Novel imaging in prostate cancer

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INTRODUCTION

Although prostate cancer (Pca) screening and current imaging modalities have led to a decrease in advanced disease and cancer-related mortality, these modalities have limitations in terms of sensitivity and specificity, resulting in missing clinically significant cancers and overdetection of clinically insignificant cancers.¹ An ideal imaging tool would be able to provide reliable PCA detection and localization, thus improving the diagnostic pathway and allowing personalized and targeted treatment (e.g., active surveillance or focal therapy).² There are several issues to be addressed, such as the assessment of tumor aggressiveness, multifocality of the tumor before the selection of any active treatment, and the prognostic evaluation of the patients with Pca. Current advances in imaging could provide an additional aid and we herein provide an insight on the available evidence.

Transrectal ultrasound

The sensitivity and specificity of transrectal ultrasound (TRUS) are limited, ranging from 18% to 96% and 46% to 91%, respectively.³ Its use also for local staging of Pca is inadequate. For example, the diagnostic accuracy of TRUS in evaluating extracapsular extension (ECE) would be improved using novel imaging tools.
ranges from 37% to 85% and depends on clinician experience in performing and interpreting this study.\[14\]

For these reasons, it is crucial to develop innovations in TRUS-based imaging in order to improve sensitivity, specificity, and predictive value of this diagnostic tool.

**High-resolution transrectal ultrasound**

Although low frequencies allow adequate imaging of the prostate in contrast to adjacent structures, they are suboptimal in delineating intraprostatic architecture. High-resolution ultrasound (US) probes were recently developed to cover this need. High-resolution TRUS demonstrated improved sensitivity (65.2% vs. 37.7%) and specificity (71.6% vs. 65.4%). High-resolution TRUS’s agreement with pathologic findings was twice as high as conventional TRUSs ($P = 0.006$). High-resolution TRUS also provided a nonsignificant increase in visualization of high-grade lesions (84% vs. 60%, $P = 0.11$).\[5\]

**Color and power Doppler ultrasound**

Color Doppler US (CDUS) could be useful in detecting isoechogenic tumors that demonstrate increased vascularity. Although increased sensitivity, specificity, and positive predictive value (PPV) were demonstrated for CDUS and power Doppler US\[6,7\] in initial studies, systemic biopsies cannot be avoided.\[8\]

**Contrast-enhanced ultrasound**

Contrast-enhanced US (CEUS) uses intravenously injected gas-filled microbubbles as a contrast agent to provide microvascular and tissue perfusion information. CEUS is better at evaluating microvasculature than CDUS, which is limited by its ability to detect flow only in vessels larger than 1 mm in diameter. Li et al. in a meta-analysis of 16 studies that included 2624 patients reported a pooled sensitivity and specificity of 70% and 74%, respectively, for the detection of Pca.\[8\] Nevertheless, the sensitivity of CEUS is lower in cases of small low-grade tumors and centrally located lesions.

**Elastography**

Elastography is an US technique that can visualize tissue elasticity and stiffness. Pca is stiffer and less elastic than normal prostatic tissue, secondary to increased cellular density, decreased glandular tissue architecture, and increased collagen deposition in the stroma surrounding the tumor. The concept of elastography is the detection of differences in elasticity between Pca and surrounding prostatic tissue. There are two types of elastography: strain elastography and shear wave elastography. In the first one, strain forces are generated by mechanical compressions and decompressions of the prostate gland by transducers.

A meta-analysis study of strain elastography reported sensitivity in the range of 71%–82% and a specificity of 60%–95%, with radical prostatectomy specimens as the reference standard.\[10\] A more recent meta-analysis by Zhang et al. reported a pooled sensitivity of 72% and specificity of 76%.\[11\] In another study, elastography-guided biopsies in patients with cancer were 2.9-folds more likely to detect Pca than systematic biopsy, while requiring fewer core samples.\[12\]

**Combination of contrast-enhanced ultrasound and elastography**

It is hypothesized that the combination of real-time elastography and CEUS would improve the detection rate of Pca (“multiparametric US”). Brock et al. demonstrated in their study that the addition of CEUS for lesions detected on real-time elastography decreased false-positive results and improved PPV.\[13\] Adapting the same multiparametric approach for the evaluation of targeted biopsies, Aigner et al. observed that the Pca detection rate was superior to that of a systematic approach, and the best detection results were observed in older patients with a small prostate volume.\[14\]

**HistoScanning**

HistoScanning (HS) is a diagnostic modality that uses computer-assisted analysis of three-dimensional-TRUS backscatter information to visualize areas of cancer within the prostate gland, estimate tumor volume, and assess extraprostatic extension (EPE).

The initial results of this method appeared impressive, with reported sensitivity, specificity, PPV, and negative predictive value (NPV) of 90%–100%, 72%–81%, 80%–83%, and 83%–100%, respectively, for lesions at least 0.2 ml.\[15,16\] Larger studies found no correlation between HS measured tumor volume and radical prostatectomy tumor volume, nor did HS accurately determine disease localization on a sextant basis, concluding that HS does not significantly improve Pca diagnostic evaluation.\[17,18\] HS failed to improve disease detection, demonstrating an area under the curve of 0.5 and a high false-positive rate of 82.6%.\[19\]

These studies demonstrate that HS does not improve diagnostic accuracy for Pca detection, disease localization, and risk stratification.

**Multiparametric magnetic resonance imaging**

Multiparametric magnetic resonance imaging (mpMRI) is defined as the combination of high-resolution T2-weighted images (T2WI) and at least two functional MRI techniques such as diffusion-weighted imaging (DWI), dynamic
contrast enhancement (DCE) assessment, or magnetic resonance spectroscopic imaging. A typical finding of Pca focal lesion on mpMRI appears as an oval or round-shaped T2-hypointense lesion, with high-signal intensity relative to the neighboring prostate due to restriction of water diffusivity on high b-value (>1000S/mm²) DWI and low signal intensity on the apparent diffusion coefficient (ADC) map, as well as a focal early and intense enhancement on DCE evaluation. However, many suspicious lesions do not have the typical appearance, whereas benign conditions may manifest as false positives. The development of Prostate Imaging Reporting and Data System, as a consortium between radiological societies, serves as guidelines to set indications for mpMRI, standardize mpMRI protocols and for integration, reporting, and communication of mpMRI data.

**Detection of prostate cancer**

A systematic review of the literature found that the detection rate of clinically significant Pca by mpMRI ranged from 44% to 87% with NPVs ranging from 63% to 98%. Similar results were published by Thompson et al. that reviewed the performance of mpMRI in several studies and found a sensitivity of 96%, specificity of 36%, PPV of 52%, and NPV of 92%. DWI sequence has proven the most useful in detecting clinically significant Pca and improving its overall diagnostic efficacy. The combination of DCE and T2-W significantly improved cancer detection sensitivity from 63% to 79%–81% in one study. The issue of MRI-guided biopsies and the benefits resulting from such a strategy has also been studied. Pokorny et al. showed that a strategy based on MR-guided biopsies could avoid unnecessary biopsies in 51% of the patients, reducing the diagnosis of insignificant Pca in 89.4% and improving the detection of intermediate/high-risk Pca in 17.7%.

**Assessment of prostate cancer aggressiveness**

The possible role of mpMRI as a noninvasive tool for predicting Pca aggressiveness has been investigated by several authors. DWI is currently the sequence with the best correlation with tumor aggressiveness. DWI measures water proton diffusion with a value called the ADC. ADC values of Pca foci were correlated with Gleason scores. Several authors found that the median ADC in the tumors showed a negative relationship with Gleason score, and the differences were statistically significant. This conclusion is valid for tumors in the peripheral zone of the prostate with MRI at both 1.5T and 3T. However, there is some overlap between Gleason score and ADC values, thus limiting its predictive value in an individual patient.

**Locoregional staging of prostate cancer**

The typical finding of ECE is the direct extension of the tumor into periprostatic fat. However, indirect findings of ECE are asymmetry of the neurovascular bundle, contour angulation, and bulging, an irregular capsule, capsular retraction, or obliteration of the rectoprostatic angle. Findings that indicate seminal vesicle invasion include direct extension of the tumor into one or both seminal vesicles and/or presence of focal low signal intensity filling defects within the normally hyperintense seminal vesicles. For seminal vesicle involvement (SVI), sensitivities and specificities vary from 57% to 65% and from 89% to 91%, respectively, for T2WI alone. With the combination of DCE and DWI, the sensitivities and specificities increased to 61% to 78% and 96% to 98%, respectively. A recent meta-analysis found an overall poor and heterogeneous sensitivity for detecting EPE (57% for ECE, 58% for SVI, and 61% for overall T3 stage), but with high specificity (91% for ECE, 96% for SVI, and 88% for overall T3 stage). Subgroup analysis revealed that the use of 3 T scanners and combination of T2WI with other sequences were generally associated with a better diagnostic performance.

**Detection of tumor recurrence**

After radical prostatectomy, tumor recurrence is depicted in T2WI as a hyperintense soft-tissue mass in the prostate fossa in comparison to the pelvic muscle signal intensity. However, postoperative fibrotic tissue can have similar appearance and mimic tumor, so T2WI alone is insufficient to diagnose local recurrence. Casciani et al. found that T2WI has a sensitivity and specificity of only 48% and 52%, respectively, when it comes to patients with biochemical recurrence. Local recurrence after radiation therapy appears as a nodular lesion of lower signal intensity than normal prostatic tissue, which increases in size over time and may exhibit a capsular bulge. DCE is the most important sequence in detecting recurrence following radical prostatectomy. Delayed postoperative changes show either no enhancement or mild enhancement on DCE, while recurrent tumors show intense, focal enhancement in early phases, and rapid washout in the venous phase. In the previous study, DCE alone or in combination with T2WI improved sensitivity from 48 to 52% to 88%–100%. In patients with recurrence after radiation therapy, DCE has significantly better sensitivity (72% vs. 38%), PPV (46% vs. 24%), and NPV (95% vs. 88%) compared to T2WI alone.

**MRI-ultrasound fusion**

MRI-US fusion is an imaging technique that combines the diagnostic advantages of MRI with the real-time use of US. In MRI-US fusion biopsy of the prostate gland,
mpMRI of the prostate is performed before the biopsy. The MR images are then coregistered with real-time TRUS either cognitively (a process which is highly dependent on operator’s experience) or using commercially marketed MRI-US fusion platforms. Both systematic and targeted biopsies of MRI-suspected lesions are obtained. There is evidence that MRI-US fusion-guided biopsy detects more clinically significant cancers and less clinically insignificant cancers than systematic biopsies alone. In a meta-analysis, MRI-US fusion-guided biopsy detected more clinically significant cancers (median 33% vs. 24%) than the systematic biopsy. The comparison of the two ways of targeting shows that software-based targeted biopsy has a superior overall Pca detection compared to cognitive targeted biopsy, but recent evidence suggests that additional cognitive biopsy cores are still useful in detecting additional cancers. Finally, MRI-US is useful in the performance of transperineal-targeted biopsy.

Positron emission tomography/computed tomography

The advantages of MRI and positron emission tomography (PET) can be combined to some extent by fusing the PET and computed tomography (CT) data (PET/CT). PET can reveal tumor-specific biochemical and metabolic alterations. Ideal characteristics of PET scans include accurate diagnosis of cancer (and specifically high-grade cancer), detect recurrent Pca even at low prostate-specific antigen (PSA) values, and localize escape sites from androgen deprivation during castration-resistant prostate cancer (CRPC). Common tracers include fluorodeoxyglucose, choline, acetate, prostate-specific membrane antigen (PSMA), NaF, and 18F-FDHT. A description of the most used PET tracers along with their advantages and disadvantages will follow.

11C/18F-Choline

The use of choline has been extensively studied in Pca. It is mainly used to detect disease in biochemically recurrent (BCR) patients. Two meta-analyses demonstrated PET choline to have high sensitivity of 85%–86% and specificity of 88%–93% in BCR patients. Detecting recurrent disease in the prostatectomy fossa had a lower sensitivity and specificity (75% and 82%, respectively) compared to metastatic disease in lymph nodes. Some studies have demonstrated only a 28%–40% detection rate in BCR patients after surgery, especially with PSA <1, questioning the ability to detect postsurgical recurrences at low PSA values. PSA and PSA doubling time were found to be significant predictors for a positive PET choline with a PSA level of 1.05 ng/ml and doubling time of 5.95 months determined to be critical values for positive PET studies. PET choline has shown limited utility in assessing response to first-line chemotherapy in CRPC patients.

In summary, choline PET can be helpful at high PSA values in distinguishing between local recurrence versus distant metastases and thus in deciding which patients are good candidates for salvage locoregional treatment.

11C-acetate

In a meta-analysis of 14 studies, there was a pooled sensitivity of 64% and a pooled specificity of 93% for 11C-acetate. The sensitivity was 20% higher in detecting recurrence in postsurgical versus postradiation therapy patients. Sensitivity was a problem in low PSA values, with 35% lower detection rates in patients with PSA values <1 ng/ml. 11C-acetate detected 90% of metastatic lesions with a specificity of 96% on a per patient basis and 7% additional bone metastases over the bone scan.

NaF

NaF is a relatively old tracer used for depicting bone metastases in several cancers including Pca. Its major advantages are the rapid bone-specific uptake, lack of blood pool, and good axial skeletal visualization. Compared to traditional bone scan, 18F-NaF PET/CT has shown improved sensitivity, but lacks specificity as it can also detect benign pathologies such as degenerative osteopathy, healing fractures, and bone dysplasia. In a literature review of 11 articles with varying PSA levels, the use of 18F-NaF for the detection of Pca bone metastases produced pooled sensitivities of 89% and 87% and specificities of 91% and 80% on a per lesion and per patient basis, respectively. In another review that compares NaF and choline PET/CT, it is concluded that both tracers have equivalent sensitivities in finding bone metastases, although specificity is higher for choline. Thus, NaF could be useful in high-risk patients to detect or eliminate bone disease in whom the conventional bone scan is equivocal or negative and potentially monitor the effects of therapy on bone metastases.

Prostate-specific membrane antigen

PSMA is a cell surface enzyme that is highly expressed in Pca and is being extensively explored as a promising target for molecular imaging. Several PET agents have been developed to bind to PSMA and serve as tracers for PET/CT, including antibodies and small-molecule inhibitors. Most studies focus in the clinical utility of 68-Ga-PSMA-11 and 18F-labeled PSMA agents in the setting of BCR Pca.

A systematic review of 16 articles with a total of 1309 patients found a sensitivity and specificity of
A systematic review by Evans et al. examined 20 clinical studies investigating radiolabeled choline, PSMA, and $^{18}$F-FACBC PET/CT positivity in the BCR setting. They found that among BCR patients with PSA $<1$ ng/ml, PSMA was more sensitive than choline or $^{18}$F-FACBC. The percentage of patients with PSA levels $<1.0$ and a positive PET ranged from 21% to 41%, 7%–44%, and 29%–67% for $^{18}$F-FACBC, choline, and PSMA, respectively. A prospective study compared choline with PSMA in patients not on systemic therapy with rising PSA after definitive treatment. This study showed that in patients with biochemical failure and low PSA level ($<0.5$ ng/ml), $^{68}$Ga-PSMA demonstrates a significantly higher detection rate (50%) than $^{18}$F-choline (12.5%).

The implementation of PSMA-PET in clinical practice might have an impact on management decisions. A prospective, multicenter study found that PSMA-PET/CT led to a change in planned management in 51% of patients, with the impact being greater in the group of patients with biochemical failure (62% change) than in patients undergoing primary staging (21% change). Other studies showed similar changes in clinical decisions.

More recently, F-labeled PSMA agents have been developed in order to solve problems concerning the production amount, availability, clinical utility, and image resolution of Ga PSMA agent. $^{18}$F-DCFBC and $^{18}$F-DCFPyL have been tested, and the preliminary experience with these tracers is promising.

**CONCLUSIONS**

The development of novel imaging techniques in recent years has not satisfied the unmet need of improving Pca diagnosis and staging. There is a demand of improving detection of clinically significant Pca and avoid overdetection of clinically insignificant cancers. As information on tumor characteristics, location, or extent is gaining importance, imaging becomes more relevant to the management of our Pca patients. Improvements in imaging techniques enable us to replace the strategy of random biopsies in the future by targeted biopsies. mpMRI appears to have advantages in Pca detection and claims for itself a bigger role in Pca diagnosis.

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There are no conflicts of interest.

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