Minerva Urology and Nephrology 2023 October;75(5):545-7
DOI: 10.23736/S2724-6051.23.05538-6

MINERVA OPINION EDITORIAL

Artificial intelligence evaluation of confocal microscope prostate images: our preliminary experience

Giampaolo BIANCHI [1], Stefano PULIATTI [1] *, Natalia RODRIGUEZ [1], Salvatore MICALI [1], Laura BERTONI [2], Luca REGGIANI BONETTI [3], Stefania CARAMASCHI [3], Federico BOLELLI [4], Maurizio PINAMONTI [5], Davide ROZZE [5], Costantino GRANA [4]

[1]Department of Urology, University of Modena and Reggio Emilia, Modena, Italy; [2]Department of Surgery, Medicine, Dentistry and Morphological Sciences with Interest in Transplant, Oncology and Regenerative Medicine, Modena, Italy; [3]Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena Polyclinic Hospital, Modena, Italy; [4]Enzo Ferrari Department of Engineering, University of Modena and Reggio Emilia, Modena, Italy; [5]Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy

*Corresponding author: Stefano Puliatti, Department of Urology, University of Modena and Reggio Emilia, Modena, Italy.
E-mail: stefano.puliatti@unimore.it

Prostate cancer is a prevalent neoplasm in men, with varying aggressiveness.[1, 2] To manage the disease optimally, both oncologic radicality and postoperative functional outcomes are essential.[3, 4] The 'gold standard' pathological assessment of prostate cancer is still a conventional, time-consuming approach, based on histomorphological evaluation of bioptic or surgical tissue samples.[5, 6]

Ex-vivo fluorescence confocal microscopy (FCM) is a promising innovative method which allows real-time evaluation of prostate tissue, producing images that highly overlap with the traditional hematoxylin and eosin-stained slides.[6, 7] FCM has shown excellent results in evaluating healthy and cancerous prostate tissue, offering high concordance, reliability, sensitivity, and specificity.[6, 7]

The application of Artificial Intelligence (AI) on FCM images seems to have great potential. Notably, confocal microscopy allows the direct acquisition of digital images, enabling the immediate utilization of AI. The annotation process could be demanding in terms of expertise, cost, and time; but AI, especially neural networks, has shown potential in overcoming these obstacles, as demonstrated also in the dermatological field.[8] The integration of confocal microscopy technology with neural networks represents a potential "game-changer" in the field of pathology.

The aim of our study is to assess the performance of a weakly supervised approach based on graph neural networks (GNNs) for detecting prostatic tumors in digitally colored FCM images obtained from prostatic biopsies. The selected algorithm, DAS-MIL,[9] integrates pyramidal GNN with multi-instance learning (MIL) to leverage the full potential of FCM high resolution images, without relying on pixel-level annotations (*i.e.*, requiring only the information about the presence/absence of the prostatic tumor inside the image).

For the examination, 506 prostatic biopsies from 64 patients affected by adenocarcinoma or non-neoplastic conditions, were collected and analyzed using the *ex-vivo* FCM device (Viva-Scope® 2500 M-G4, Mavig GmbH, Munich, Germany; Caliber I.D.; Rochester NY, USA) at the Department of Urology, University of Modena and Reggio Emilia, Italy. Written informed consent was obtained from each patient preoperatively. Fresh samples were analyzed as described elsewhere.[10]

The 506 digitalized prostatic biopsies were split into two sets: 307 images for training DAS-MIL and 199 images for testing and validating the automatic approach. Both sets were randomly generated while preserving the class distribution (around 20% of images contained tumor tissue in both sets). The model was trained to distinguish between images with tumor tissue and healthy ones, utilizing available ground-truth labels. The final performance was assessed using the area under the ROC curve (AUC) and accuracy metrics. The AUC achieved a value of 0.93, and the accuracy score was 0.86. Additionally, the algorithm's behavior was analyzed through the confusion matrix presented in Table I. This enabled the calculation of sensitivity (true positive rate) and specificity (true negative rate) of the algorithm on the target dataset. DAS-MIL demonstrated a sensitivity of 0.8 and a specificity of 0.88.

Leveraging on MIL, the final prediction of DAS-MIL is performed by calculating the criticality of each instance and comparing all of them with the most significant one. Such an approach can be also exploited to produce a heatmap highlighting the portions of the images that contributed the most to the final prediction. Since no label at pixel-level is available the heatmaps can be used only for qualitative evaluation. An example is provided in Figure 1.

Up until now, AI has been employed in analyzing conventional pathologic prostate cancer images directly or that were later digitized, yielding remarkably high accuracy[11-13]and strong concurrence with expert uropathologists' diagnoses.[14] Our study sought to utilize real-time fluorescence confocal microscope (FCM) images, eliminating the need for specimen processing

Table I.—*Confusion matrix summarizing DAS-MIL predictions on the selected test-set. Among the 199 images available, 172 (86.43%) are predicted correctly with high sensitivity (0.8) and specificity (0.88).*

Output	Target		
	Non-tumor	Tumor	Sum
Non-tumor	144 72.36%	7 3.52%	151 95.36% 4.64%
Tumor	20 10.05%	28 14.07%	48 58.33% 41.67%
Sum	164 87.80% 12.20%	35 80.00% 20.00%	172/199 86.43% 13.57%

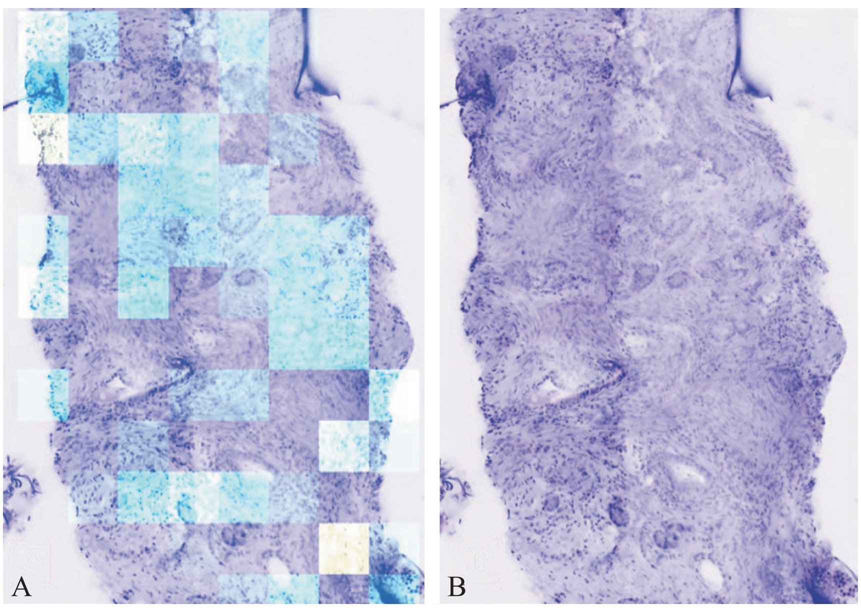

Figure 1.—A) Example heatmap produced by DAS-MIL on a positive FMC image predicted as positive also by the model. To better appreciate the details only a portion of the entire image is reported. Instances highlighted in yellowish identify more critical areas and the relevance decreases with color intensity. No highlighted areas are those that the automatic model considers less significant for the prediction. B) The same image, obtained with confocal microscopy, unprocessed by AI.

and the following image digitalization, thereby expediting the application process. Surprisingly, the artificial neural network achieved in our preliminary experience an AUC value of 0.93, and an accuracy score of 0.86, even though it had not undergone prior training to recognize neoplastic lesions. On a following analysis performed by our expert pathologist (LRB) on the AI-sensitive areas, although it was a non-machine learning neural network application, those areas were largely recognized as glandular areas with features of neoplasia. In our experience, the application of AI on FCM images could allow a remarkable time advantage, thanks to a real-time intraoperative assessment that could directly address the pathologist to initially evaluate those areas flagged by the machine as neoplastic. This study constitutes a preliminary experience. By training the machine to recognize pathologic patterns, in our opinion, even more encouraging results will be possible.

References

1. D'Agostino D, Casablanca C, Mineo Bianchi F, Corsi P, Romagnoli D, Giampaoli M, *et al.* The role of magnetic resonance imaging-guided biopsy for diagnosis of prostate cancer; comparison between FUSION and "IN-BORE" approaches. Minerva Urol Nephrol 2021;73:90–7.

2. Nocera L, Collà Ruvolo C, Stolzenbach LF, Deuker M, Tian Z, Gandaglia G, *et al.* Improving the stratification of intermediate risk prostate cancer. Minerva Urol Nephrol 2022;74:590–8.

3. Eissa A, Zoeir A, Sighinolfi MC, Puliatti S, Bevilacqua L, Del Prete C, *et al.* "Real-time" Assessment of Surgical Margins During Radical Prostatectomy: State-of-the-Art. Clin Genitourin Cancer 2020;18:95–104.

4. Albisinni S, Dasnoy C, Diamand R, Mjaess G, Aoun F, Esperto F, *et al.* Anterior vs. Retzius-sparing robotic assisted radical prostatectomy: can the approach really make a difference? Minerva Urol Nephrol 2022;74:137–45.

5. Mir MC, Bancalari B, Calatrava A, Casanova J, Dominguez Escrig JL, Ramirez-Backhaus M, *et al.* Ex-vivo confocal fluorescence microscopy for rapid evaluation of renal core biopsy. Minerva Urol Nefrol 2020;72:109–13.

6. Puliatti S, Bertoni L, Pirola GM, Azzoni P, Bevilacqua L, Eissa A, *et al.* Ex vivo fluorescence confocal microscopy: the first application for real-time pathological examination of prostatic tissue. BJU Int 2019;124:469–76.

7. Bertoni L, Puliatti S, Reggiani Bonetti L, Maiorana A, Eissa A, Azzoni P, *et al.* Ex vivo fluorescence confocal microscopy: prostatic and periprostatic tissues atlas and evaluation of the learning curve. Virchows Arch 2020;476:511–20.

8. Sendín-Martín M, Lara-Caro M, Harris U, Moronta M, Rossi A, Lee E, *et al.* Classification of Basal Cell Carcinoma in Ex Vivo Confocal Microscopy Images from Freshly Excised Tissues Using a Deep Learning Algorithm. J Invest Dermatol 2022;142:1291–1299.e2.

9. Bontempo G. Marta Lovino, Federico Bolelli, Anni Virtanen, Elisa Ficarra. Enhancing PFI Prediction with GDS-MIL: A Graph-based Dual Stream MIL Approach; 2023 [Internet]. Available from: https://iris.unimore.it/retrieve/fd6dd815-9d7e-4b5e-b64d-9b405f70fcf0/2023ICIAP_Enhancing%20PFI%20Prediction%20with%20GDS-MIL%3A%20A%20Graph-based%20Dual%20Stream%20MIL%20Approach.pdf [cited 2023, Aug 1].

10. Rocco B, Sighinolfi MC, Sandri M, Spandri V, Cimadamore A, Volavsek M, *et al.* Digital Biopsy with Fluorescence Confocal Microscope for Effective Real-time Diagnosis of Prostate Cancer: A Prospective, Comparative Study. Eur Urol Oncol 2021;4:784–91.

11. Ström P, Kartasalo K, Olsson H, Solorzano L, Delahunt B, Berney DM, *et al.* Artificial intelligence for diagnosis and grading of prostate cancer in biopsies: a population-based, diagnostic study. Lancet Oncol 2020;21:222–32.

12. Campanella G, Hanna MG, Geneslaw L, Miraflor A, Werneck Krauss Silva V, Busam KJ, *et al.* Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. Nat Med 2019;25:1301–9.

13. Wessels F, Kuntz S, Krieghoff-Henning E, Schmitt M, Braun V, Worst TS, *et al.* Artificial intelligence to predict oncological outcome directly from hematoxylin and eosin-stained slides in urology. Minerva Urol Nephrol 2022;74:538–50.

14. Nagpal K, Foote D, Tan F, Liu Y, Chen PC, Steiner DF, *et al.* Development and Validation of a Deep Learning Algorithm for Gleason Grading of Prostate Cancer From Biopsy Specimens. JAMA Oncol 2020;6:1372–80.

Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Giampaolo Bianchi and Costantino Grana conceptualized the study. Stefano Puliatti, Federico Bolelli and Salvatore Micali designed the study. Laura Bertoni acquired FCM images. Federico Bolelli developed and tested the graph neural network algorithms. Luca Reggiani Bonetti, Stefania Caramaschi, Davide Rozze, and Maurizio Pinamonti were responsible for the pathologic evaluation of the FCM images. Federico Bolelli was responsible for data analysis. Natali Rodriguez, Laura Bertoni, and Federico Bolelli wrote the draft of the paper. Giampaolo Bianchi, Stefano Puliatti, Luca Reggiani Bonetti, Costantino Grana reviewed the paper. All authors read and approved the final version of the manuscript.

History
Manuscript accepted: July 31, 2023. - Manuscript received: July 31, 2023.

(*Cite this article as:* Bianchi G, Puliatti S, Rodriguez N, Micali S, Bertoni L, Reggiani Bonetti L, *et al*. Artificial intelligence evaluation of confocal microscope prostate images: our preliminary experience. Minerva Urol Nephrol 2023;75:545-7. DOI: 10.23736/S2724-6051.23.05538-6)