Contemporary application of artificial intelligence in prostate cancer: an i-TRUE study

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***Abstract*:** Artificial intelligence (AI) involves technology that is able to emulate tasks previously carried out by humans. The growing incidence, novel diagnostic strategies and newer available therapeutic options have had resource and economic impacts on the healthcare organizations providing prostate cancer care. AI has the potential to be an adjunct to and, in certain cases, a replacement for human input in prostate cancer care delivery. Automation can also address issues such as inter- and intra-observer variability and has the ability to deliver analysis of large volume datasets quickly and accurately. The continuous training and testing of AI algorithms will facilitate development of futuristic AI models that will have integral roles to play in diagnostics, enhanced training and surgical outcomes and developments of prostate cancer predictive tools. These AI related innovations will enable clinicians to provide individualized care. Despite its potential benefits, it is vital that governance with AI related care is maintained and responsible adoption is achieved.

Keywords: artificial intelligence, deep learning, prostate cancer, prostate specific antigen, machine learning, uro-oncology

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Introduction

Artificial intelligence (AI) involves technology that is able to emulate tasks, previously carried out by humans.[1–3] Machine learning (ML), deep learning (DL) based artificial neural networks (ANNs) and convolutional neural networks (CNNs) are commonly used forms of AI in healthcare.[1,2] The deep learning convolutional neural network (DL-CNN) is a commonly used technique for image recognition. Classifiers are data from individual circumstances that is input onto an AI model. AI models subsequently integrate this data and can potentially predict outcomes. Common types of classifiers are k-nearest neighbour, linear discriminant analysis, Gaussian mixture model, support vector machine and random forest classifier (RF).

Conventional manual large-scale data analysis is cumbersome, time-consuming and often inefficient in integrating multiple variables. AI-assisted models allow quick and accurate analysis of large volume data (big data) with ability to stratify individualized care. AI is increasingly finding application in healthcare and is adopted in numerous disciplines for diagnostics, training, research, data management and improving operational efficiency. Prostate cancer is a common cancer in men, with the annual incidence on the rise.[4,5] The growing incidence, novel diagnostic strategies and newer available therapeutic options have had resource and economic impacts on the healthcare organizations providing prostate cancer care.[5,6] AI has the potential to be an adjunct to, in certain cases a replacement for, human input, mitigating some of the aforementioned resource implications, and therefore reducing costs. Automation also addresses issues such as inter- and intra-observer variability and has the ability to deliver analysis of large volume datasets quickly and accurately.[1–3] In this

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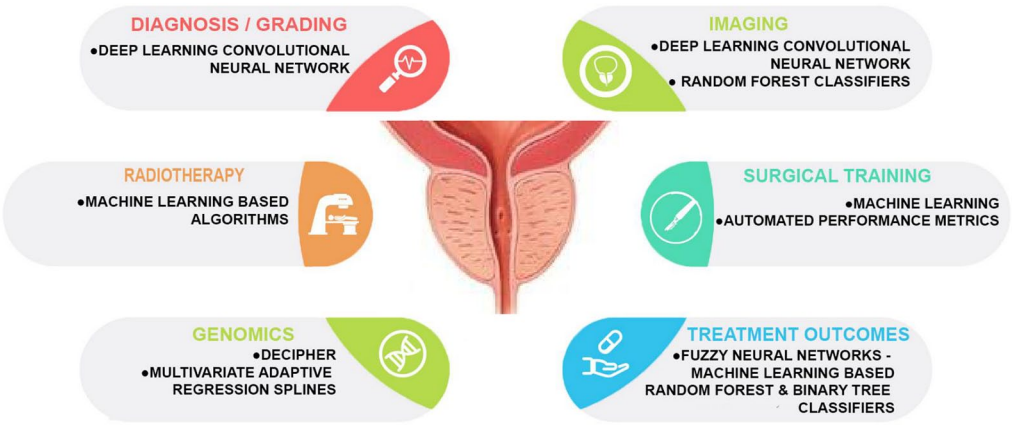

Figure 1. Applications of artificial intelligence and its subfields in prostate cancer.

article, we review the ever growing applications of AI and its subfields in prostate cancer (Figure 1).

Studies related to AI in diagnosis, Gleason grade and classification of prostate cancer (Table 1)

Contemporary epidemiological, diagnostic and therapeutic trends in prostate cancer have created particular stress on pathological and radiological services. The ability to digitalize pathological slides has allowed the use of two stage DL-CNNs with k-nearest-neighbour-based whole-slide Gleason grade group classification in prostate cancer histological evaluation [Figure 2(a) and (b)]. Litjens *et al.* reported one of the earliest studies using DL-CNN in the histological evaluation of prostate cancer.[7] They reported that all slides with prostate cancer were reliably identified by this technique and nearly 40% of benign slides could be excluded without the need for further evaluation. Campanella *et al.* reported the diagnostic performance of a novel weakly supervised DL model in a large dataset of 44,732 whole slide images from 15,187 patients. They reported an area under the curve (AUC) of 0.991, which is significantly better than the traditional model.[8] Bulten *et al.* reported on a DL method for Gleason grading.[9] The model was trained using a data set of 4712 biopsy samples and validation was performed using a data set of 535 biopsy cores for which three expert pathologists were assigned. The test dataset consisted of 886 tissue cores out of which 245 were separately examined by two pathologists. The automated grading system had strong agreement with the three expert uro-pathologists (quadratic Cohen's kappa 0.918, 95% confidence interval 0.891–0.941). Interestingly, the model had better performance than 10 general pathologists. Strom *et al.* developed an AI model and trained it with a data set collected prospectively from a clinical trial (STLHM3 study) for identification, Gleason grading and localization of prostate cancer.[10] The model was trained with 6953 cores from 1069 individuals out of which 330 cores from 73 men were used for validation and the final test set constituted 1631 biopsies from 246 men. DL-CNN ensembles consisting of 30 InceptionV3 models trained on ImageNet were used. It achieved a diagnostic accuracy of 0.997 (AUC) to differentiate between a malignant and benign tumour and the results were comparable to those achieved by the expert pathologists. Subjectivity and long processing time are often issues with predictive and prognostic biomarkers identification in tissue microarrays when performed manually. Calle *et al.* reported an automated method using DL algorithms for the analysis of these biomarkers. The authors used 648 samples for immunofluorescence staining with anti-Ki-67, ERG antibodies to train the model.[11] The results were promising, with a 5% difference between manual and algorithm based biomarker detection.

Contemporary imaging in prostate cancer involves independent and integrated evaluation of morphological and functional parameters.[6,15] This evaluation is therefore complex and can be burdensome on radiologists. Inter-observer variability in the interpretation of these images has been reported both in the primary diagnosis and in patients on active surveillance.[15,16] Preliminary

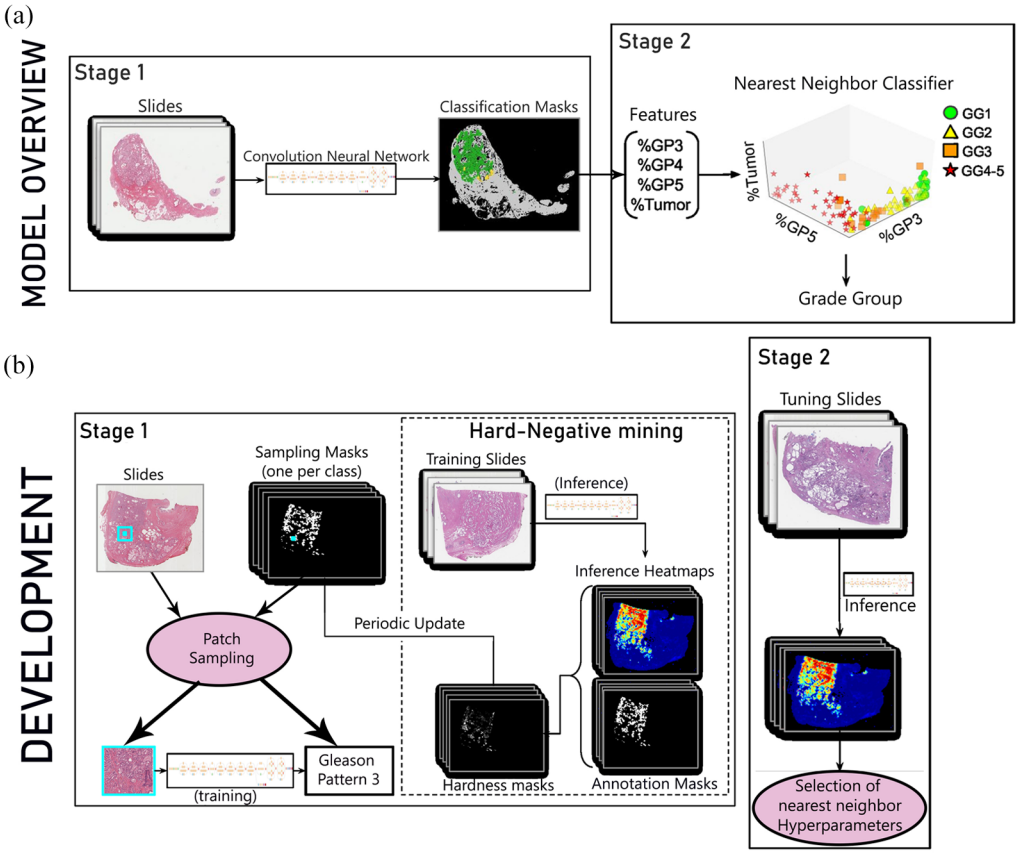

Figure 2. (a) Two stage deep learning-convolutional neural networks with k-nearest-neighbour-based whole-slide Gleason grade group classification and (b) illustration of the development and usage of the two-stage deep learning system.

reports from AI directed computer aided diagnosis have suggested promising outcomes, with a potential to mitigate some of the aforementioned challenges. Chen *et al.* reported outcomes on a weakly supervised CNN model.[12] The CNN model was trained on the three-dimensional images obtained from the 10,000 magnetic resonance–ultrasound fusion biopsy cores of 600 patients. This model was then applied to the T2 weighted images of multi-parametric magnetic resonance imaging (mpMRI). The model aimed to differentiate between benign and malignant cases and it achieved an AUC of 0.78. Yuan *et al.* reported on a novel CNN model, the mpMRI transfer learning (MPTL) model.[13] MPTL studies the features of T2 weighted and apparent diffusion coefficient sequences of mpMRI images. The objective of the model was to classify prostate cancer based on Gleason grading. The model achieved an accuracy of 86.92% in Gleason score classification of prostate cancer. The model was superior to previously evaluated DL models. Wildeboer *et al.* assessed the efficacy of machine learning through RF algorithm to localize the prostate cancer lesions on transrectal ultrasound based on the radiomic features obtained from dynamic contrast-enhanced ultrasound, shear-wave electrography and B mode.[14] The tests showed promising results, especially for high grade prostate cancer.

Automated performance metrics in robotic assisted radical prostatectomy (Table 2)

Kinematic and systems event data can be extracted from the recording device in 'the Da Vinci robotic system'. The automated performance metrics (APM) that is achieved from this information can be used for predicting outcomes and surgical training. Data from serial automated performance metrics of individual cases can be provided into ML algorithms. A trained machine algorithm can subsequently predict outcomes following a robotic

Table 1. Studies related to artificial intelligence in diagnosis, Gleason grade and classification of prostate cancer.

Study	Objective	Study design	Algorithm/model	Accuracy	AUC	Sensitivity	Specificity
Studies related to AI in diagnosis, Gleason grade and classification of CaP							
Litjens *et al.*[7]	To detect CaP from biopsy cores using DL-CNN	254 patients	DL-CNN	32% slides not containing the disease identified	0.99 for CaP 0.80 for sentinel lymph node	99% for CaP 90% for sentinel lymph node	NA
Campanella *et al.*[8]	To detect CaP from biopsy cores using DL-CNN	44,732 whole slide images from 15,187 patients	DL-CNN ResNet34 model	NA	0.98	100%	NA
Bulten W *et al.*[9]	To assign Gleason grade to prostate biopsies using AI	1243 patients (5759 biopsies)	DL system	Benign *versus* malignant: 96–97% Grade group 2 or more: 79–83% Grade group 3 or more: 76–82%	NA	Benign *versus* malignant: 97.4% Grade group 2 or more: 86–95% Grade group 3 or more: 76–92%	Benign *versus* malignant: 83–100% Grade group 2 or more: 52–70% Grade group 3 or more: 72–782%
Ström P *et al.*[10]	To diagnose and grade CaP in biopsies	Training set: 976 patients (6682 slides) Test set: 246 patients (1631 slides)	ANN	NA	0.997	99%	94.9%
De la Calle *et al.*[11]	To predict recurrence and progression of CaP based on biomarker analysis	648 samples (424 tumours, 224 normal tissue) Tissue micro assays anti Ki-67, ERG antibodies	AI algorithm	100% in identification of ERG+ tumour	NA	NA	NA
Chen *et al.*[12]	To detect CaP cases from 3D MR–US fusion biopsy images	600 patients 10,000 3D MR–US fusion biopsy images	DCNN model	NA	0.78	NA	NA
Yuan *et al.*[13]	To localize CaP lesions on mpMRI (T2W and ADC) images		DL-CNN based MPTL model	86.92%	NA	NA	NA
Wildeboer *et al.*[14]	For automated localization of CaP based on radiomics of TRUS	50 men with biopsy confirmed CaP	ML techniques using B-mode, shear-wave elastography, and dynamic contrast-enhanced ultrasound radiomics	NA	0.75–0.90	NA	NA

ADC, apparent diffusion coefficient; AI, artificial intelligence; ANN, artificial neural network; AUC, area under the curve; CaP, prostate cancer; DCNN, deep convolutional neural network; DL, deep learning; DL-CNN, deep learning and convolutional neural network; ML, machine learning; mpMRI, multiparametric magnetic resonance imaging; MPTL, mpMRI transfer learning; MR–US, magnetic resonance–ultrasound; NA, not available; T2W, T2 weighted; TRUS, transrectal ultrasound.

assisted radical prostatectomy.[17] Hung *et al.* reported one of the earliest studies that evaluated three trained ML algorithms to predict peri-operative outcomes following a robotic assisted radical prostatectomy (RARP).[17] The random forest classifier-50 algorithm was the most accurate algorithm. The classifier's prediction of operative time, length of stay and duration of catheter had

Table 2. Automated performance metrics in robotic assisted radical prostatectomy (RARP).

Study	Objective	Study design	Algorithm/ model	Accuracy	AUC
Hung *et al.*[17]	To evaluate RARP performance and predict outcomes	78 RARP cases	APMs ANN based random forest-50 classifier	87.2%	NA
Hung *et al.*[18]	To predict the recovery of urinary continence after RARP based on the APMs of the surgeon to perform robotic surgery	100 cases of RARP performed by two groups of four each. Group 1/APM consisted of expert surgeons, Group 2/APM consisted of other surgeons	DL-based model DeepSurv	85.9% in predicting continence	NA
Jian *et al.*[19]	To measure surgeon performance during robotic vesicourethral anastomosis and methodical development of a training tutorial	70 cases 1745 stitches	APMs	NA	NA

ANN, artificial neural network; APM, automated performance metrics; AUC, area under the curve; DL, deep learning; NA, not available.

a statistically significant association with the respective true outcomes. Hung *et al.* utilized a DL-based model (DeepSurv) using APMs and clinico-pathological features in predicting continence outcomes.[18] The model had higher predictive accuracy than ML models and conventional regression analysis models. Additionally the model reported APMs to be more accurate predictors of continence than clinico-pathological features. Chen *et al.* compared APM and non-APM (NAPM) to evaluate the skills of a surgeon while performing vesicourethral anastomoses (VUAs) during a RALP.[19] Seventy VUAs with 1745 stitches were assessed. Classification of needle driving gestures was performed and compared. Differentials such as operative time, camera movement and manipulation, efficiency of instrument movement and articulation of EndoWrist could be accurately evaluated with APMs. These factors were found to be superior in expert surgeons (more than 100 console cases) when compared with novice surgeons (fewer than 100 console cases). NAPM could identify fewer differential features such as fewer traumas by the experts, less needle driving attempts and optimal angle of needle entry.

Prediction of treatment outcomes in prostate cancer and other applications (Table 3)

Lee *et al.* reported outcomes of an AI-assisted model which was able to predict biochemical recurrence (BCR) rates following radical prostatectomy. A RF was used to predict BCR rates. The model achieved a mean and a maximum AUC of 0.74 and 0.9286 respectively.[20] Panfilo *et al.* reported outcome of two ML methods (RF and binary tree classifier) to predict the histological upgrading of prostate cancer following a radical prostatectomy. The model integrated multiple variables such as PSA density, total PSA, volume of prostate, clinical stage, body mass index, number of positive cores, primary Gleason, percentage of cancer, secondary Gleason and ASA (American Society of Anaesthesiologits) score. The RF was superior to a conventional logistic regression model in predicting histological upgrading in prostatectomy specimens.[21] Deng *et al.* reported a ML model which was able to predict adverse side effects following docetaxel chemotherapy.[22] One of the earliest reported applications of ML methods in genomic studies was to predict metastasis free survival rate by validating the genomic classifier Decipher.[23] This classifier was used by Nguyen *et al.* to predict prostate cancer-specific mortality (PCSM) following a radical prostatectomy or radiation therapy.[24] It achieved a C-index of 0.71 and 0.74 in predicting metastases and PCSM respectively. Koo *et al.* used ANNs to predict survival outcomes.[25] The authors used multilayer perceptron and long–short term memory ANN models. A data set of 7267 prostate cancer patients was used to train the models. Nineteen clinical and pathological variables were integrated into the models. The ANN models were superior to conventional Cox regression analysis models in predicting 5–10 year survival outcomes.

Table 3. Prediction of treatment outcomes in prostate cancer and other applications.

Study	Objective	Study design	Algorithm/model	Accuracy	AUC
Lee *et al.*[20]	To predict BCR in patients of prostate cancer who underwent RP and had Gleason score of 6–8	189 features 40 patients	ML based random forest classifier	NA	0.92 (max) 0.74 (mean)
Panfilo *et al.*[21]	To predict the upgrading of prostate cancer post robotic radical prostatectomy using multiple variables and AI	8357 patients	ML based random forest classifier BT classifier	NA	RF: 0.78 BTC: 0.76 Logistic model: 0.67
Deng *et al.*[22]	For treatment stratification of patients with metastatic castrate resistant CaP	78 features associated with the patient clinical and medical history, lab reports and metastases	ML based model	NA	NA
Nguyen *et al.*[24]	To predict PCSM and metastases in intermediate to high risk patients who have undergone RP or RT	235 patients	ML based genomic classifier Decipher	NA	Metastases: 0.71 PCSM: 0.74
Koo *et al.*[25]	To predict the treatment outcomes in terms of OM, CSM and CRPC free survival	7267 patients 19 variables	ANN models MLP Long–short term memory	**5 years** CRPC: 85.5% CSM: 80.2% OM: 79.5% **10 years** CRPC: 84.6% CSM: 79.5% OM: 96.4%	NA
Nouranian *et al.*[26]	To reduce the segmentation variability of TRUS images and planning time by proposing an efficient learning-based multi-label segmentation algorithm	590 brachytherapy treatment records by 5-fold cross validation	Learning based multi-label segmentation algorithm	NA	NA
Nicolae *et al.*[27]	To plan RT in CaP cases using AI	100 high-quality LDR treatment plans (training set).	ML algorithm	NA	NA

AI, artificial intelligence; ANN, artificial neural network; AUC, area under the curve; BCR, biochemical recurrence; BT, binary tree; BTC, binary tree classifier; CaP, prostate cancer; CRPC, castrate resistant prostate cancer; CSM, cancer specific mortality; LDR, low dose radiotherapy; ML, machine learning; MLP, multilayer perceptron; NA, not available; OM, overall mortality; PCSM, prostate cancer-specific mortality; RF, random forest; RP, radical prostatectomy; RT, radiation therapy; TRUS, transrectal ultrasound.

Big data in prostate cancer

Big Data for Better Outcomes Programme (BD4BO) is a European research programme aiming to develop key enablers to support health care system transformation using big data. Innovative Medicines Initiative-2 and BD4BO launched a comprehensive network across Europe known as Prostate Cancer Diagnosis and Treatment Enhancement through the Power of Big Data in Europe (PIONEER). PIONEER aims to achieve high quality outcomes with automated analysis of big data.[28,29] Observational Medical Outcomes Partnership and Observational Health Data Sciences and Informatics technology will be used for the collection and analysis of the data from the registries while tranSMART technology will be used for genomics/radiomics and clinical data.

Other applications

Nouranian *et al.* developed learning based multi-label segmentation algorithm with an aim to reduce the planning time and segmentation variability during radiotherapy planning.[26] The algorithm was tested on a data set of 590 treatment plans. The authors reported the outcomes to be clinically acceptable. Nicolae *et al.* reported ML algorithm to automatically generate high quality, prostate low-dose-rate brachytherapy treatment plans.[27] The algorithm was trained with 100 treatment plans. The results showed that the ML based algorithm was faster than the expert brachytherapists in planning a treatment without compromising quality. The use of AI will have a big role in future cancer and non-cancer guidelines and revolutionize the decision-making process.[30]

Conclusion

The roles of various facets of AI in prostate cancer are in their infancy. The preliminary outcomes of AI models in various domains of prostate cancer care are promising. The continuous training and testing of AI algorithms will facilitate development of futuristic AI models that will have integral roles to play in diagnostics, enhanced training and surgical outcomes and developments of prostate cancer predictive tools. These AI related innovations will enable clinicians to provide individualized care. Despite its potential benefits, it is vital that governance with AI related care is maintained and responsible adoption is paramount.

Author contributions

Study conception and design, B.S., B.P.R. and N.N.; Acquisition of data, B.M.Z.H., M.S., S.I. and P.R.; Analysis and interpretation of data, N.N., B.M.Z.H. and P.R.; Drafting of manuscript, B.M.Z.H. and M.S.; Critical revision, B.S., N.S., B.P.R. and N.N.; All authors reviewed and approved the final version of the manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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