Digital diagnostics and artificial intelligence in prostate cancer treatment in 5 years from now

The range of novelties included in this special series on "Update on molecular classification and individualized treatments of genitourinary tumors" published in the journal *Translational Andrology and Urology* (1-8) has led us to considerations on diagnosing and treating patients with genitourinary tumors in 5 years from now.

Digital pathology (DP)

This digital-based approach to histological diagnosis, also called DP, is a new approach in the morphologic analyses of glass slides either with tissue sections obtained from formalin-fixed paraffin embedded tissue (FFPE) or with frozen sections. Slide scanners are designed to obtain virtual slides of entire tissue sections, i.e., whole slide image (WSI), including large format histology, from large glass slides. The whole tissue section is represented in the virtual slide (*Figure 1*). The advantage of the virtual slides, compared with still images, is that a the user can change magnification to zoom in and out, while looking for diagnostic features as with an optical microscope (9,10). WSI technology has attracted the greatest attention in the pathology community. DP will become commonplace in five years from now.

Artificial intelligence

AI is defined as "the ability of a machine to perform cognitive tasks to achieve a particular goal based on provided data" (11). The use of DP will allow the routine implementation of AI-based algorithms in the pathology (12,13). The most commonly used image-based AI algorithms are "convolutional neural networks" (14-16). These algorithms are based on WSI as learn and input associations and links between items such as a diagnosis made by a histopathologist, underlying molecular features and patients' survival or response to adjuvant/neoadjuvant therapy, i.e., outcome measures (16). Such algorithms have the capability of going beyond the visual evaluation of morphologic features to identify tissue patterns that are not perceived by human recognition. This includes the tumor microenvironment. AI can combine together pieces of information derived from a host of features in order to make the overall final diagnosis. The features are then link to additional patients-related information in order to give data of potential value on the behavior of the disease, outcome of the patient and prediction of response to a certain therapeutic strategy (11).

Computational pathology and Gleason grading

Computer-based diagnosis of prostate cancer (PCa) on glass slides can be achieved by machine learning (ML) (*Figure 2*) to optimize reproducibility and accuracy as well as improve "health-care delivery by enabling the use of customized precision-care pathways" (11).

It is now feasible to grade PCa on virtual slides, thus improving reproducibility and accuracy by applying computer-based methods (17). Several investigators have dealt with PCa grading based on DP and AI (18). Lucas *et al*. (19) have attempted in a recent study to build an automatic classification of the Gleason pattern. This method can assist pathologists in the definition of the PCa Grade Groups (GG) in prostate biopsies. When distinguishing between Gleason patterns 4 or higher and Gleason pattern 3, accuracy was 90%, specificity and sensitivity were 94% and 77%, respectively. Concordance of their computer-based GG evaluation with the evaluation made by a pathologist was 65% (κ being 0.70). This indicates a substantial agreement.

AI can create algorithms that can allow a generalist to function as a specialist. Nagpal *et al*. (20) adopted "a supervised learning method to develop a deep learning system (DLS) for PCa grading" on radical prostatectomy specimens. Accuracy was assessed for the assignment of GG by generalists, in comparison to specialists. The DLS outperformed the generalist pathologists (accuracy of 0.70 *vs.* 0.64).

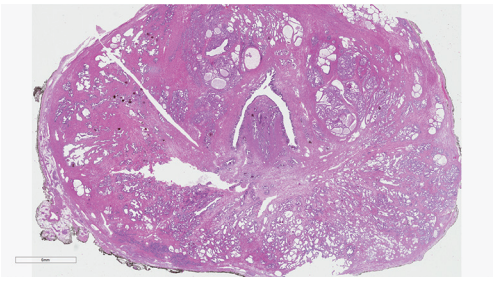

Figure 1 Virtual slide of radical prostatectomy specimen examined with whole mount technique. H&E (magnification 2×).

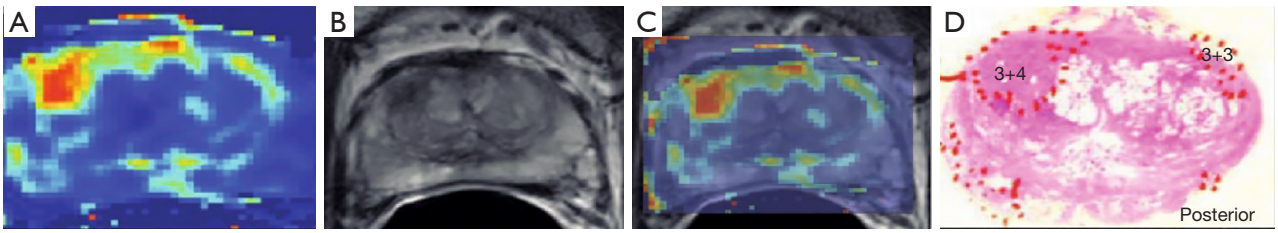

Figure 2 Machine Learning technique to detect prostate cancer and create a cancer probability map. (A) A support vector machine classifier, trained and validated by Moradi *et al*. (13), has produced this probability map. Hot colors show increased probability of cancer on a T2-weighted MRI image. (B) T2-weighted image of the mid-gland with a suspicious region in the anterior horn of the right peripheral zone. (C) The T2-weighted image with the probability map shown as a transparent overlay. (D) The corresponding histopathology whole-mount slide in which the main pathological finding is a Gleason 3+4 tumor in the anterior horn of the right peripheral zone. H&E (magnification 2×). ML, machine learning. Reproduced with permission from Goldenberg *et al*. (11). (For further details, please see the legend of *Figure 3* of the paper from which the image was reproduced).

Digital microscopy of PCa with a fluorescence confocal microscope

Fluorescence confocal microscopy (FCM) is an optical imaging technique that provides digital microscopic images of fresh tissue in a real time fashion, without conventional processing (15). FCM has been widely applied in several fields including dermatopathology, for the detection of basal cell carcinoma and for the diagnosis of skin inflammatory diseases. In all studies, the acquisition of FCM images takes 2 to 5 minutes, without the need for conventional processing. There is no need for dedicated personnel and equipped laboratory (21). FCM digital images can be web-shared and interpreted by a remote pathologist in a real time, without the need for on-site personnel, i.e., a pathologist, other than the surgeon already involved in the surgical procedure. All studies showed the preservation of tissue integrity for further conventional tissue evaluation (*Figure 3*) as well as for immunohistochemistry after the initial FCM analysis.

In a study from our group, detection of PCa with FCM was aligned with routine pathology reports in hematoxylin and eosin (HE) stained sections (95.1% of correct-diagnosis with FCM, κ being0.84). "Inter-rater agreement between pathologists was almost perfect for both HE and FCM for PCa detection (0.98 for HE, κ=0.95; 0.95 for FCM, κ=0.86); for cancer grade attribution only a moderate agreement was reached for both HE and FCM (HE κ=0.47; FCM κ=0.49)" (21).

PCa grade by radiomics

Radiomic analysis, "involving feature extraction from images with classifier techniques", "can automatically predict the grade of cancer with a precision and speed beyond the scope of human visual analysis" (22).

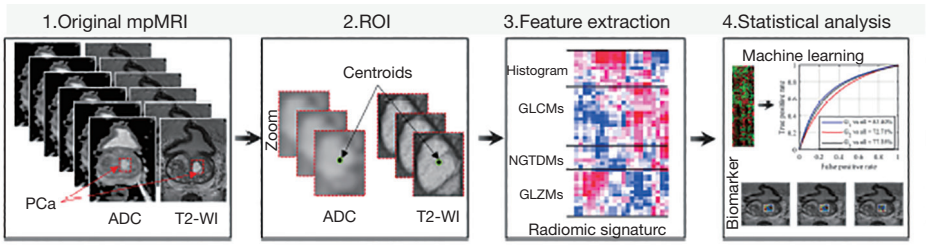

Figure 3 Schema of a radiomic model for patients with PCa. Acquisition of pre-treatment PCa patient's MR images; Regions of interest (i.e., subvolume 21×21×3 voxels); Extraction of 41 radiomic features from ROIs; Feature significance analysis based on Spearman rank correlation and Kruskal-Wallis, and multivariate prediction of Gleason score groups using the random forest model. Reproduced under the terms of the Creative Commons Attribution License (CC BY) from Chaddad *et al*. (22).

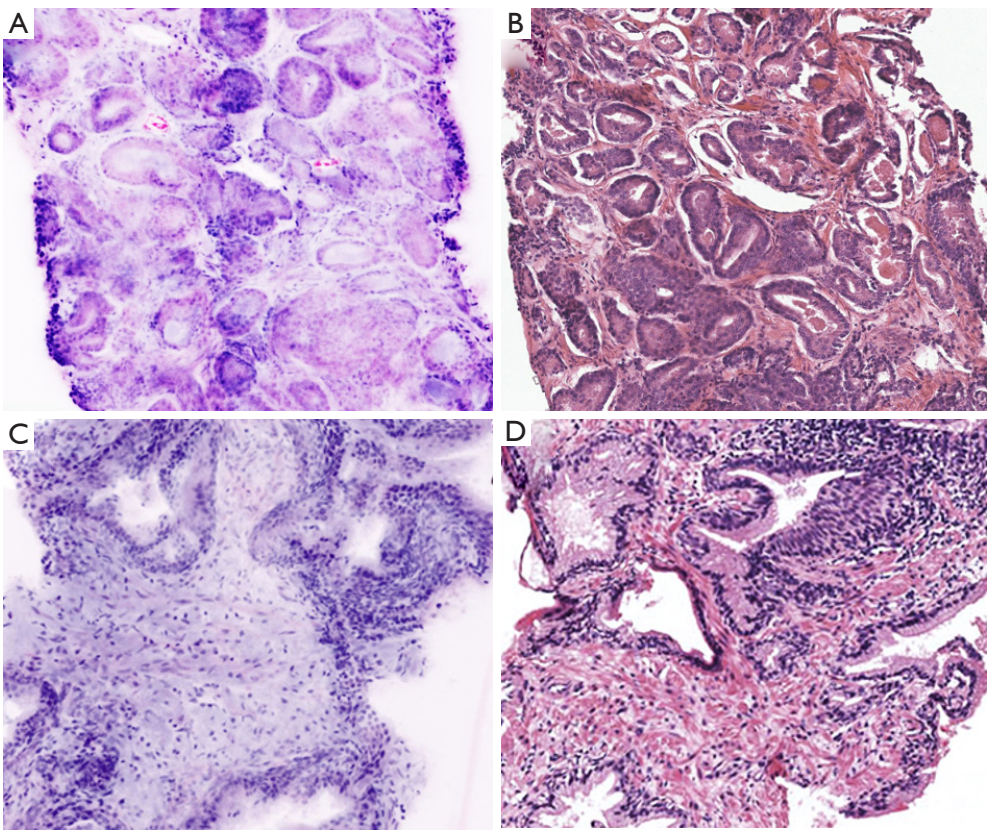

Figure 4 Prostate biopsy examined with confocal microscopy and standard hematoxylin and eosin (H&E). Prostatic adenocarcinoma in confocal microscopy (A) and H&E (B). Normal prostatic glands with confocal microscopy (C) and with H&E (D). Magnification 10×.

Investigations have utilized radiomic features, obtained from magnetic resonance (MR) images, for computer-based diagnosis (23-25). In addition to basic diagnostic information, such analyses may detect subtle features and insights of the neoplasms, making additional evaluation into the "radiomic assessment of PCa as a priority" (*Figure 4*).

Radiomic features most important to predict the grade of PCa in order to estimate the aggressivity of the tumor under evaluation remain largely unexplored. Chaddad *et al*. (22) identified those radiomic features derived from both T2-WI and ADC images for the

identification of three groups of Gleason scores (GS) and "classifying these groups using the RF classifier model". Their evaluations found that three features, i.e., zone size non-uniformity, large zone size emphasis and zone size percentage, can discriminate groups of GS and correlate individual groups with aggressiveness Such items are of importance in predicting GS 6. The sum entropy is the most important to predict GS 4+3 (7). Radiomics, as a noninvasive test, has the potential, to predict the GS in men with PCa.

Conclusions: multi-criteria decision making and information fusion

Management of men with PCa is challenging due to the fact that there is biological "diversity between patients and histopathology alone cannot accurately predict PCa outcomes" (26).

In the last few years, utilization of genomic- based risk prediction models and molecular profiling has received a great interest. ML techniques are adopted in such evaluations in order to identify either the individual genes or groups of them for "which expression specificity to predict a certain clinical outcome is high" (27). Data can then be utilized to develop risk stratification and diagnostic tools, for producing targeted drug approaches. as well as for determining individualized treatment

ML algorithms are useful to improve treatment in patients with PCa by increasing the surgeon's display with additional features including PCa location at the time of the robotic and other image-guided procedures. It can be used for the "autonomous manipulation of tools for assistance in the operating room" (11).

The process of merging data originating from multiple sources, including digital diagnostics, radiomics, diagnostic imaging and robotic surgery, "is defined as multi-criteria decision making and information fusion" (28). The resulting information, including the diagnostic and therapeutic decisions, when applied to men with PCa examined with large format histology and whole slide imaging (28), and with multiple biomarkers deriving from tissue, urine and blood samples, is far more accurate than when the various sources are evaluated separately and individually" (28). All this involves the utilization of AI.

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Footnote

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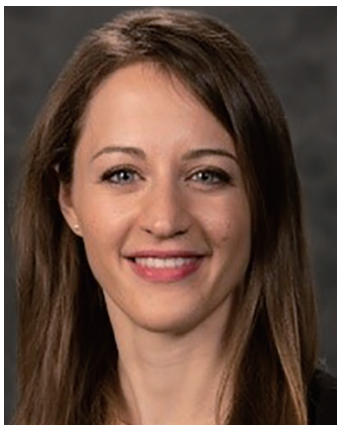

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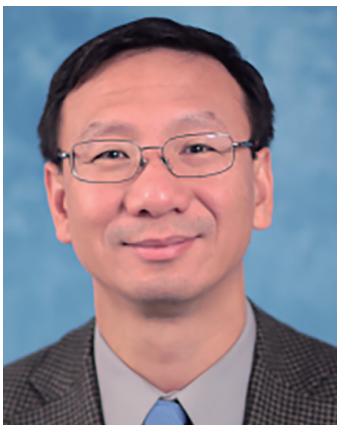

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