.; Donswijk, M.L.; Vis, A.N.; Emmett, L.; Stricker, P.D.; Roobol, M.J. Use of gallium-68 prostate-specific membrane antigen positron-emission tomography for detecting lymph node metastases in primary and recurrent prostate cancer and location of recurrence after radical prostatectomy: An overview of the current literature. *BJU Int.* **2020**, *125*, 206–214. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/31680398> (accessed on 16 April 2022). [CrossRef]
64. Maurer, T.; Eiber, M.; Schwaiger, M.; Gschwend, J.E. Current use of PSMA-PET in prostate cancer management. *Nat. Rev. Urol.* **2016**, *13*, 226–235. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/26902337> (accessed on 16 April 2022). [CrossRef]
65. Razik, A.; Das, C.J.; Sharma, S. PET-CT and PET-MR in urological cancers other than prostate cancer: An update on state of the art. *Indian J. Urol.* **2018**, *34*, 20–27. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/29343908> (accessed on 16 April 2022).
66. Eiber, M.; Maurer, T.; Souvatzoglou, M.; Beer, A.J.; Ruffani, A.; Haller, B.; Graner, F.-P.; Kübler, H.; Haberkorn, U.; Eisenhut, M.; et al. Evaluation of Hybrid 68Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. *J. Nucl. Med.* **2015**, *56*, 668–674. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/25791990> (accessed on 16 April 2022). [CrossRef]
67. Einspieler, I.; Rauscher, I.; Düwel, C.; Krönke, M.; Rischpler, C.; Habl, G.; Dewes, S.; Ott, A.; Wester, H.-J.; Schwaiger, M.; et al. Detection Efficacy of Hybrid 68Ga-PSMA Ligand PET/CT in Prostate Cancer Patients with Biochemical Recurrence After Primary Radiation Therapy Defined by Phoenix Criteria. *J. Nucl. Med.* **2017**, *58*, 1081–1087. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/28209912> (accessed on 16 April 2022). [CrossRef]
68. Pan, K.-H.; Wang, J.-F.; Wang, C.-Y.; Nikzad, A.A.; Kong, F.Q.; Jian, L.; Zhang, Y.-Q.; Lu, X.-M.; Xu, B.; Wang, Y.-L.; et al. Evaluation of 18F-DCFPyL PSMA PET/CT for Prostate Cancer: A Meta-Analysis. *Front. Oncol.* **2020**, *10*, 597422. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/33680924> (accessed on 16 April 2022). [CrossRef]
69. Hartrampf, P.E.; Petritsch, B.; Buck, A.K.; Serfling, S.E. Pitfalls in PSMA-PET/CT: Intensive bone marrow uptake in a case with polycythemia vera. *Eur. J. Nucl. Med. Mol. Imaging* **2021**, *48*, 1669–1670. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/33111182> (accessed on 16 April 2022). [CrossRef]
70. Cantiello, F.; Gangemi, V.; Cascini, G.L.; Calabria, F.; Moschini, M.; Ferro, M.; Musi, G.; Buttici, S.; Salonia, A.; Briganti, A.; et al. Diagnostic Accuracy of 64Copper Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography for Primary Lymph Node Staging of Intermediate- to High-risk Prostate Cancer: Our Preliminary Experience. *Urology* **2017**, *106*, 139–145. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/28438628> (accessed on 16 April 2022). [CrossRef]
71. Shen, G.; Deng, H.; Hu, S.; Jia, Z. Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: A meta-analysis. *Skelet. Radiol.* **2014**, *43*, 1503–1513. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/24841276> (accessed on 16 April 2022). [CrossRef]
72. Beheshti, M.; Langsteger, W.; Fogelman, I. Prostate cancer: Role of SPECT and PET in imaging bone metastases. *Semin. Nucl. Med.* **2009**, *39*, 396–407. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/19801219> (accessed on 16 April 2022). [CrossRef] [PubMed]
73. O’Sullivan, J.M.; Norman, A.R.; Cook, G.J.; Fisher, C.; Dearnaley, D.P. Broadening the criteria for avoiding staging bone scans in prostate cancer: A retrospective study of patients at the Royal Marsden Hospital. *BJU Int.* **2003**, *92*, 685–689. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/14616446> (accessed on 16 April 2022). [CrossRef] [PubMed]
74. Lin, K.; Szabo, Z.; Chin, B.B.; Civelek, A.C. The value of a baseline bone scan in patients with newly diagnosed prostate cancer. *Clin. Nucl. Med.* **1999**, *24*, 579–582. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/10439178> (accessed on 16 April 2022). [CrossRef]

75. Abuzallouf, S.; Dayes, I.; Lukka, H. Baseline staging of newly diagnosed prostate cancer: A summary of the literature. *J. Urol.* **2004**, *171 Pt 1*, 2122–2127. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/15126770> (accessed on 16 April 2022). [CrossRef] [PubMed]
76. Harisinghani, M.G.; Barentsz, J.; Hahn, P.F.; Deserno, W.M.; Tabatabaei, S.; van de Kaa, C.H.; de la Rosette, J.; Weissleder, R. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *N. Engl. J. Med.* **2003**, *348*, 2491–2499. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/12815134> (accessed on 16 April 2022). [CrossRef]
77. Perez-Lopez, R.; Tunariu, N.; Padhani, A.R.; Oyen, W.J.G.; Fanti, S.; Vargas, H.A.; Omlin, A.; Morris, M.J.; de Bono, J.; Koh, D.-M. Imaging Diagnosis and Follow-up of Advanced Prostate Cancer: Clinical Perspectives and State of the Art. *Radiology* **2019**, *292*, 273–286. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/31237493> (accessed on 16 April 2022). [CrossRef]
78. Westphalen, A.C.; Reed, G.D.; Vinh, P.P.; Sotto, C.; Vigneron, D.B.; Kurhanewicz, J. Multiparametric 3T endorectal mri after external beam radiation therapy for prostate cancer. *J. Magn. Reson. Imaging* **2012**, *36*, 430–437. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/22535708> (accessed on 16 April 2022). [CrossRef]
79. Pucar, D.; Shukla-Dave, A.; Hricak, H.; Moskowitz, C.S.; Kuroiwa, K.; Olgac, S.; Ebor, L.E.; Scardino, P.T.; Koutcher, J.A.; Zakian, K.L. Prostate cancer: Correlation of MR imaging and MR spectroscopy with pathologic findings after radiation therapy-initial experience. *Radiology* **2005**, *236*, 545–553. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/15972335> (accessed on 16 April 2022). [CrossRef]
80. Thoeny, H.C.; Froehlich, J.M.; Triantafyllou, M.; Huesler, J.; Bains, L.J.; Vermathen, P.; Fleischmann, A.; Studer, U.E. Metastases in normal-sized pelvic lymph nodes: Detection with diffusion-weighted MR imaging. *Radiology* **2014**, *273*, 125–135. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/24893049> (accessed on 16 April 2022). [CrossRef]
81. Woo, S.; Suh, C.H.; Kim, S.Y.; Cho, J.Y.; Kim, S.H. The Diagnostic Performance of MRI for Detection of Lymph Node Metastasis in Bladder and Prostate Cancer: An Updated Systematic Review and Diagnostic Meta-Analysis. *Am. J. Roentgenol.* **2018**, *210*, W95–W109. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/29381380> (accessed on 16 April 2022). [CrossRef]
82. Birkhäuser, F.D.; Studer, U.E.; Froehlich, J.M.; Triantafyllou, M.; Bains, L.J.; Petralia, G.; Vermathen, P.; Fleischmann, A.; Thoeny, H.C. Combined ultrasmall superparamagnetic particles of iron oxide-enhanced and diffusion-weighted magnetic resonance imaging facilitates detection of metastases in normal-sized pelvic lymph nodes of patients with bladder and prostate cancer. *Eur. Urol.* **2013**, *64*, 953–960. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/23916692> (accessed on 16 April 2022). [CrossRef] [PubMed]
83. Pasoglou, V.; Larbi, A.; Collette, L.; Annet, L.; Jamar, F.; Machiels, J.-P.; Michoux, N.; Vande Berg, B.C.; Tombal, B.; Lecouvet, F.E. One-step TNM staging of high-risk prostate cancer using magnetic resonance imaging (MRI): Toward an upfront simplified “all-in-one” imaging approach? *Prostate* **2014**, *74*, 469–477. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/24375774> (accessed on 16 April 2022). [CrossRef] [PubMed]
84. Padhani, A.R.; Lecouvet, F.E.; Tunariu, N.; Koh, D.-M.; De Keyser, F.; Collins, D.J.; Sala, E.; Schlemmer, H.P.; Petralia, G.; Vargas, H.A.; et al. METastasis Reporting and Data System for Prostate Cancer: Practical Guidelines for Acquisition, Interpretation, and Reporting of Whole-body Magnetic Resonance Imaging-based Evaluations of Multiorgan Involvement in Advanced Prostate Cancer. *Eur. Urol.* **2017**, *71*, 81–92. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/27317091> (accessed on 16 April 2022). [CrossRef] [PubMed]
85. Barnes, A.; Alonzi, R.; Blackledge, M.; Charles-Edwards, G.; Collins, D.J.; Cook, G.; Coutts, G.; Goh, V.; Graves, M.; Kelly, C.; et al. UK quantitative WB-DWI technical workgroup: Consensus meeting recommendations on optimisation, quality control, processing and analysis of quantitative whole-body diffusion-weighted imaging for cancer. *Br. J. Radiol.* **2018**, *91*, 20170577. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/29076749> (accessed on 16 April 2022). [CrossRef]