THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

JU Insight

Stimulated Raman Histology Interpretation by Artificial Intelligence Provides Near-Real-Time Pathologic Feedback for Unprocessed Prostate Biopsies

M. P. Mannas, F. M. Deng, A. Ion-Margineanu, et al.

Correspondence: Miles P. Mannas (m.mannas@alumni.ubc.ca).

Full-length article available at https://doi.org/10.1097/JU.0000000000003811.

Study Need and Importance: Prostate cancer diagnosis has a long history that relies on time-consuming and sometimes inaccurate methodologies. The emergence of stimulated Raman histology (SRH) coupled with artificial intelligence (AI) presents a novel opportunity for real-time, accurate diagnosis of prostate cancer. This study evaluated the effectiveness of an AI convolutional neural network in interpreting prostate biopsy images created by SRH, offering a potential paradigm shift in prostate cancer diagnostics and patient care.

What We Found: Our study revealed that SRH can generate high-quality AI-interpretable images of fresh, unstained prostate biopsies within 2 to 2.75 minutes. At the gland level the AI showed an accuracy of 98.6% (Table).

The AI demonstrated remarkable accuracy (96.5%), sensitivity (96.3%), and specificity (96.6%) in identifying prostate cancer in whole biopsies as well (Table).

Limitations: While promising, this technology's current iteration cannot yet assign tumor grades. Furthermore, the study's generalizability may be limited due to the testing in a single center on patients with confirmed prostate cancer. Future studies should focus on validating the accuracy of SRH interpretation with AI in diverse patient populations in a multicenter study and assessing its ability to grade prostate cancer.

Interpretation for Patient Care: Implementing SRH interpreted by AI in clinical practice could significantly impact patient care. It offers the potential for real-time tissue evaluation, improved targeting during biopsy procedures, and reduced rates of false-negative diagnostic procedures. Additionally, this technology could be instrumental in identifying positive surgical margins during radical prostatectomy or focal therapy, enhancing oncologic outcomes.

Table. *Results of Prostate Cancer Identification on Stimulated Raman Histology With Convolutional Neural Network at Full Scan Speed and 4× Increased Scan Speed*

	AUC	Accuracy training patches	Accuracy validation patches	Ex vivo whole biopsy accuracy	In vivo whole biopsy accuracy	Ex vivo, in vivo whole biopsy combined sensitivity	Ex vivo, in vivo whole biopsy combined specificity	Ex vivo, in vivo whole biopsy combined accuracy
Full scan speed	99	99.6%	98.6%	98.3%	94.4%	96.3%	96.6%	96.5%
4× increased scan speed	99.5	N/A	93.8%	96.6%	94.4%	94.6%	96.5%	95.6%

Abbreviations: AUC, area under the curve; N/A, not available.
The algorithm's performance was evaluated on prostate biopsies obtained from various sources, including training patches (representing 96% of the total training patches), validation patches (representing 4% of the total patches), ex vivo biopsies from radical prostatectomy specimens, and in vivo biopsies.

THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000003811
Vol. 211, 384-391, March 2024
Printed in U.S.A.

THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

Stimulated Raman Histology Interpretation by Artificial Intelligence Provides Near-Real-Time Pathologic Feedback for Unprocessed Prostate Biopsies

M. P. Mannas,[1,2,3] F. M. Deng,[4] A. Ion-Margineanu,[5] D. Jones,[4] D. Hoskoppal,[4] J. Melamed,[4] S. Pastore,[5] C. Freudiger,[5] D. A. Orringer,[6] and S. S. Taneja[3,7,8]

[1]*Department of Urologic Sciences, University of British Columbia, Vancouver, British Columbia, Canada*
[2]*Vancouver Prostate Centre, Vancouver, British Columbia, Canada*
[3]*Department of Urology, NYU Langone Health, New York, New York*
[4]*Department of Pathology, NYU Langone Health, New York, New York*
[5]*Invenio Imaging, Santa Clara, California*
[6]*Department of Neurosurgery, NYU Langone Health, New York, New York*
[7]*Department of Radiology, NYU Langone Health, New York, New York*
[8]*Department of Biomedical Engineering, NYU Langone Health, New York, New York*

Purpose: Stimulated Raman histology is an innovative technology that generates real-time, high-resolution microscopic images of unprocessed tissue, significantly reducing prostate biopsy interpretation time. This study aims to evaluate the ability for an artificial intelligence convolutional neural network to interpretate prostate biopsy histologic images created with stimulated Raman histology.

Materials and Methods: Unprocessed, unlabeled prostate biopsies were prospectively imaged using a stimulated Raman histology microscope. Following stimulated Raman histology creation, the cores underwent standard pathological processing and interpretation by at least 2 genitourinary pathologists to establish a ground truth assessment. A network, trained on 303 prostate biopsies from 100 participants, was used to measure the accuracy, sensitivity, and specificity of detecting prostate cancer on stimulated Raman histology relative to conventional pathology. The performance of the artificial intelligence was evaluated on an independent 113-biopsy test set.

Results: Prostate biopsy images obtained through stimulated Raman histology can be generated within a time frame of 2 to 2.75 minutes. The artificial intelligence system achieved a rapid classification of prostate biopsies with cancer, with a potential identification time of approximately 1 minute. The artificial intelligence demonstrated an impressive accuracy of 96.5% in detecting prostate cancer. Moreover, the artificial intelligence exhibited a sensitivity of 96.3% and a specificity of 96.6%.

Conclusions: Stimulated Raman histology generates microscopic images capable of accurately identifying prostate cancer in real time, without the need for sectioning or tissue processing. These images can be interpreted by artificial intelligence, providing physicians with near-real-time pathological feedback during the diagnosis or treatment of prostate cancer.

Key Words: Raman spectroscopy, prostate cancer, artificial intelligence

Submitted October 17, 2023; accepted November 30, 2023; published December 15, 2023.

Recusal: Dr Taneja is a member of *The Journal of Urology®* Urological Survey editorial committee and was recused from the editorial and peer review processes.

Support: This study was supported by NIH Grant UL1TR001445 (M.P.M.), NIH Grant 1R01CA226527 TO 01 (M.P.M.), and the National Cancer Institute (D.O.).

Conflict of Interest Disclosures: A.I.M.: Invenio Imaging: Paid consultant, shareholder; J.M.: Department of Defense: Grant recipient; C.M.: Harvard: Royalty payments, Invenio Imaging: Employee, director, and shareholder; D.O.: Stryker Instruments: Paid consultant, Invenio Imaging, NXDC, Medexus: Paid consultant, Designs for Vision: Paid consultant; S.S.T.: Francis Medical, Exact Imaging, Janssen, Lantheus, Imagin Medical, Genomic Health, MDx Health.

Ethics Statement: This study received Institutional Review Board approval (IRB No. S19-01931).

The NIO Laser Imaging Systems is a Class 1 Exempt device intended for the imaging of tissue specimen. The AI algorithms evaluated in this manuscript have not been approved by the Food and Drug Administration and are for research use only.

Corresponding Author: Miles P. Mannas, MD, Level 6, 2775 Laural St, Vancouver, British Columbia, V5Z 1M9 (mmannas@mail.ubc.ca).

TECHNIQUES offering real-time pathologic interpretation of prostate tissues have significant potential in the management of prostate cancer (PCa). In the diagnostic setting, such techniques can provide immediate clarity about the adequacy of biopsy sampling, thus potentially reducing the number of

https://doi.org/10.1097/JU.0000000000003811
Vol. 211, 384-391, March 2024
Printed in U.S.A.

samples and the need for repeat procedures. Recently, it was reported that patients with a persistently visible lesion on MRI, despite an initially negative targeted biopsy, had approximately a 70% risk of harboring PCa.[1] Furthermore, real-time mapping of margins in the therapeutic setting may enhance the effectiveness of radical prostatectomy or partial gland ablative procedures.

Despite the promise of real-time tissue analysis, its application has been limited by factors such as extended processing times (up to 30-40 minutes), which reduces tissue availability for standard pathologic processing, and limited availability of specialized pathologists.[2,3] Furthermore, most diagnostic prostate biopsies are carried out in office settings, where frozen section analysis is impractical. However, a clinical microscope utilizing stimulated Raman spectroscopy offers a potential solution. It creates images, known as stimulated Raman histology (SRH), that are visually similar to conventional hematoxylin and eosin (H&E) staining.[1-3] SRH rapidly creates high-resolution images of unprocessed, unlabeled, undyed fresh tissue, delivering both structural and functional histologic information of diagnostic quality for rapid prostate biopsy (PB) interpretation, thereby providing expedited histologic information within minutes.[4,5] Nonetheless, the presence of interobserver variability in genitourinary pathologists' interpretation of PB SRH remains a significant challenge, possibly acting as a barrier to widespread adoption.[5]

The use of artificial intelligence (AI) to interpret SRH could overcome these limitations, facilitating procedural pathology in the diagnostic setting and accelerating tissue diagnosis. AI interpretation of central nervous system pathology using SRH has demonstrated noninferiority to pathologists in tumor diagnosis, significantly reducing the time needed for tissue diagnosis from over 30 minutes to just 2.5 minutes, and recently, enabling the identification of genetic mutations.[3,6] By expediting diagnosis in cases of MRI-targeted prostate biopsies, AI could guide additional biopsies when necessary, reducing false-negatives and assisting in margin assessments during extirpative therapy. We hypothesize that SRH can generate diagnostic-quality histologic images that an AI convolutional neural network (CNN) can interpret rapidly while preserving tissue for conventional analysis or molecular profiling.

MATERIALS AND METHODS

Tissue Acquisition, Preparation, and Scanning

In this Institutional Review Board–approved (IRB No. S19-01931) prospective study, 18-gauge fresh PB cores were obtained in vivo or ex vivo from participants' prostates or radical prostatectomy specimens, respectively. Figure 1 demonstrates the acquisition of 2 to 9 cores per participant. The samples were kept fresh, unstained, and unlabeled in Roswell Park Memorial Institute Medium 1640 solution before scanning in the NIO system, an SRH microscope at 20 μm depth (Figure 2). The device has been previously documented, and a concise overview of the process for PB visualization described in Supplementary Appendix 1 (https://www.jurology.com).[7]

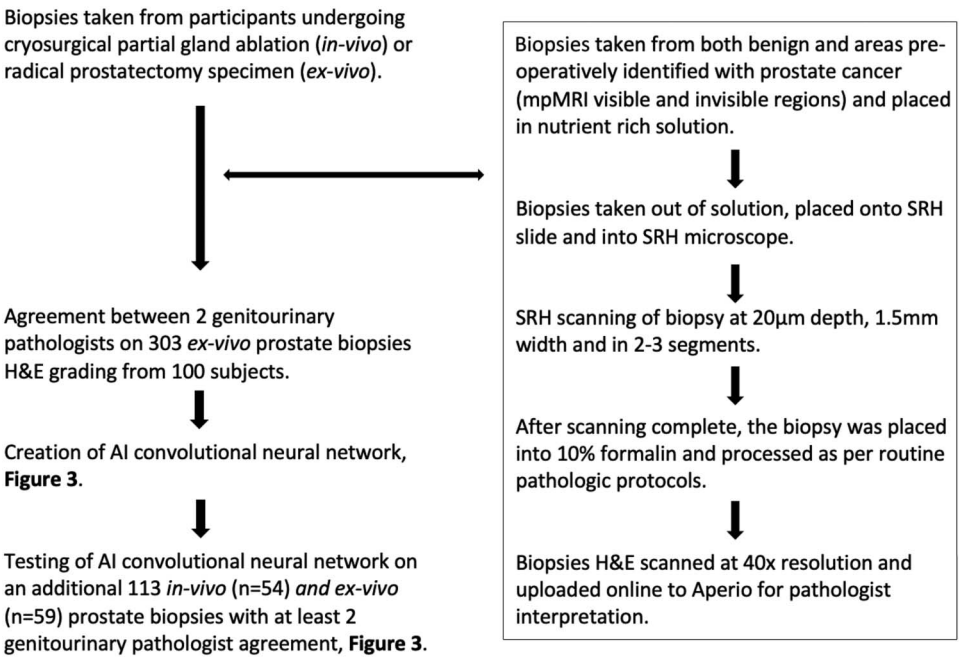

Figure 1. Workflow of sample collection, hematoxylin and eosin (H&E) staining, conventional pathologic assessment, and artificial intelligence (AI) interpretation of stimulated Raman histology (SRH) testing. mpMRI indicates multiparametric magnetic resonance imaging.

SRH scan time was optimized to 8 to 11 minutes for high quality image generation but further reduced for AI testing, to 2 to 2.75 minutes by skipping image lines and utilizing 1 Raman spectra instead of 2, further described in Supplementary Appendix 1 (https://www.jurology.com). This increased speed could potentially enable a cancer diagnosis within as little as 1 minute if a region of the biopsy containing PCa was scanned first. After completing the SRH process, the PBs followed standard pathological protocols: formalin fixation and H&E staining. Subsequently, the PBs were digitally uploaded at 40× resolution to Aperio eSlide Manager for pathologist interpretation. Prior to participation in the study, the 4 genitourinary pathologists (with 1, 3, and 2 having over 15 years of experience, respectively) underwent training on Aperio eSlide Manager.

CNN Creation

An Inception-ResNet-v2 CNN was trained using 303 ex vivo prostate biopsies obtained from 100 radical prostatectomy specimens between September 2020 and June 2021 (Figure 3). These biopsies were imaged with SRH, creating Digital Imaging and Communication in Medicine images which were annotated in QuPath v0.2.3. Pathologic annotations were created by assigning all PCa glands in a biopsy as per biopsy level ISUP (International Society of Urological Pathology) Grade Group (GG) assessment from ground truth H&E diagnosis. Ground truth for these annotations was established by 2 genitourinary pathologists using ISUP 2019 consensus grading on H&E-stained specimens (Figure 1).[8] Full details on CNN development and testing can be found in Supplementary Appendix 1 (https://www.jurology.com).

CNN Testing

Genitourinary pathologist consensus was used to establish the ground truth for the 113-biopsy CNN test set mimicking MRI-targeted and systematic biopsies, where biopsies were cognitively obtained from and contralateral to MRI identified PCa (Table 1). Biopsies containing PCa had a mean length of 14 mm and mean cancer core length of 5.7. This test set, collected between August 2020 and June 2022 consisting of both ex vivo (n = 59) and in vivo (n = 54) prostatic biopsies, encompasses both benign and malignant specimens. The test set was created from a total of 44 participants, including 11 in vivo and 33 ex vivo cases. The performance of the CNN was evaluated in terms of its ability to detect malignancy, with a comparison made against the predefined H&E ground truth for matched samples. All statistical analysis was conducted with SPSS.

RESULTS

Deep Learning Internal Patch Level Testing on 303 Biopsy Test Set

As an internal validation step, we assessed the performance of the CNN by testing it on the training patches, which accounted for 96% of the total patches. The weighted accuracy achieved on all training patches was 99.6%. Furthermore, we evaluated the CNN on the validation set that was utilized during the training process, representing 4% of the total patches, and observed a weighted accuracy of 98.6% (Table 2).

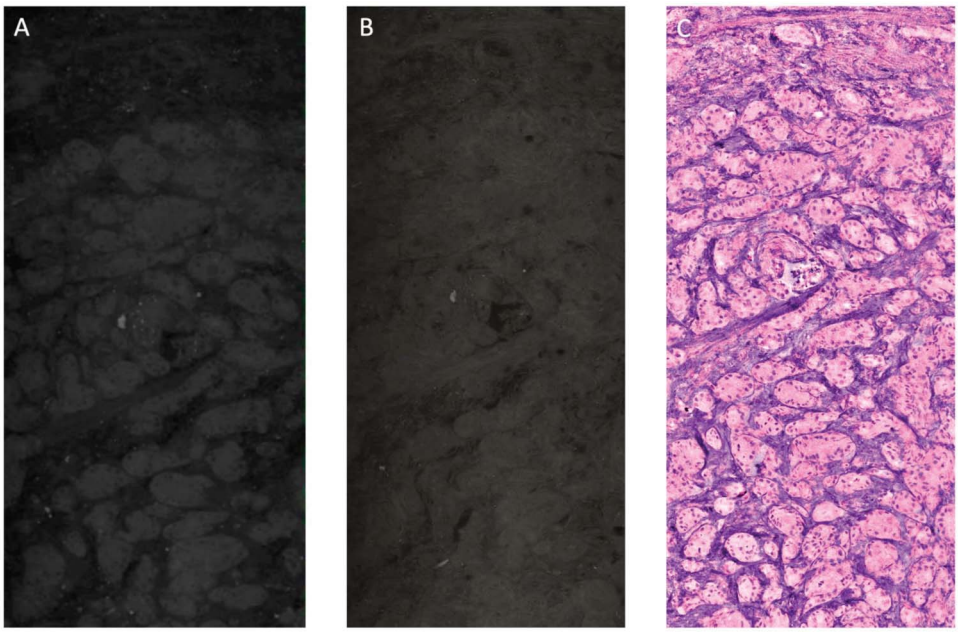

Figure 2. Virtual images of prostate biopsies using stimulated Raman spectroscopy microscope and stimulated Raman spectroscopy. The stimulated Raman spectroscopy microscope utilizes stimulated Raman spectroscopy to create virtual images of prostate biopsies, as demonstrated here for International Society of Urological Pathology Grade Group 3 prostate cancer. The visualization of CH_2 bonds is achieved through the 2845 cm^{-1} Raman spectra (A), while the visualization of CH_3 bonds is achieved through the 2930 cm^{-1} Raman spectra (B). The stimulated Raman spectroscopy image (C) is created by overlaying pseudocolors on the CH_2 (A) and CH_3 (B) images.

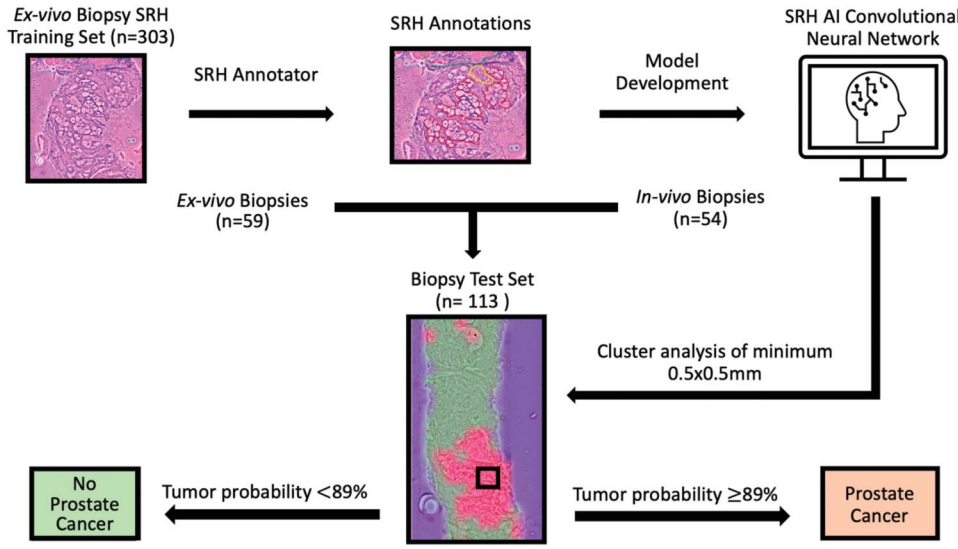

Figure 3. Workflow for stimulated Raman histology (SRH) convolutional neural network development and testing. The convolutional neural network model was developed using 1.75 million patches from 303 biopsies of 100 participants. Hematoxylin and eosin–stained histologic diagnoses were agreed upon by 2 genitourinary pathologists. The convolutional neural network testing phase involved 113 SRH prostate biopsies obtained from in vivo participants (n = 54) and ex vivo radical prostatectomy specimens (n = 59). AI indicates artificial intelligence.

Deep Learning Biopsy Level Testing on 113 Biopsy Test Set

The performance of the CNN in identifying PCa was further evaluated using an independent biopsy set comprising 113 PBs, which were obtained from both in vivo (n = 54) and ex vivo prostatectomy specimens (n = 59). The CNN achieved an accuracy of 96.5%, sensitivity of 96.3%, and a specificity of 96.6% (Table 2). Notably, the CNN only misclassified 3 PBs as benign despite the presence of PCa. Specifically, these misclassifications included 2 GG1 lesions measuring less than 1.5 mm and 1 GG3 lesion measuring less than 0.5 mm, which exhibited ill-formed glands.

Deep Learning Biopsy Level Testing on 113 Biopsy Test Set 4× Scanning Speeds

By implementing the speed increasing modifications, we achieved a remarkable 4× reduction in PB scan time, ranging from 2 to 2.75 minutes. Notably, despite the decreased scan time, we obtained comparable diagnostic outcomes on the 113-biopsy test cohort, with a biopsy level accuracy of 95.6%, sensitivity of 94.6%, and a specificity of 96.5% (Table 2). Specifically, by skipping 1 line and utilizing only the 2930 cm^{-1} Raman spectra, we were able to achieve these results. The expedited scanning also facilitated the diagnosis of cancer within as little as 1 minute if a region of the biopsy containing PCa was scanned first. It is worth noting that the CNN continued to misclassify the same 3 PBs as benign, despite their underlying presence of PCa, consistent with the analysis conducted at full speed.

DISCUSSION

Real-time pathologic analysis of prostate tissues holds significant potential for enhancing the diagnostic and therapeutic landscape of PCa. In this study, we demonstrate the utility of SRH as a technique capable of providing rapid, label-free images of unprocessed PBs, which can be accurately interpreted by AI to identify PCa in as little as 1 minute.

SRH integration into PB interpretation provides numerous advantages, notably facilitating swift diagnostic tissue assessment. First, it may reduce the risk of false-negative MRI-targeted biopsies caused by sampling errors, as rebiopsy of negative Prostate Imaging Reporting and Data System 4 to 5 may identify 20% of patients with an initially false-negative procedure who harbor PCa.[1] Additionally, it may guide biopsy intensity by determining the necessary quantity of targeted cores, the requirement for systematic sampling, and sampling frequency in both diagnostic and surveillance settings, as it can identify PCa during the biopsy process. Thirdly, it also allows real-time tissue evaluation and cancer mapping during focal ablative procedures. In these settings the identification of PCa adjacent to treatment margin may guide further treatment making the identification of PCa within 1 minute invaluable. Lastly, if SRH interpreted by AI proves reliable and efficient in the intraoperative setting, it could be instrumental in assessing surgical margins during radical prostatectomy.[7]

Real-time pathological feedback necessitates trained genitourinary pathologists and resources for

Table 1. *International Society of Urological Pathology Grade Group of Prostate Biopsies Used for Artificial Intelligence Convolutional Neural Network Training and Testing*

GG	Training biopsies (n = 303)	Testing biopsies (n = 113)	Testing biopsies mean cancer core length, mm	Testing biopsy interquartile range cancer core length, mm	Testing biopsies mean length, mm
Benign	165	60	0	N/A	14.1
1	35	17	4.2	1-6.5	14.9
2	63	22	6.5	4-7.7	13.7
3	27	13	7.5	4.7-10.8	12.7
4	6	1	10	N/A	16.4
5	7	0	N/A	N/A	N/A

Abbreviations: GG, Grade Group; N/A, not available.

tissue interpretation. The shortage of specialized pathologists and the impracticality of frozen section analysis in outpatient settings, where most PCa diagnoses occur, pose challenges. Moreover, variability in prostate histology interpretation, which includes SRH, complicates this process.[5] Thus, developing swift, accurate AI networks is essential for SRH implementation. An AI for H&E-stained prostate pathology, approved clinically, showed high sensitivity (97.7%) and specificity (99.3%).[9] Our preliminary tests indicate that an SRH-based CNN performs comparably, providing real-time assessment. AI integration could reduce the learning curve and interobserver variability in SRH interpretation. Moreover, AI's ability to interpret tissue rapidly with fewer data suggests that future interpretations may not need human-readable images. AI also utilizes raw data from cellular molecular components unseen on H&E slides, broadening its potential beyond histologic morphology. Though our study did not focus on the grading of PCa identified, the morphological features that allow for accurate PCa grading on digitized H&E may be identified with SRH, in addition to the further functional information that SRH may glean from interrogation of proteins, DNA and lipids innate in the technique. We have previous found moderate grading of PCa on SRH and AI may allow for the highlighting of such areas to guide PCa grading.[1]

In our study, the CNN's accuracy mirrored the consensus of 4 genitourinary pathologists reading SRH.[6] Only 1 false-negative classification of GG > 1 PCa occurred, which concurred with the pathologists' benign assessment. With further training and refinement, we can address these limitations. Importantly, SRH combined with AI interpretation shows promise, especially for MRI-targeted biopsy where PCa cancer core length approaches 8 mm.[10] Our results show a diverse range of cancer core length per PB and actually harbor less cancer than would be expected from a MRI-targeted biopsy cohort and is more representative of the reduce cancer length and prevalence of systematic targeted biopsy cohorts.[10]

This study has notable strengths, including the application of a novel technology for PCa identification and characterization, as well as the assessment of AI interpretation of PB SRH. In addition to describing SRH tissue imaging characteristics and optimizing the technique, we successfully trained and tested an AI algorithm for accurate interpretation of prostate biopsies using SRH in a cohort of biopsies that mimics those in the diagnostic setting. The AI demonstrated excellent diagnostic performance, comparable to an approved AI application for PB H&E interpretation.

However, this study has limitations in terms of generalizability to different patient populations with varying age, race, and genetic distribution. Another limitation of our work is that PB were all obtained from prostates with known PCa; however, our testing cohort only contained 46.9% PB with PCa, and these PB contained maximum cancer core lengths shorter than would be expected from diagnostic biopsies.[10] PCa variability in grading among pathologists may also affect the performance of the AI application, particularly when trained on pathology readings

Table 2. *Results of Prostate Cancer Identification on Stimulated Raman Histology With Convolutional Neural Network at Full Scan Speed and 4× Increased Scan Speed*

	AUC	Accuracy training patches	Accuracy validation patches	Ex vivo whole biopsy accuracy	In vivo whole biopsy accuracy	Ex vivo, in vivo whole biopsy combined sensitivity	Ex vivo, in vivo whole biopsy combined specificity	Ex vivo, in vivo whole biopsy combined accuracy
Full scan speed	99	99.6%	98.6%	98.3%	94.4%	96.3%	96.6%	96.5%
4× increased scan speed	99.5	N/A	93.8%	96.6%	94.4%	94.6%	96.5%	95.6%

Abbreviations: AUC, area under the curve; N/A, not available.
The algorithm's performance was evaluated on prostate biopsies obtained from various sources, including training patches (representing 96% of the total training patches), validation patches (representing 4% of the total patches), ex vivo biopsies from radical prostatectomy specimens, and in vivo biopsies.

from a single institution. Additionally, pathologists required training on unfamiliar viewing platforms (Aperio eSlide Manager), which may have impacted their ability to interpret the images. Furthermore, the testing cohort had minimal high-grade PCa cases, limiting the evaluation of AI performance in this specific pathology.

Future research should focus on validating the accuracy of SRH interpretation with AI in diverse patient populations. AI assessment of prostate H&E has shown excellent diagnostic abilities for grade and larger studies need to assess the ability for AI to grade prostate SRH. A comprehensive investigation of SRH during the diagnosis of PCa through assessment of MRI-targeted biopsies and the implication of AI interpretation of procedural SRH on PCa false-negative diagnostic rates, and biopsy intensity is essential to assess the impact of this novel technique. In the treatment setting the implications of SRH with AI interpretation on PCa oncologic outcomes during ablative procedures or at a margin during radical prostatectomy is also necessary. Future efforts assessing effect of this techniques ability to visualize biopsies without tissue processing may improve tissue capture, as conventional processing can reduce the available tissue volume for analysis.[11] Additionally, the identification of cellular metabolites through Raman spectroscopy, suggests that SRH-derived images and data may enhance risk stratification beyond morphological assessments in the future.[12] This is further strengthened by advanced in the neurosurgical field where SRH has been able to identify individual genetic mutations with $> 97\%$ accuracy, and we hypothesize that such advances could be made with PCa SRH AI interpretation.[6]

CONCLUSIONS

SRH provides a novel methodology for rapid prostate tissue assessment in the procedural suite, with broad applicability in PCa diagnosis and treatment settings. AI can accurately and rapidly interpret SRH to identify PCa in a PB in approximately 1 minute and may reduce the interobserver variability seen with human interpretation. Real-time access to pathology information has the potential to expedite the diagnostic process, minimize the need for repeated biopsies, and enhance oncologic outcomes through improved utilization of extirpative and ablative techniques. The combined implementation of SRH and AI holds great promise for advancing PCa diagnosis and treatment.

ACKNOWLEDGMENTS

We thank Thomas Chen for his work with the initiation of this research project.

REFERENCES

1. Becher E, Wysock JS, Taneja SS, Huang WC, Lepor H. A prospective study of cancer detection rates following early repeat imaging and biopsy of PI-RADS 4 and 5 regions of interest exhibiting no clinically significant prostate cancer on prior biopsy. *Can Urol Assoc J.* 2022;16(12):418-422.
2. van der Slot MA, den Bakker MA, Klaver S, et al. Intraoperative assessment and reporting of radical prostatectomy specimens to guide nerve-sparing surgery in prostate cancer patients (NeuroSAFE). *Histopathology.* 2020;77(4):539-547.
3. Hollon TC, Pandian B, Adapa AR, et al. Near real-time intraoperative brain tumor diagnosis using stimulated Raman histology and deep neural networks. *Nat Med.* 2020;26(1):52-58.
4. Freudiger CW, Min W, Saar BG, et al. Label-free biomedical imaging with high sensitivity by stimulated Raman scattering microscopy. *Science.* 2008;322(5909):1857-1861.
5. Mannas MP, Jones D, Deng FM, et al. Stimulated Raman histology, a novel method to allow for rapid pathologic examination of unprocessed, fresh prostate biopsies. *Prostate Prod.* 2023;83(11):1060-1067.
6. Hollon T, Jiang C, Chowdury A, et al. Artificial-intelligence-based molecular classification of diffuse gliomas using rapid, label-free optical imaging. *Nat Med.* 2023;29(4):828-832.
7. Orringer DA, Pandian B, Niknafs YS, et al. Rapid intraoperative histology of unprocessed surgical specimens via fibre-laser-based stimulated Raman scattering microscopy. *Nat Biomed Eng.* 2017;1:27.
8. van Leenders G, van der Kwast TH, Grignon DJ, et al. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on grading of prostatic carcinoma. *Am J Surg Pathol.* 2020;44(8):e87-e99.
9. Perincheri S, Levi AW, Celli R, et al. An independent assessment of an artificial intelligence system for prostate cancer detection shows strong diagnostic accuracy. *Mod Pathol.* 2021;34(8):1588-1595.
10. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med.* 2018;378(19):1767-1777.
11. Masarwa I, Bahouth Z, Shefler A, et al. The value of the SmartBx™ system in improving the detection of prostate cancer in patients undergoing transrectal ultrasound-guided biopsy. *J Mol Clin Med.* 2020;20:33-36.
12. Yue S, Li J, Lee SY, et al. Cholesteryl ester accumulation induced by PTEN loss and PI3K/AKT activation underlies human prostate cancer aggressiveness. *Cell Metab.* 2014;19(3):393-406.

EDITORIAL COMMENTS

Real-time pathologic interpretation of prostate tissues provides valuable information to aid prostate cancer management. Intraoperative frozen sections of surgical margins, currently performed at some centers,[1] have significant limitations in clinical use including long turnaround time, tissue exhaustion

for final pathologic confirmation, and interpretational errors. Alternative methods of rapid image acquisition and interpretation are highly desirable.

Within this context, Mannas et al[2] asked 2 questions: first, whether prostate biopsy images of diagnostic quality could be rapidly generated by the stimulated Raman histology (SRH) on Raman spectroscopy using unprocessed fresh tissue, and second, whether an artificial intelligence (AI) algorithm could be used to render accurate diagnoses. The answers to both questions are a very impressive yes. Prostate cores were obtained from the prostate glands undergoing partial ablation or radical prostatectomy. SRH images of these cores were obtained in 2 to 2.75 minutes. An AI algorithm was developed to interpret the SRH images with a sensitivity of 96.3%, a specificity of 96.6%, and an overall accuracy of 96.5%. SRH coupled with AI system therefore allows rapid interpretation of prostate specimens. This technology can potentially be used for biopsy adequacy check during MRI-targeted biopsies, cancer mapping during focal ablative therapy, and assessment of radical prostatectomy surgical margins.

These results obviously need to be validated by independent prospective cohorts, especially whether the use of this technology will improve the clinical outcomes. Studies are also needed to assess if the technology can accurately grade cancer. SRH is new to most pathologists, so they will need to learn how to interpret the SRH images with the aid of AI. Finally, I hope this study can spur research into other novel methods for rapid intraprocedural diagnostic confirmation, such as mass spectrometry imaging.[3]

Ming Zhou[1]
[1]*Tufts Medical Center, Boston, Massachusetts*

REFERENCES

1. Dinneen EP, Van Der Slot M, Adasonla K, et al. Intraoperative frozen section for margin evaluation during radical prostatectomy: a systematic review. *Eur Urol Focus.* 2020;6(4):664-673.
2. Mannas MP, Deng FM, Ion-Margineanu A, et al. Stimulated Raman histology interpretation by artificial intelligence provides near-real-time pathologic feedback for unprocessed prostate biopsies. *J Urol.* 2024;211(3):384-391.
3. Basu SS, Agar NYR. Bringing matrix-assisted laser desorption/ionization mass spectrometry imaging to the clinics. *Clin Lab Med.* 2021;41(2):309-324.

The need for and desirability of real-time pathology at the time of prostate biopsy dates back to the pre-PSA era, when half of newly diagnosed men presented with metastatic disease and the safest treatment was bilateral orchiectomy. In that era, men presenting with bone pain were put under general anesthesia, a finger-guided transperineal biopsy was performed (at the risk of the finger), and the team would wait for confirmation of the presence of cancer on frozen section before proceeding with orchiectomy. Given the inherent randomness of finger-guided biopsy, sometimes they needed to be repeated several times before cancer was found. Technology has, of course, changed the game, making accurate biopsy an office-based procedure under local anesthesia (and much safer for fingers). In this paper the authors move the needle further into the future, using Raman spectroscopy to create virtual histologic images of prostate biopsies, and training an artificial intelligence–based algorithm to recognize cancer with a high degree of concordance with expert review of standard hematoxylin and eosin slides.[1] When optimized, the system promises to deliver a dichotomous read of "cancer present or absent" in just a few minutes. As the authors highlight, such real-time feedback could be used to improve targeting and reduce the rate of false-negative biopsies (especially in those highly likely to have cancer based on MRI or other criteria), reduce the number of needle cores required to establish a diagnosis, and help identify margins for both focal therapy and radical prostatectomy. One limitation in the present iteration of the technology is the inability to accurately assign tumor grade, though it seems likely that with a sufficient number of additional cases the algorithm can be trained to do that as well. This innovative approach marks another step forward in prostate cancer diagnostics, offering hope for more precision and efficiency.

Eric A. Klein[1]
[1]*Glickman Urological and Kidney Institute and Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio*

REFERENCES

1. Mannas MP, Deng FM, Ion-Margineanu A, et al. Stimulated Raman histology interpretation by artificial intelligence provides near-real-time pathologic feedback for unprocessed prostate biopsies. *J Urol.* 2024;211(3):384-391.