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Artificial intelligence in multiparametric prostate cancer imaging with focus on deep-learning methods

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ABSTRACT

Prostate cancer represents today the most typical example of a pathology whose diagnosis requires multiparametric imaging, a strategy where multiple imaging techniques are combined to reach an acceptable diagnostic performance. However, the reviewing, weighing and coupling of multiple images not only places additional burden on the radiologist, it also complicates the reviewing process. Prostate cancer imaging has therefore been an important target for the development of computer-aided diagnostic (CAD) tools. In this survey, we discuss the advances in CAD for prostate cancer over the last decades with special attention to the deep-learning techniques that have been designed in the last few years. Moreover, we elaborate and compare the methods employed to deliver the CAD output to the operator for further medical decision making.

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1. Introduction

1.1. Computer-aided diagnosis and prostate cancer

For a significant part, the field of radiology concerns the interaction of medical imaging technology and human observers. The diagnostic value of a radiological technique is to a large extent dependent on the human capability to interpret the provided information. Diagnostic performances therefore not only suffer from the natural patient variability on imaging, but also from the variability in observer experience, training and capabilities [1]. Recent advances in artificial intelligence (AI), and more specifically in machine and deep learning technology, enable computer-aided diagnosis (CAD), where computer algorithms support or perform part of the image interpretation [2,3]. This is especially useful in multiparametric imaging, in which multiple modalities or techniques are combined to make the final diagnosis [4].

There is a wide variety of techniques to combine medical images; from subjective reviewing of the modalities simply shown alongside each other to dedicated machine-learning algorithms. However, whereas radiological images typically display physical parameters – such as relaxation times in magnetic resonance imaging

(MRI), echogenicity in ultrasound (US) imaging, and radiodensity in computed tomography (CT) – the combined interpretation of multiple techniques is complicated by the need for an appropriate method to weigh a combination of parameters. Moreover, the field of radiomics (i.e., the use of quantitative imaging features that are often ill-recognised by the human eye) increasingly adds parameters to the multiparametric approach [5]. Multiparametric combination by using a scoring system (such as a Likert scale [6,7]) can only be applied with a relatively low number of parameters. On the other hand, some learning algorithms for classification are known to handle and exploit more than millions of parameters. These learning algorithms form the basis of modern CAD technology.

Today, multiparametric imaging is considered for e.g. hepatocellular carcinoma [8], glioblastoma [9], thyroid nodules [10], brain tumours [11], and lung lesions [12]. However, prostate cancer (PCa) imaging is the most typical example of multiparametric approach [13]. Ranking as the most prevalent form of cancer among men in America [14] and Europe [15], PCa imaging has shown limited reliability and systematic biopsy has remained the standard diagnostic route despite its associated risks [16,17]. Recent years have seen rapid developments in multiparametric MRI, in particular by means of the PI-RADS scoring system [18,19]. Due to the high PCa prevalence and the difficulties in imaging, CAD algorithms have been developed for this purpose since the 1990s. Previous reviews into CAD for PCa, such as those of Wang et al. in 2014 [20] and

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Lemaître et al. in 2015 [21] have highlighted this development. In this review, we discuss the progress in multiparametric CAD for PCa during the deep-learning revolution. Moreover, as the output of CAD algorithms still has to be delivered to the operator, we specifically survey the current methods employed at the interface between algorithm and observer.

1.2. Classical machine learning

Machine learning is a field of AI covering computer algorithms that can be trained to execute a certain task, for example classification. Supervised machine learning for classification requires a set of training samples (i.e., instances) that are characterised by the input variables (i.e., features) and belong to several output classes (i.e., labels). In the training phase, the classifier is trained to predict the output label of each instance based on the input features [22]. After being trained, the classifier can be used to classify new data. An example of unsupervised machine learning is the clustering of voxels with the same characteristics, which in the perspective of CAD algorithms could correspond to different tissue types [23]. Over the years, many machine-learning algorithms have been developed for classification purposes (see Table 1 for a selection). Traditionally, we distinguish discriminative and generative approaches. The first entails algorithms that are solely trained to separate two or more classes, whereas the latter works by modelling the classes and classifying new input based on the underlying characteristics.

Perhaps one of the simplest discriminative methods is based on the resemblance of a sample to those already seen by the classifier. A k -nearest neighbour (k -NN) classifier is a discriminative algorithm that assigns a class based on the k training instances that most closely match the input variables, based on a certain distance metric [24]. In line with this, k -means clustering techniques can be employed to find k clusters of training instances that are most alike in terms of image features, which then have to be matched to certain classes [25]. In addition, Support vector machines (SVMs) aim to separate classes in multidimensional space (i.e., each input variable represents a dimension) by computing a hyperplane that maximises the margin between the training instances of each class that are closest to that of the other class, the support vectors [26]. When the data are not strictly separable, training instances at the wrong side of the hyperplane are penalised in the maximisation procedure. SVMs with linear as well as nonlinear hyper-surfaces, exploiting the (local) transformation of the feature space by a kernel, have been developed [27]. Another discriminative approach features classification and regression trees (CARTs), which are intuitive tools for decision making as they classify by a series of consecutive logical decisions based the input variables [28]. CARTs are trained by evaluating each input variable for the most efficient separation of the data classes based on a splitting criterion (e.g., Gini's diversity index and the cross entropy) [29]. A single CART is considered a weak learner. To enhance their performance, random forest classifiers (RFC) were developed. They consist of an ensemble of CARTs that are trained on a random subset of the training data (i.e., bootstrap aggregating [30]) and features [31]. The final classification is generated by a combination of all trees in the RFC, for instance by majority vote. More in general, RFCs are categorised as ensemble classifiers (EC) that exploit multiple (weak) learners (of any architecture) to come to one decision [32].

Among generative (i.e., probabilistic) approaches, Bayesian classifiers (BC) exploit Bayes' theorem to calculate output probability based on input features that are assumed independent [33]. Alternatively, in discriminant analyses (DA) models are established optimally separate two classes by maximising their (co)variance, assuming the independent input variables to be Gaussian distributed [34]. Similarly, logistic regression models the probability of belong-

Table 1
Selection of machine-learning methods for classification.

type classify	k -NN	DA	GMM	SVM	EC, RFC	ANN
hyperparameters	discriminative as most similar k training instances	generative according to probability model	generative following class probability density	discriminative according position to hyperplane features, hyperplane shape, etc.	discriminative vote by ensemble	discriminative/ generative neural network outcome
# of trainable parameters	number of samples	features, distance metric, k , etc.	features, number of Gaussians, regularisation	etc.	weak learners, number of trees, randomness, split criterion, etc.	network architecture, cost function, etc.
advantages	simple, fast training, etc.	1–10 simple, fast training, etc.	10–100 parametric, high generalisability, etc.	10–100 fast classification, high dimensionality, etc.	100–1000 intuitive, internal feature selection, etc.	$\geq 100,000$ powerful, internal feature extraction, etc.
drawbacks	not versatile, large storage needed, etc.	strong assumption data requirements, etc.	computationally complex, dimensionality limited, etc.	long training time, limited interpretability, etc.	large number of hyperparameters, etc.	complex, many training samples needed, limited interpretability, etc.

Abbreviations: k -NN = k -Nearest Neighbour; DA = Discriminant Analysis; GMM = Gaussian Mixture Model; SVM = Support Vector Machine; EC = Ensemble Classifiers; RFC = Random Forest Classifier; ANN = Artificial Neural Network.

Table 2

Overview of MRI imaging techniques for PCa.

	T2-Weighted	Diffusion-Weighted	Spectroscopy	Contrast-Enhanced
physics	spin-spin relaxation times	water diffusion	metabolite concentration	contrast concentration
suspicious for PCa	hypointense lesions	hypodiffusive lesions	lesions with high choline/creatine	early enhancing regions
underlying physiology	diminished water content	high collagen content and cell density	high cell turnover and cell density	hyper- and neovascularisation
parameters	T2W, T1W, PD, etc.	ADC, DTI, etc.	SVS, MRSI, etc.	DCE-MRI, dispersion MRI, etc.

Abbreviations: T2W = T2-weighted MRI; T1W = T1-weighted MRI; PD = Positron Density Imaging; ADC = Apparent Diffusion Coefficient; DTI = Diffusion Tensor Imaging; SVS = Single-Voxel Spectroscopy; Magnetic Resonance Spectroscopic Imaging; DCE-MRI = Dynamic Contrast-Enhanced MRI.

ing to one of the two classes as a logistic function in the input space [35]. Another generative approach is Gaussian mixture modelling (GMM), in which the distribution of the input variables of a certain class in the training set is approximated by an explicit mixture of Gaussian functions [36,37]. This allows us to calculate the probability of each combination of input variables to be drawn from either of the classes, and classify that instance accordingly. An advantage of GMMs is that they generalise well due to their generative and approximate nature; on the other hand, GMMs tend to be computationally complex, non-Gaussian parameter distributions have to be approximated with large mixtures, and rigorous feature selection is required [37,38].

1.3. Deep learning

Artificial neural networks (ANNs) are universal function approximators [39,40] and can be both discriminative and generative in nature [41]. ANNs can be small, consisting of a few layers such as multilayer perceptrons (MLPs), but they can also form the base for deep neural networks (such as deep feedforward and recurrent neural networks), belonging to the family of deep-learning techniques, probably the most powerful but complex approaches to machine learning [42]. Deep learning is characterised by an architecture of connected nonlinear functions (i.e., layers) that learn multiple levels of representations of the input data, thereby extracting possibly millions of features [43]. Especially convolutional neural networks (CNNs) in which a series of convolutional filter layers are exploited are suitable for image processing [43], leveraging translational invariances as an image prior to drastically reduce its number of parameters. Although medical application of deep learning is challenged by its need for vast amounts of expansive (labelled) training data [44], this constraint is increasingly lifted by techniques such as transfer learning [45], data augmentation [46], or the application of generative methods [47].

1.4. Prostate cancer imaging

PCa imaging is still a highly active field in biomedical development. The choice of the imaging modalities that should serve as the input for CAD technology can depend on many factors, such as cost, availability, accuracy, and general clinical practice. We briefly discuss the nature and diagnostic potential of PCa imaging techniques, as knowledge of the data is paramount to the development of meaningful CAD approaches.

1.4.1. Magnetic resonance imaging

MRI, and in particular the multiparametric approach of this technique, is most often used for PCa diagnosis (see Table 2). Traditionally, the mapping of spin-lattice (i.e., longitudinal or T1W) and spin-spin (i.e., transverse or T2W) relaxation times is used to visualise soft tissue anatomy, in particular water and fat content [48]. T1W images suffer from low zonal anatomy discrimination and post-biopsy artefacts [49], limiting their use for PCa imaging. Instead, in T2W images, PCa appears as a homogeneous, hypointense, and ill-delineated [50,51] lesion due to its diminished water content [52]. Diagnosis is nonetheless often complicated by

benign abnormalities having a similar appearance or healthy tissue being more heterogeneous in nature [53]. For reference, sensitivities and specificities of 55%–68% and 71%–82% are reported for T2W images [54].

Diffusion-weighted images visualise tissue structures based on the diffusive behaviour of the water molecules within; when Brownian motion is hindered by interaction with fibres, membranes, or other structures – which is typically the case in the dense collagen-rich tumour environment – bright lesions occur on diffusion-weighted images [55,56]. At the same time, the apparent diffusion coefficient (ADC) is lower [57] and PCa lesions therefore appear as dark nodules on the ADC map [51]. In terms of sensitivity and specificity, diffusion-weighted imaging achieves a performance of 67%–72% and 87%–90%, respectively [58].

Metabolic information is obtained through magnetic resonance spectroscopy (MRS), which assesses the peaks in the resonance frequency spectrum to identify specific metabolites. PCa lesions are known to exhibit higher quantities of choline whilst citrate levels are lower [59,60], caused by higher cell membrane turnover and density [61]. Even though techniques are rapidly advancing [62], MRS imaging currently suffers from a relatively poor spatial resolution (i.e., ‘meta’-voxels) and its added value in primary PCa detection is not confirmed [63].

Functional imaging of the prostate is conducted through dynamic contrast-enhanced (DCE) MRI, where the distribution of gadolinium-based contrast agents is monitored for a period of time after intravenous injection. The high density and increased permeability of angiogenic microvasculature results in PCa appearing as earlier, faster, and more intensely enhancing areas [64]. Unfortunately, prostatitis-induced perfusion increase can result in false positives as well [19]. In a meta-analysis, DCE-MRI was characterised by a sensitivity of 53%–62% and a specificity of 80%–85% [58]. Several techniques are available to quantify contrast-agent behaviour in the prostate [65–67], for example the Brix, Tofts, and dispersion models [68].

A standardised procedure for multiparametric MRI (mpMRI) was introduced in 2012 [18], the Prostate Imaging Reporting and Data System (PI-RADS), a system in which the clinician grades a lesion on a 1-to-5 scale from benign to malignant. Its second version, that is, PI-RADS v2 [19,69], has been subjected to several large clinical trials [70–72]. A sensitivity and specificity of 93% and 41%, respectively, were reported for Gleason $\geq 4+3$ PCa [70]. A large portion of the false-negative findings in mpMRI are due to significant lesions that are invisible or incorrectly classified as benign [73], whereas false-positive findings are associated with benign hyperplasia, prostatitis, and especially the combination of the two [74]. Currently, especially a more practical biparametric MRI approach (based on T2-weighted and diffusion-weighted MRI) is being investigated [75,76].

1.4.2. Ultrasound imaging

Transrectal ultrasound (TRUS) was introduced in 1968 [77] and is mostly used for guiding systematic biopsy [78]. Still, TRUS-guided biopsy in suspicious hypoechoic lesions, for instance, is highly recommended [79]. The fact remains, however, that a fraction of over 30% of prostate malignancies are isoechoic [78,80]. An

Table 3
Overview of ultrasound imaging techniques for PCa.

	B-mode	Elastography	Doppler Sonography	Contrast-Enhanced
physics	echogenicity	elasticity	blood flow	contrast concentration
suspicious for PCa	hypoechoic lesions	hypoelastic lesions	hyperperfused lesions	early-enhancing lesions
underlying physiology	high cell density	high collagen content and cell density	hypervascularisation	hyper- and neovascularisation
parameters	greyscale, C-TRUS, QUS, etc.	QSE, ARFI, SWE, etc.	CDU, PDU, etc.	CEUS, CUDI, USMI, etc.

Abbreviations: C-TRUS = Computerised TRUS; QUS = Quantitative Ultrasound; QSE = Quasi-Static Elastography; ARFI = Acoustic Radiation Force Imaging; SWE = Shear-Wave Elastography; CDU = Colour Doppler Ultrasonography; PDU = Power Doppler Ultrasonography; CEUS = Contrast-Enhanced Elastography; CUDI = Contrast Ultrasound Dispersion Imaging; USMI = Ultrasound Molecular Imaging.

additional problem of greyscale TRUS is that benign hyperplasia and prostatitis are also hypoechoic lesions [78]. Fortunately, also within the field of US, there are multiple other techniques available (see Table 3 for an overview).

For example, it is also possible to assess strain (i.e., the deformation resulting from a certain stress, the force applied on the tissue) and tissue stiffness [81]. We distinguish quasi-static methods, where stress is delivered to the tissue manually, and dynamic methods, which employ an acoustic-radiation-force “push” pulse [82]. The most used dynamic technique for the prostate is shear-wave elastography (SWE). Here, the transversally moving shear waves generated by the “push” are analysed, their speed being related to tissue elasticity in terms of the Young’s modulus [82]. Typical elasticity values for healthy and malignant tissue are higher for the transition zone compared to the peripheral zone [83]. In meta-analysis on the performance of quasi-static elastography (QSE), appreciable specificities (60%–95%) and sensitivities (71%–82%) have been reported [84]. As for SWE, a recent meta-analysis indicates that it yields a sensitivity and specificity of 84% and 86%, respectively [85].

Alternatively, with Doppler sonography, (blood) flow and perfusion in tissue are visualised based on the reflected echo data. Here, we distinguish colour Doppler ultrasonography (CDU) and power Doppler ultrasonography (PDU). CDU depicts flow toward and away from the transducer shown in a colour-coded image. In contrast, PDU is based on the power of the Doppler signal, which is usually correlated with number of scatterers (i.e., cells) that are moving in the sample volume, and is not sensitive to aliasing [86]. Although vascularisation is a prime marker of PCa [87], the feasibility of Doppler imaging in PCa diagnosis is limited and studies indicate that it is unable to detect the small flows in the microvasculature [86,88,89].

Contrast-enhanced ultrasound (CEUS) was first observed in 1968 during imaging of the aortic root [90]. Nowadays, commercially available gas-filled microbubbles (i.e., of a size $< 8 \mu\text{m}$) are extensively used as ultrasound contrast agents (UCAs) [91]. In dynamic CEUS, microbubble collapse is prevented by using low-energy US pulses [92]. On the other hand, microbubble bursting with a high-energy ultrasound pulse can also be exploited, assessing UCA refilling of the (micro)vessels to estimate perfusion [88,93]. Meta-analyses on CEUS confirm its value in PCa diagnostics, with sensitivities of 70% and specificities of 74% [94], but stress the lack of standardisation and therefore inhomogeneous findings [95]. Quantification of CEUS is often based on measured time-intensity curves (TICs) [96], extracting features such as the bolus arrival time, maximum enhancement (time), and the wash-in rate from the TICs [97–99]. Rather than perfusion, also dispersion characteristics can be extracted by so-called contrast-ultrasound dispersion imaging (CUDI), which is based on modelling of the contrast spreading through the prostate as a convective-dispersion process [100–104].

Where mpMRI has been widely investigated, to date, only few studies looked at the combination of US modalities [98,105]. Matsuoto et al. combined greyscale TRUS and CEUS [106], Brock

et al. as well as Aigner et al. appended CEUS scanning with real-time QSE [107,108], and CEUS was also combined with ultrasound Doppler imaging [109,110]. Multiparametric ultrasound has not been investigated yet in a standardised fashion, although 2018, there are trials underway combining B-Mode, Doppler sonography, elastography, and CEUS [111,112].

2. Implementation of CAD in prostate cancer

A comprehensive table of the literature on CAD in PCa is shown in Table 4. Its contents will be more elaborately discussed in the following sections.

2.1. Input modalities

In the light of the recent advances in multiparametric imaging for PCa, a majority of the CAD tools are MRI-based. Most recent studies feature T2W and ADC (and DWI) acquisitions, sometimes with the addition of DCE, which is in line with the latest developments in PI-RADS v2 [69] and biparametric MRI [76,113] scoring. When DCE recordings are used, model-based features are generally first extracted to map the temporal information in one volumetric frame that matches T2W or DWI. A significant subset of the CAD algorithms require MRS as input and, as a result, their output is most often on a meta-voxel level. Algorithms that only require a T2W input are based on texture analysis and pattern recognition, with either hand-crafted or auto-learned features. US-based CAD systems are almost exclusively designed for B-mode or radiofrequency-TRUS, aiming to extract patterns that are invisible to the naked eye but are meaningful in a collective setting. Unlike MRI, algorithms exploiting the plurality of US techniques (such as CEUS or SWE) are scarce. There is no clear difference in input modalities between classical and deep learning approaches.

2.2. Prostate segmentation

Prostate segmentation, and more importantly zonal segmentation (i.e., distinguishing also the peripheral and transition/central zones of the prostate), is an important step in the CAD framework. During training, segmentation allows the classifiers to focus on prostate tissue only; as for implementation, it enables the algorithm to visualise suspicious areas inside the gland. Over the years many techniques have been developed for automatic segmentation [197,198], but in recent years deep-learning approaches have become staple for segmentation purposes. Several papers make use of zone-specific classification algorithms [115,132,158,180,199], only study the peripheral zone [131,139], or specify the zone as different classes within classification [173,174]. This observation is in line with the PI-RADS guidelines [69], which are also zone-dependent, suggesting that both healthy tissue and malignant tissue can look different among zonal location. Deep learning has shown clear benefit for segmentation in CAD. Currently, in MRI [200] as well as in US [201] there are algorithms available for automatic zonal segmentation, outperforming many previous approaches in terms of accuracy and robustness.

Table 4

Overview of the published CAD designs in terms of artificial intelligence method, performance, and visualisation techniques employed.

Reference			Imaging		AI	Validation			Performance				Visualisation			Remarks
Author	Year		Modality	Techniques	Method	Approach	#	GT	ROC	Acc	Sens	Spec	Input	Output	Map	Dataset
Bayesian Classifiers																
Giannini	2013	[114]	MRI	T2W, DWI, DCE	BN	LOOCV	10	RP	0.87		79	84	imaging	voxel	probability	
Jin	2018	[115]	MRI	ADC, DCE	BN	LOOCV	34	RP	0.82				imaging	voxel	probability	
Mazzetti	2011	[116]	MRI	T2W, MRS	BN	LOOCV	10	RA	0.90		82	82	lesions	voxel	probability	
Rampun	2016	[117]	MRI	T2W	BN	9-fold CV	45	RP	0.90				imaging	voxel	classification	
Clustering Algorithms																
Rundo	2017	[118]	MRI	T1W, T2W	c-means	LOOCV	21	-					imaging	cluster	classification	
Tiwari	2007	[119]	MRI	MRS	k-means	N/A	14	Bx		78			imaging	cluster	classification	ACRIN
Tiwari	2008	[120]	MRI	T2W, MRS	k-means	N/A	18	Bx		87	85		imaging	voxel	classification	ACRIN
Tiwari	2009	[121]	MRI	MRS	k-means	5-fold CV	18	Bx			81	65	imaging	cluster	classification	ACRIN
Viswanath	2008	[122]	MRI	DCE	k-means	N/A	21	RP		77			imaging	cluster	classification	
Viswanath	2008	[123]	MRI	MRI, MRS	k-means	N/A	16	RP			87	84	imaging	cluster	classification	ACRIN
Gómez-Ferrer	2011	[124]	US	B-mode	k-NN	hold-out	66	Bx	0.6				imaging	voxel	classification	
Llobet	2007	[125]	US	B-mode	k-NN	hold-out	289	Bx	0.62		92	18	imaging	voxel	classification	
Discriminant Analysis																
Chan	2003	[126]	MRI	T2W, PD, ADC,	LDA	LOOCV	15	RP	0.84				imaging	voxel	probability	
Peng	2013	[127]	MRI	T2W, ADC, DCE	LDA	LOOCV	48	Bx	0.95		82	95	lesions	lesion	classification	
Rohrbach	2018	[128]	US	RF-US, Clin Vars	LDA	10-fold CV	163	Bx	0.81				imaging	voxel	probability	
Vos	2012	[129]	MRI	TW2, ADC, DCE	LDA	3-fold CV	200	MR-Bx			92		imaging	voxel	probability+lesion	
Langer	2009	[130]	MRI	T2W, DWI, DCE	LRA	bootstrapping	25	RP	0.71				imaging	voxel	probability	
Viswanath	2019	[131]	MRI	T2W	QDA	hold-out	85	RP	0.74				imaging	voxel	classification	
Viswanath	2012	[132]	MRI	T2W	QDA	3-fold CV	22	RP	0.86				imaging	voxel	probability	
Rule-based Classifiers																
Dinh	2016	[133]	MRI	ADC, DCE	Rule-based	hold-out	106	MR-Bx	0.89				lesions	lesion	probability	
Puech	2009	[134]	MRI	DCE	Rule-based	N/A	100	Bx	0.77				lesions	lesion	classification	
Support Vector Machines																
Ozer	2009	[135]	MRI	T2W, DWI, DCE	RVM	LOOCV	20	RP			78	74	imaging	voxel	classification	
Niaf	2014	[136]	MRI	T2W, ADC, DCE	P-SVM	LOOCV	49	RA	0.89				lesions	lesion	probability	
Artan	2010	[137]	MRI	T2W, DWI, DCE, FSE	SVM	LOOCV	21	RP	0.79		73	67	imaging	voxel	classification	
Fehr	2015	[138]	MRI	T2W, ADC	SVM	10-fold CV	217	RP		84	87	84	lesions	lesion	classification	
Giannini	2015	[139]	MRI	T2W, DWI, DCE	SVM	LOOCV	56	RP	0.91				imaging	voxel	probability+lesion	
Han	2008	[140]	US	B-mode	SVM	hold-out	51	Bx			92	95.9	imaging	lesion	classification	
Kelm	2007	[141]	MRI	MRS	SVM	LOOCV	24	RA	0.99				imaging	voxel	classification	
Kwak	2015	[142]	MRI	T2W, DWI	SVM	hold-out	244	MR-Bx	0.89				imaging	voxel	probability	
Litjens	2011	[143]	MRI	T2W, ADC, DCE	SVM	LOOCV	188	RA		75	83		imaging	voxel	probability	
Litjens	2012	[144]	MRI	T2W, ADC, DCE	SVM	LOOCV	288	MR-Bx					imaging	voxel	probability+lesion	
Liu	2013	[145]	MRI	T2W, ADC, DCE	SVM	hold-out	54	Bx	0.82				lesions	lesion	classification	
Liu	2011	[146]	MRI	T2W, ADC, DCE	SVM	LOOCV	20	RP	0.89		90	74	imaging	voxel	classification	
Lopes	2010	[147]	MRI	T2W	SVM	hold-out	27	RP			85	93	imaging	voxel	classification	
Moradi	2012	[148]	MRI	DTI, DCE	SVM	LOOCV	29	Bx	0.96				imaging	voxel	probability	
Niaf	2012	[149]	MRI	T2W, ADC, DCE	SVM	LOOCV	30	RP	0.89				lesions	lesion	classification	
Parfait	2012	[150]	MRI	MRS	SVM	5-fold CV	22	RA			84	98	imaging	voxel	classification	
Shah	2012	[151]	MRI	T2W, ADC, DCE	SVM	LOOCV	24	Bx					lesions	voxel	probability	
Sung	2011	[152]	MRI	DCE	SVM	LOOCV	42	RP		83	77	77	imaging	voxel	classification	
Tiwari	2012	[153]	MRI	T2W, MRS	SVM	3-fold CV	36	RP	0.90	84			imaging	voxel	probability	
Vos	2008	[154]	MRI	T2W, DCE	SVM	LOOCV	34	RP	0.83				lesions	lesion	probability	
Vos	2010	[155]	MRI	T2W, DCE	SVM	LOOCV	34	RP	0.89				lesions	lesion	probability	

(continued on next page)

Table 4 (continued)

Reference		Imaging		AI	Validation			Performance				Visualisation			Remarks
Author	Year	Modality	Techniques	Method	Approach	#	GT	ROC	Acc	Sens	Spec	Input	Output	Map	Dataset
Ensemble Classifiers															
Huynen	1994	[156]	US	B-mode	CART	hold-out	51	Bx		80	88	imaging	voxel	probability	PROSTATEx PROSTATEx I2CVB
Tiwari	2010	[157]	MRI	T2W, MRS	PBT	LOOCV	19	-	91			imaging	cluster	classification	
Kwon	2018	[158]	MRI	T2W, PD, DWI, DCE	RFC	hold-out	244	Bx	0.82			lesions	lesion	probability	
Lay	2018	[159]	MRI	T2W, ADC, DWI	RFC	hold-out	223	Bx	0.90			imaging	lesion	probability	
Lemaître	2017	[160]	MRI	T2W, DWI, DCE, MRS	RFC	LOOCV	17	RP	0.58			imaging	voxel	probability	
Litjens	2014	[161]	MRI	T2W, PD, DWI, DCE	RFC	LOOCV	347	MR-Bx	0.89			imaging	voxel	probability	
Tiwari	2013	[162]	MRI	T2W, MRS	RFC	LOOCV	29	RP	0.89			imaging	voxel	probability	
Trigui	2017	[163]	MRI	DWI, DCE, MRS	RFC	10-fold CV	34	RA				imaging	voxel	classification	
Viswanath	2009	[164]	MRI	T2W, DCE	RFC	3-fold CV	6	RP	0.82			imaging	voxel	classification	
Wildeboer	2019	[165]	US	CEUS, B-mode, SWE	RFC	LOOCV	48	RP	0.90			imaging	voxel	probability	
Gaussian Mixture Modelling															
Wildeboer	2016	[166]	US	CEUS, CUDI	GMM	LOOCV	19	RP		81		imaging	voxel	probability	
Wildeboer	2019	[167]	US	CEUS, CUDI	GMM	LOOCV	43	RP	0.81			imaging	voxel	probability	
Neural Networks															
Giannini	2017	[168]	MRI	T2W, ADC	ANN	N/A	58	RP				imaging	voxel	probability+lesion	PROSTATEx I2CVB I2CVB
Loch	1999	[169]	US	B-mode	ANN	hold-out	61	RP		79	99	lesions	lesion	classification	
Matulewicz	2014	[170]	MRI	DCE	ANN	hold-out	18	RP+RA	0.97			imaging	voxel	classification	
Schmitz	1999	[171]	US	RF-US	ANN	LOOCV	33	RP		82	88	imaging	voxel	probability	
Abraham	2018	[172]	MRI	T2W, ADC, DWI	CNN	10-fold CV	204	Bx	0.98	94		lesions	lesion	classification	
Alkadi	2018	[173]	MRI	T2W	CNN	LOOCV	19	RA	1.00	89		imaging	voxel	probability	
Alkadi	2019	[174]	MRI	T2W	CNN	LOOCV	19	RA	1.00	89		imaging	voxel	probability	
Cao	2019	[175]	MRI	T2W, ADC	CNN	5-fold CV	417	RP	0.81			imaging	voxel	probability+lesion	
Kiraly	2017	[176]	MRI	T2W, ADC, DWI, DCE	CNN	5-fold CV	202	Bx	0.83			lesions	lesion	classification	
Kohl	2017	[177]	MRI	T2W, ADC, DWI	CNN	4-fold CV	152	RP		55	98	imaging	voxel	classification	TJPCa PROSTATEx PROSTATEx
Le	2015	[178]	MRI	T2W, ADC	CNN	hold-out	364	Bx		90	96	imaging	voxel	probability	
Liu	2017	[179]	MRI	T2W, ADC, DWI, DCE	CNN	hold-out	341	Bx	0.84			imaging	patient	probability	
Mehrtash	2017	[180]	MRI	DWI, DCE	CNN	hold-out	344	Bx	0.80			lesions	patient	probability	PROSTATEx
Reda	2018	[181]	MRI	DWI, Clin Vars	CNN	LOOCV	18	Bx		94	89	100	imaging	patient	probability
Reda	2017	[182]	MRI	DWI, ADC	CNN	4-fold CV	53	RP		92	83	100	imaging	patient	probability
Schelb	2019	[183]	MRI	T2W, ADC, DWI	CNN	hold-out	312	Bx		96	31	imaging	voxel	probability	PROSTATEx
Song	2018	[184]	MRI	T2W, ADC, DWI	CNN	hold-out	195	Bx	0.94	87	91	lesions	lesion	classification	
Sumathipala	2018	[185]	MRI	T2W, ADC, DWI	CNN	hold-out	186	RP	0.93			imaging	voxel	probability	
Tsehay	2017	[186]	MRI	T2W, ADC, DWI	CNN	2-fold CV	108	RP	0.90			imaging	voxel	probability	PROSTATEx
Wang	2017	[187]	MRI	T1W, T2W, DWI, DCE	CNN	10-fold CV	172	RP	0.84			imaging	patient	classification	
Wang	2018	[188]	MRI	T1W, T2W, DWI, DCE	CNN	hold-out	195	RP		85		imaging	voxel	classification	
Wang	2018	[189]	MRI	T2W, ADC	CNN	5-fold CV	360	RP	0.96			imaging	biopsy	probability+lesion	PROSTATEx
Xu	2019	[190]	MRI	T2W, ADC, DWI	CNN	hold-out	346	Bx	0.97	93		imaging	voxel	probability+lesion	
Yang	2017	[191]	MRI	T2W, ADC	CNN	hold-out	160	Bx	1.00			imaging	voxel	probability+lesion	
Yuan	2019	[192]	MRI	T2W, ADC	CNN	hold-out	132	Bx		87		lesions	lesion	classification	PROSTATEx
Zhong	2018	[193]	MRI	T2W, ADC	CNN	hold-out	140	RP	0.73			lesions	lesion	classification	
Feleppa	2001	[194]	US	RF-US	MLP	14-fold CV	250	Bx	0.848			lesions	lesion	classification	
Feleppa	2004	[195]	US	RF-US, Clin Vars	MLP	10-fold CV	67	Bx	0.8			imaging	voxel	probability	
Ampeliotis	2008	[196]	MRI	DCE, T2W	PNN	25-fold CV (paired)	10	Bx	0.90			lesions	lesion	classification	

Abbreviations: **Imaging** B-mode = Brightness Mode; T1W = T1-weighted imaging; T2W = T2-weighted imaging; MRS = Magnetic Resonance Spectroscopy; PD = Proton Density Imaging; DWI = Diffusion-Weighted Imaging; DCE = Dynamic Contrast-Enhanced Imaging; ADC = Apparent Diffusion Coefficient; CEUS = Contrast-Enhanced Ultrasound; RF-US = Radiofrequency Ultrasound; Clin Vars = Clinical Variables; FSE = Fast-Spin Echo; **Artificial Intelligence (AI)** BC = Bayesian Classifier; k-NN = k-Nearest Neighbour; LDA = Linear Discriminant Analysis; LRA = Logistic Regression Analysis; QDA = Quadratic Discriminant Analysis; RVM = Relevance Vector Machine; (P-)SVM = (Probabilistic) Support Vector Machine; RFC = Random Forest Classifier; GMM = Gaussian Mixture Model; ANN = Artificial Neural Network; CNN = Convolutional Neural Network; MLP; Multi-layer Perceptron; PNN = Probabilistic Neural Network; Validation (LOOCV) = (Leave-One-Out) Cross Validation; **Ground Truth (GT)** (MR-)Bx = (MRI-targeted) Biopsy; RP = Radical Prostatectomy; RA = Radiologist's Annotation.

2.3. Inter-modality registration

As tissue might have moved between several acquisitions, registration between techniques or modalities is especially important for CAD algorithms generating voxelwise maps that require local information to be matched voxel-to-voxel [202]. Usually, this involves affine (e.g., [154,158,164,196,203,204]) and/or elastic (e.g., [114,155,176,184]) transformation towards the target technique, optimised for image similarity (e.g., correlation and mutual information) or visual landmarks. In addition, for voxelwise validation, the imaging has to be correlated to registered histopathology. We refer to [205] for an overview of appropriate registration techniques. In recent years, deep learning has also been employed for registration [206], including in the prostate [207]. Image registration is also important with regard to therapy [208]; neural networks are currently being explored for this purpose as well [209–211].

2.4. Feature extraction

CAD tools rely to a great extent on the extraction of texture features, radiomic features or model-based features, either to reveal subtle patterns that can be typical for malignancy or to reduce the dimensionality of imaging. Image-based, texture-based, or statistical features are especially important in multiparametric imaging of individual techniques [212,213].

As DCE-MRI or CEUS often have a temporal component, feature extraction is an important step to reduce the dimensionality of the input by describing the voxelwise dynamics by one or a few values. For this, semi-quantitative features such as the peak enhancement or contrast-onset time can be used [214,215]. Usually, however, the contrast dynamics are quantitatively modelled. As US contrast agents generally remain intravascular, whereas MRI contrast agents can extravasate, different models are applied. For MRI, pharmacokinetic models such as mostly Tofts [114–116,130,143,144,149,158,176,188], but also Brix [135,137,152,216] or the Weibull function as well as the phenomenological universalities approach [114,116] are used for AI. Gamma variate, lognormal, (modified) local density random walk, and more advanced convective-dispersion-based models are available for US [68,217], and a few of these have been used for multiparametric combination [166].

Also data-driven feature extraction methods can be employed, most notably blind source separation approaches such as principal component analysis and nonnegative matrix factorisation [119,120,141,181], and embedding methods such as non-linear mapping [121–123,157]. Deep-learning-based autoencoders have added to the spectrum of features that can be extracted from imaging [181,182,218]. Often, feature selection is employed to prune the feature space for those that are relevant and complementary for decision making.

2.5. CAD Validation

In terms of validation, the most common problem in machine learning is that the classifier represents the input data so well that it does not generalise to new samples (i.e., overfitting). Therefore, a classifier has to be validated on a test set of unseen samples. The most common ways to implement this paradigm are “hold-out” (i.e., separating a subset of samples that is only used to test the final classifier), “ k -fold cross-validation” (k -fold CV; i.e., separating the training set in k subsets that are consecutively used to validate a classifier trained on the other subsets), and “leave-one-out cross-validation” (LOOCV; i.e., a special case of k -fold cross-validation where k equals the number of independent samples in the training set) [219,220]. Moreover, classifiers depend on hyperparameters that define, for example, their structure or the features

to be used. These parameters can be globally defined, or optimised in the training process. It is important to be aware of the impact of hyperparameters on the generalisability of the classifier. In this respect, the test set allocated in the hold-out procedure should be used completely independent of the optimization to obtain the classifier performance.

Due to the relatively small sample sizes, most researchers use an LOOCV procedure, thereby maximising the training set while maintaining an independent test set. Deep learning algorithms, which are most powerful but require larger patient databases, are more frequently validated with a hold-out procedure with a separate training, validation, and test dataset. The PROSTATEx challenge [221], as well as I2CVB and ACRIN datasets have allowed the use of larger datasets and better means of comparison. Multi-centre or multi-vendor studies, however, are still scarce.

Some studies [136,143,173,174], especially those using MRS [116,141,150,163], use (biopsy-based) expert annotations as ground truth. This way, algorithms are trained to replicate human interpretation, and histology-confirmed cancer localisation rates cannot be assessed.

Lesion classification are most often validated using biopsy results as a ground truth. Although sometimes targeted biopsies are performed, most often only the results of systematic biopsy are considered. This procedure is based on a 10- to 12 biopsy-core template [79,222] and has served as the guideline-recommended approach to PCa diagnosis [223]. However, the use of biopsy results for whole-prostate maps remains hampered by the fact that biopsy notoriously leads to underdiagnoses, with malignancies being found in up to 30% of the negative-biopsy patients that underwent repeat biopsy [79]. In patients with persisting PCa suspicion despite repeated negative ≥ 8 -core biopsy, there is still a 40% chance of finding PCa using saturation biopsy (~ 25 cores) [224].

Therefore, PCa localisation should initially be validated with radical prostatectomy (RP) specimens as ground truth. RP entails the surgical removal of the prostate [225] and it is the standard-of-care for intermediate- and high-risk nonmetastatic PCa [223]. Subsequent histopathological examination of the RP specimen is paramount to prognosis and treatment evaluation [226,227], and, in this case, serves as an excellent ground truth map for validation, provided that it is well registered with imaging [205].

Although RP seems the most thorough approach to validation, the population in diagnostic practice is inherently misrepresented as PCa-free prostates with benign hyperplasia and prostatitis cannot be part of such a validation set. Therefore, a CAD algorithm's performance in PCa detection can only be tested by a (prospective) targeted biopsy study, with the risk that the results are to some extent corrupted by targeting inaccuracies and missed PCa lesions remaining unnoticed.

3. Deep-learning-based CAD in prostate cancer

The AI techniques used in CAD algorithms are generally correlated to their respective years of publication. Whereas clustering algorithms were mostly proposed between 2005 and 2010, the period between 2010 and 2015 showed a clear preference for SVM-based and EC-based classification. Clustering algorithms are mostly used for classification of MRS data, exploiting class-specific spectral features relating to the molecular composition. SVMs are more generally applied. Its design choices are centred around the selected features, the kernel architecture (i.e., linear or radial basis functions) and the optimization of hyperparameters. ECs are somewhat more flexible in terms of the number of included features. In the last three years, there has been a clear trend towards deep-learning-based methods. Referring to [21] for a more in-depth discussion of the classic machine-learning algorithms for CAD, we will specifically elaborate on deep-learning approaches.

Fig. 1. Schematic representations of (a) encoder, (b) decoder, and (c) auto-encoder networks for image classification.

In general, we see that deep-learning approaches especially employ CNNs. A clear benefit of deep learning compared to classical machine-learning techniques resides in its lower dependence on feature extraction techniques. Moreover, classification with a trained network is relatively fast. On the other hand, decision transparency (i.e., insight in the crucial image features leading to a certain classification) remains challenging in most deep-learning implementations, even though more and more techniques have become available to overcome this issue [228,229].

3.1. Network architectures

The most general employed CNNs consist of a ~10-layer encoder network, after which the latent space is used for patient- or lesion-wise classification [178–180,182,184,187,193] or subsequently expanded in a decoder configuration for full-image probability maps [173,174,176,189]. In some papers, residual connections within the encoding structure (e.g., ResNet architectures) are used to ease training and reduce the impact of vanishing gradients by preserving information for subsequent layers [175,190,193]. Auto-encoder networks enforcing sparsity or non-negativity in the feature space have been developed for feature extraction [181,182,218], subsequently employing other classification algorithms for a final classification output. A schematic overview of these architectures is given in Figure 1. In addition to these architectures, also (conditional) generative adversarial configurations can be used to train a model for semantic segmentation of PCa lesions as well as the zonal anatomy [177]. This kind of configuration employs an adversarial network to discriminate expert from CNN-generated segmentations, thereby enhancing the global quality of the segmentations and making it more suitable for use in small datasets, but also increasing its reliance on a stable (pixel-wise) loss function to avoid hallucinatory behaviour.

The network architectures used for PCa classification are designed such that the different modalities of multiparametric imaging are either registered and multidimensionally fed into the network [176,179,184,188] or in a way where the information from each modality is only combined in the latent space [180,189,191,193]. Le et al. [178] found an superior performance in multiparametric fusion in the latent space by including similarity between the feature maps in the loss function compared to simple feature concatenation or elementwise feature map summation, enforcing spatially consistent visual patterns among the feature maps. For the same reason, a number of other papers [175,189,191,192] also use mutual findings among techniques as part of the loss function. The underlying idea is that false positives found on single techniques are less likely to be shared than localisations corresponding actual PCa foci. Alternatively, in the approach of Kohl et al. [177], the semantic/zonal segmentations of the different techniques are rigidly registered in the final step of the network based on the predicted zonal anatomy, whereafter they are fused by label consensus.

Several architectural strategies are employed to produce meaningful PCa likelihood maps (see also Section 4). To maintain high spatial resolution, authors report on the employment of skip-connections, either between encoder and decoder [173,174,176,188] or by directly combining the network (side)outputs of each (increasingly higher-level) layer in the network [185,186]. In the latter configuration, the final fused map is the result of a multiscale approach, of which each scale has its own loss function [185,186]. A large majority of the authors do not specifically exploit the 3D nature of the data, employing 2D convolutional filters to treat each slice independently, but Mehrtaash et al. and Wang et al. [180,188] explicitly use this 3D information, both in the convolutional filters as in the 3D max-pooling operations. Likewise, Alkadi et al. [173] use an encoder-decoder configuration in which also the two adjacent slices are taken into account. This way the receptive field of the CNN is limited, the number of trainable weights is reduced and it is ensured that the model is appropriate for prostate acquisitions of all volumes/sizes.

3.2. Training strategies

As deep-learning approaches typically rely on vast amounts of training data, and with the collection of well-labelled data being very laborious, several approaches are exploited to minimize the required number of independent samples. Whereas filter weights are usually randomly initialised, some authors report the use of pre-trained models, for example, an edge detection model [186], ImageNet models [178,187,191], or an object classification model [175] for the weight initialisation. This so-called transfer learning is more explicitly performed by Yuan et al. and Zhong et al., who used the pre-trained AlexNet [192] or CIFAR10 ResNet [193] to extract features from different MR techniques, replacing the last layer by a few fully-connected layers, which are subsequently fine-tuned for cancer classification leaving the rest of the network unaltered. Alternatively, adversarial networks exploit a generator-discriminator configuration to deal with datasets of limited size [177]. Furthermore, data augmentation is an intrinsic part of the training process in most frameworks, usually employing limited rotation and lateral flipping.

For training, the choice of cost function ranges from the maximum-likelihood-motivated (binary) cross-entropy [180], mean squared error [176], sigmoid cross entropy [186], weighted cross-entropy [173], and multi-class cross-entropy [177] to carefully designed loss functions that incorporate PCa grading loss [175], registration and segmentation loss [189], and inter-technique correspondence and overlap [175,189,191,192]. To accelerate the convergence during back-propagation, many author mention the use

of batch-normalization [176,180,184,185,190] or instance normalisation (i.e., where the normalisation takes place across spatial locations rather than over the entire batch) [177]. Moreover, also dropout [180,184] and other regularisation techniques (e.g. L_2 [180]) are used. In terms of optimizer, most authors report the use of Adam [177,179,180,184,185,188], but a few also employ batch gradient descent or stochastic gradient descent (with momentum) [173,176,192]. Batch sizes of a few to nearly a hundred patients have been reported [173,180]; this range can be explained by the variable trade-off between the noisiness of the gradients, overfitting behaviour of the network and memory requirements.

3.3. Network output

There are several networks that combine the feature representations or normalised output logits produced by the main deep architecture with other non-deep features in the final stage of classification. For instance, Le et al. [178] use a separate SVM to fuse the multiparametric classification of a CNN network with the output of another SVM trained on handcrafted features. Similarly, Reda et al. [181] auto-encoded DWI-images of different b -values (enforcing sparsity and nonnegativity [182] at the latent space) to combine the resulting probabilities with a PSA-level-based k -NN classifier. Apart from custom features or clinical variables, explicit zone information was added by Mehrtaash et al. [180] in the latent space during multiparametric merging, followed by a few fully connected layers for the final classification.

A few networks go beyond PCa classification or probability, and also distinguish cancer aggressiveness. For example, Yuan et al. [192] trained the network to distinguish high-grade and low-grade prostate cancer. In another approach, by Yang et al. [191], the trained latent feature space just before the classification layer was used as input for a multi-class SVM to predict Gleason Score in addition to the PCa likelihood. For this, global average pooling was used rather than global max pooling with the aim to better preserve grade-related information. By ordinal encoding the Gleason Score in the training target, Cao et al. [175] developed a so-called FocalNet approach (as it employs a *focal* loss function, a binary cross-entropy incorporating the imbalance of positive and negative pixels) towards a five-channel prediction of cancer aggressiveness.

3.4. Performance

Differences in dataset composition, validation methods, and evaluation metrics make it difficult to compare the CAD algorithm performances reported in Table 4. In addition, whereas some authors evaluate their algorithm's ability to distinguish benign from malignant lesions, others compare PCa tissue versus healthy tissue. Moreover, also in the light of developments in the clinical classification of PCa, the definition of clinically significant or insignificant disease might differ from paper to paper.

Taking into account the above mentioned difficulties in quantitative comparison, CNN architectures seem an increasingly promising approach to CAD of PCa. With many algorithms being validated through hold-out and on relatively larger number of patients, we see growing evidence of CNNs performing equal or better than SVMs or ECs that were previously considered state-of-the-art [21]. The PROSTATEx challenge committee reports about half of the submissions to be based on a CNN architecture [221]; the top results were almost exclusively generated through deep learning.

Indeed, a head-to-head comparison, such as enabled by PROSTATEx [221], is of great value when comparing different algorithms. However, it should be noted that the results reported are biopsy validated and region based; ROC curves are not generated by testing the probability output but rather by maximum-likelihood binormal modelling of the test-set classification [230].

Moreover, in the end, clinical applicability of CAD techniques is dependent on how effectively the information is delivered to the operator.

Due to differences in set-up, validation and output, it is difficult to compare the reported performance of the networks. For deep learning, ROC curve areas ranging from 0.73 to 1.00 have been obtained, and accuracies between 85% and 94%. Those studies reporting sensitivity and specificity, almost all observe a higher specificity (31%-100%) than sensitivity (55%-90%) [169,171,177,178,181,182,184]. Generally speaking, well-performing biopsy- and RP-validated algorithms have shown performance greater than 0.9 in ROC curve area or accuracies around 90% [172,189-191]. Although these results still have to be consolidated through clinical studies, we recognise that most of these papers use T2W, ADC and, for some, DWI as input modalities. Interestingly, two of these networks specifically exploit inter-modality agreement within their networks [189,191]. Only one of them also distinguishes cancer aggressiveness [172]. All of them, however, had a large dataset of over 150 patients available for the CAD development.

4. Algorithm-operator interface

Currently, classification algorithms are intended to be used as an image-interpretation aid and not as an imaging modality by itself. However, especially when reviewing many features, CAD might serve as a better interpreter than a clinician, especially those with little experience, and play an increasingly important role. Throughout the literature, there are three main approaches to deliver the CAD output to the clinician: through lesionwise classification, voxelwise cancer likelihood maps, or by suggesting an appropriate location for targeting biopsy.

The most straightforward output of a PCa CAD tool is binary classification of the data, either of a lesion delineated by the operator, or for each voxel in the sample volume. Clustering-based algorithms always have a two- or three-class output. Some papers distinguish multiple classes such as healthy, benign, and malignant, or benign, indeterminate, and malignant. On voxelwise classification maps, lesions are often visually well recognised, although it might be harder to localise the cancer hotspot.

Another approach would be the mapping of either the actual probability or a proxy for cancer likelihood. This way, the clinician can also take into account clinical variables such as the prostate-specific antigen levels or age to assess the level of suspicion. Just a few papers output a lesionwise probability [136,154,155,158,214] or a cancer likelihood for a specific patient [179-181]; the probability is mostly mapped voxelwise. Bayesian classifiers readily output probability [114,116,215], as well as the likelihood estimates found by logistic regression [130] and discriminant analyses [126,128,132], while other algorithms require a posteriori probability estimator. For SVMs, (sigmoid) posterior probability estimators [148,151] or pseudoprobabilities corresponding to the instance distance to the hyperplane [153] are used. ECs, on the other hand, usually use the level of agreement among its aggregated weak learners as likelihood [162] and GMM probability has been calculated through the ratio between the probabilities of an instance being drawn from the malignant or benign distribution [166]. Depending on the neural network architecture, voxelwise probabilities are estimated by weighting individual latent feature contributions [171], the voxel's log-probability [173,174], the sigmoid value [191], or the outcome of the rectifier linear unit (so, unnormalised) output activation layer, while weighting the loss function in order to prevent the imbalance between malignant and benign labels to bias the estimation [185,186].

A few papers report on CAD algorithms that suggest biopsy/lesion locations [144], in most cases accompanied with

a likelihood map [139,191,231,232]. The localisation procedure can be based on adaptive thresholding of local maxima in tumour likelihood using Otsu's algorithm [233]; in lesions with multiple localisations only the one with the largest likelihood is shown [191,232]. Alternatively, lesions can be localised by subjecting $>60\%$ -probability regions of sufficient size ($\geq 100 \text{ mm}^2$) to several heuristic DCE criteria [139] or by only considering malignantly-classified regions above a certain size [231]. Finally, some authors select a region in the likelihood map, either by a growing algorithm [144] or by using empirical criteria on size and DWI parameters [129], and subsequently apply a custom classifier for final classification.

5. Discussion and conclusions

Over the last decades, CAD algorithms exploiting multiparametric imaging to detect or localise PCa have been consistently developed. Advances in AI as well as registration, segmentation, and radiomics, have defined the trends in CAD implementation. Increasingly, CAD systems integrate pre-processing, segmentation, and registration, so that the whole diagnostic pipeline is automated.

Up until now, there is little focus on methods to deliver CAD information effectively to the operator. Some algorithms are lesion based, and require manually or automatically delineated regions as input. (Colour-coded) cancer probability heat maps and the use of transparency to reflect low probabilities or low classification confidence seem to be the most advanced automatic visualisation methods. Beyond PCa research, techniques are being developed to present multiple maps by colour [234], targets, or transparency to the operator. The effectiveness of these methods remains to be investigated. For example, whereas the reading of likelihood maps requires additional experience, biopsy location suggestion could lead to missing lesions in high-risk patients.

Furthermore, it should be noted that accurate targeted prostate biopsy is still a challenge [235]. Targeting errors are caused by movement, prostate deformation or misalignments, and are more severe when imaging and biopsy targeting are performed in different sessions. Current guidelines state that at least multiple samples have to be taken per identified lesions to prevent inadvertent underdiagnosis. If CAD were carried out in real time, (in-bore) biopsy could be integrated in the procedure and MRI/US fusion or cognitive biopsy targeting could be performed in the same session.

As the user interpretation of CAD remains a determining aspect in clinical practice, true diagnostic performance of these algorithms can only be determined in prospective studies. As this requires pre-trained algorithms, generalisability and operator-dependence are instantly revealed this way. A good example of this is the CAD technique called HistoScanningTM, which achieved promising small-sample results [236,237], but did not have a sufficiently high reliability in tumour detection in retrospective analyses to be recommended in routine clinical practice [95,238–240]. Of the algorithms mentioned in this survey, a few researchers have published some prospective clinical results [214,231,241,242]. For example, Dinh et al. showed their rule-based CAD algorithm [133] to yield a ROC-AUC of 0.95 in a validation study [214]. Grabski et al. [241] and Tokas et al. [242] found that their US-based CAD tool [169] maintained its accuracy in further validation. Furthermore, Hambrook et al. found that the addition of their CAD system's results [154] improved the diagnostic performance of inexperienced and experienced observers [243]. Similar results were found by Greer et al. [244] for their CAD system [159], and Giannini et al. [231] with their CAD tool [139]. In general, one could expect more complex AI methods likely to be more sensitive to changes in the imaging equipment or settings. Results can therefore not be viewed independently from the employed imaging system, and domain adaptation becomes an important technical aspect. Super-

vised and transfer adaptation techniques can play an important role in this respect.

In conclusion, CAD technology in multiparametric imaging of PCa remains a vibrant and active field in radiology. Aside improvements in diagnostic accuracy, developments in (in particular) deep-learning techniques might alleviate the problems in inter- and intra-observer variability as well as long learning curves associated with multiparametric scoring systems such as PI-RADS [245]. However, full implementation in the PCa diagnostic pipeline, either as support tool or as part of the investigation, is still awaited.

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