

Artificial intelligence for target prostate biopsy outcomes prediction the potential application of fuzzy logic

Original

Artificial intelligence for target prostate biopsy outcomes prediction the potential application of fuzzy logic / Checcucci, Enrico; Rosati, Samanta; De Cillis, Sabrina; Vagni, Marica; Giordano, Noemi; Piana, Alberto; Granato, Stefano; Amparore, Daniele; De Luca, Stefano; Fiori, Cristian; Balestra, Gabriella; Porpiglia, Francesco. - In: PROSTATE CANCER AND PROSTATIC DISEASES. - ISSN 1365-7852. - ELETTRONICO. - (2021). [10.1038/s41391-021-00441-1]

Availability:

This version is available at: 11583/2921458 since: 2021-09-27T16:40:05Z

Publisher:

NATURE PUBLISHING GROUP

Published

DOI:10.1038/s41391-021-00441-1

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright

GENERIC -- per es. EPJ (European Physical Journal) : quando richiesto un rinvio generico specifico per

This is a post-peer-review, pre-copyedit version of an article published in PROSTATE CANCER AND PROSTATIC DISEASES. The final authenticated version is available online at: <http://dx.doi.org/10.1038/s41391-021-00441-1>

(Article begins on next page)

**Artificial intelligence for target prostate biopsy outcomes prediction:
the potential application of fuzzy logic**

Running title: artificial intelligence predicts target biopsy outcomes

^{1-3*}Enrico Checcucci, ^{4*}Samanta Rosati, ³Sabrina De Cillis, ⁴Marica Vagni,

⁴Noemi Giordano, ³Alberto Piana, ³Stefano Granato, ³Daniele Amparore,

³Stefano De Luca, ³Cristian Fiori, ^{4§}Gabriella Balestra, ^{3§}Francesco Porpiglia

on behalf of the Uro-technology and SoMe Working Group of the Young Academic Urologists

Working Party of the European Association of Urology

¹Department of Surgery, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Turin, Italy

²Uro-technology and SoMe Working Group of the Young Academic Urologists (YAU) Working Party of
the European Association of Urology (EAU), Arnhem, The Netherlands

³Department of Oncology, Division of Urology, University of Turin, San Luigi Gonzaga Hospital,
Orbassano (Turin), Italy

⁴Department of Electronics and Telecommunications, Politecnico di Torino, Italy

*These authors contributed equally to the first authorship

§These authors contributed equally to senior authorship

Corresponding author:

Enrico Checcucci, MD

Department of Surgery, Candiolo Cancer Institute, FPO-IRCCS

Strada Provinciale 142, km 3,95 10060 Candiolo, Turin – Italy

Email address: checcu.e@hotmail.it

Key words: *Prostate cancer, artificial intelligence, prostate biopsy, fuzzy logic,*

Word Count: 1052 (abs 250 words)

ABSTRACT:

Background: In current precision prostate cancer (PCa) surgery era the identification of the best patients candidate for prostate biopsy still remains an open issue. The aim of this study was to evaluate if the prostate target biopsy (TB) outcomes could be predicted by using artificial intelligence approach based on a set of clinical prebiopsy.

Methods: Prebiopsy characteristics in terms of PSA, PSA density, digital rectal examination (DRE), previous prostate biopsies, number of suspicious lesions at mp-MRI, lesion volume, lesion location and Pi-Rads score were extracted from our prospectively maintained TB database from March 2014 to December 2019. Our approach is based on Fuzzy logic and associative rules mining, with the aim to predict TB outcomes.

Results: A total of 1448 patients were included. Using the Frequent-Pattern growth algorithm we extracted 875 rules and used to build the fuzzy classifier. 963 subjects were classified whereas for the remaining 484 subjects were not classified since no rules matched with their input variables. Analyzing the classified subjects we obtained a specificity of 59.2% and sensitivity of 90.8% with a negative and the positive predictive values of 81.3% and 76.6%, respectively. In particular, focusing on ISUP ≥ 3 PCa, our model is able to correctly predict the biopsy outcomes in 98.1% of the cases.

Conclusions: in this study we demonstrated that the possibility to look at several prebiopsy variables simultaneously with Artificial Intelligence algorithms can improve the prediction of TB outcomes, outclassing the performance of PSA, its derivatives and MRI alone.

In precision prostate cancer (PCa) surgery era [1], an early recognition of subjects with the risk of developing PCa still remains an unmet need. In the last years, notwithstanding the advent of mp-MRI the excessive variability in the performance and interpretation of its findings together with the intrinsic biological heterogeneity of PCa features cause 40% of the patients who underwent mp-MRI guided target biopsy (TB) to have a negative pathological report. Hence the necessity to better identify the ideal candidate for TB with risk of PCa. Nowadays, artificial intelligence (AI) helps physicians to build personalized predictive models (PPMs), which are gaining a wide diffusion even in urology [2–4]. The possibility of analyzing several variables at the same time and focusing on underlying patterns by including whole data packets simultaneously, makes this technology very appealing [5,6]. As mentioned in a recently published systematic review that included 55 papers, 26 studies explored the role of AI in prostate cancer diagnosis; the majority of them were focused on the distinction between benign and malignant samples at pathological analysis or on mp-MRI images [7], whilst the role of AI as predictive tool by using the clinical variables was less explored.

Fuzzy logic (FL) is a powerful tool belonging to the AI allowing to manage uncertainty that affects most real-world problems and characterizes human reasoning, representing uncertain information in a form that can be understood by a computer and, thus, it is suitable for developing PPMs in many medical fields [8].

In this study we evaluate the role of FL-based PPM in the identification right candidate for TB, based on a set of clinical prebiopsy variables.

For this study, we retrospectively reviewed our prospectively maintained TB database from March 2014 to December 2019. Prebiopsy features in terms of PSA, PSA density, digital rectal examination (DRE), previous prostate biopsies, number of suspicious lesions at mp-MRI, lesion volume, lesion location and Pi-Rads score were collected [9, 10]. A total of 1447 patients were finally included in this analysis: 824 patients with positive TB outcome, 623 with negative TB outcome.

The proposed PPM was based on a Fuzzy Inference System (FIS), requiring the definition of a set of fuzzy input and output variables and a list of rules. Specifically, the 8 prebiopsy variables were used as input and described in fuzzy terms according to the

thresholds/categories showed in Figure 1A, using trapezoidal or triangular membership functions. The output variable of the FIS represented the patient classification, and it was described using two triangular membership functions corresponding to the negative (no risk of PCa) and positive class (risk of PCa), respectively. In order to connect input and output variables and to obtain the final patient classification, a set of IF-THEN rules is required by the FIS. In this study, a total of 875 rules were automatically extracted from the entire dataset of patients, using the FP-Growth (frequent-pattern growth) algorithm, that is a basic algorithm for association rules mining [11]. The patient classification was then obtained by entering in the PPM the values of his prebiopsy variables: if one or more rules matched with his input values, one of the two classes (positive or negative) was assigned by the FIS, otherwise the patient was labeled as not classified.

Our Personalized Predictive Model (PPM) was tested on the entire dataset and the results are summarized in Figure 1.B. 963 subjects were classified whereas for the remaining 484 subjects were not classified. Focusing on the classified subjects, 231 out of 390 patients (specificity; $Sp = 59.2\%$) were correctly classified as negative and 520 out of 573 patients (sensitivity; $Se = 90.8\%$) were correctly recognized as positive. The negative and the positive predictive values (NPV and PPV) of the PPM were 81.3% and 76.6%, respectively. The distribution of the ISUP score among the positive patients is showed in Figure 1.C. The ROC curve obtained for the 963 classified patients, corresponding to an AUC value of 0.77 (Figure 1D).

The results presented above show how taking together 8 pre-biopsy characteristics makes it possible to correctly classify patients with suspicious PCa by using AI algorithms.

Our findings are particularly noteworthy if we focus on more aggressive PCa, defined as $ISUP \geq 3$, for which our PPM is able to correctly predict the biopsy outcomes in 98.1% of the cases. These results outclass the performance of PSA and its derivatives such as PSA density or free PSA, which Sp ranging from 30-40% and Se between 70% and 80%. Similarly, considering the indication to perform TB with respect to mp-MRI findings [12], the PPV of suspicious mpMRI for csPCa was 40% (95% confidence interval 36–43%), with large heterogeneity between the studies analyzed in a recent metanalysis ($I^2 94\%$, $p < 0.01$) [13]. If these are the findings that analyzed one single variable (serum markers or images) alone, different risk calculators (RC) were already published with the aim to better identify the

111 patients with risk of Pca taking together multiple variables. However, none of them have
112 clearly shown superiority, therefore it remains a personal decision as to which one to use
113 [14]. A comparative analysis showed RCs containing MRI to be most predictive.

114 In fact, the discriminative ability of MRI RCs for the detection of csPCa was superior (AUC
115 0.81-0.87) to the traditional RCs (AUC 0.76-0.80) [15]

116 On the other side, few studies explored the role of AI in the creation of a predictive models
117 [7]. Roffman et al. published the largest series of data [16] including 2016 patients with the
118 aim to create and validate a multi-parametric Artificial Neuronal Network model, able to
119 simultaneously examine anamnestic details of each patients in order to predict PCa risk and
120 stratification. They showed a Se of 23%, Sp of 89%, AUC of 0.72, and positive predictive
121 value of 27%.

122 We think that the possibility of correctly prioritizing the patients who require TB by using AI
123 is particularly appealing for two reasons: firstly because, especially in re-biopsy setting (a
124 fortiori after previously negative TB), the correct indication to a further biopsy is an
125 unsolved issue of the current literature; secondarily, because in actual COVID-19 pandemic
126 era, characterized by limited access to medical facilities and limited resources, the
127 individuation of patients with higher risk of PCa could lead to a better assignment of the
128 assets [17, 18].

129 Under a technical point of view, one of the main strengths of such approach for PPMs
130 construction lies in the understandability of FIS results that allow to know the subset of
131 rules matching with the input parameters and, thus, to evaluate the confidence in the
132 obtained result.

133 The main limit of our study is the presence of patients that were not classified. This finding
134 encourages the reflection on the huge biological heterogeneity of PCa and further studies
135 are warranted trying to reclassify also this rate of missed patients using other supervised AI
136 techniques such as Random Forest.

137 Notwithstanding the above-mentioned limitation, together with the unavailability of a
138 validation cohort, the proposed PPMs based on AI FL algorithms showed how looking at
139 multiple prebiopsy variables simultaneously is possible to improve the prediction of TB
140 outcomes.

REFERENCES

1. Checcucci E, Amparore D, De Luca S, Autorino R, Fiori C, Porpiglia F. Precision prostate cancer surgery: An overview of new technologies and techniques. *Minerva Urol e Nefrol.* 2019;71(5):487–501.
2. Checcucci E, Autorino R, Cacciamani GE, Amparore D, De Cillis S, Piana A, et al. Artificial intelligence and neural networks in Urology: Current clinical applications. *Minerva Urol e Nefrol.* 2020;72(1):49–57.
3. Giannini V, Rosati S, Regge D, Balestra G. Specificity improvement of a CAD system for multiparametric MR prostate cancer using texture features and artificial neural networks. *Health Technol (Berl).* 2017;7(1):71–80.
4. Rosati S, Balestra G, Giannini V, Mazzetti S, Russo F, Regge D. ChiMerge discretization method: Impact on a computer aided diagnosis system for prostate cancer in MRI. In: 2015 IEEE International Symposium on Medical Measurements and Applications (MeMeA) Proceedings. IEEE; 2015. p. 297–302.
5. Bhandari M, Reddiboina M. Building artificial intelligence-based personalized predictive models. *BJU Int.* 2019;124(2):189–91.
6. Hung AJ. Can machine-learning algorithms replace conventional statistics? *BJU Int.* 2019;123(1):1.
7. Checcucci E, De Cillis S, Granato S, Chang P, Afyouni AS, Okhunov Z; Uro-technology and SoMe Working Group of the Young Academic Urologists Working Party of the European Association of Urology. Applications of neural networks in urology: a systematic review. *Curr Opin Urol.* 2020 Nov;30(6):788–807. doi: 10.1097/MOU.0000000000000814. PMID: 32881726.

8. Rosati S, Agostini V, Balestra G, Knaflitz M. Basographic gait impairment score: A fuzzy classifier based on foot-floor contact parameters. In: 2014 IEEE International Symposium on Medical Measurements and Applications (MeMeA). 2014. p. 1–5.
9. Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. *Eur Radiol.* 2012;22(4):746-757. doi:10.1007/s00330-011-2377-y
10. Barentsz JO, Weinreb JC, Verma S, et al. Synopsis of the PI-RADS v2 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging and Recommendations for Use. *Eur Urol.* 2016;69(1):41-49. doi:10.1016/j.eururo.2015.08.038
11. Han J, Pei J, Yin Y, Mao R. Mining frequent patterns without candidate generation: A frequent-pattern tree approach. *Data Min Knowl Discov.* 2004;8:53–87.
12. Checcucci E, de Cillis S, Piramide F, Amparore D, Kasivisvanathan V, Giganti F, et al. The role of additional standard biopsy in the MRI-targeted biopsy era. *Minerva Urol e Nefrol.* 2020;72(5):637–9.
13. Mazzone E, Stabile A, Pellegrino F, Basile G, Cignoli D, Cirulli GO et al. Positive Predictive Value of Prostate Imaging Reporting and Data System Version 2 for the Detection of Clinically Significant Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol Oncol.* 2020 Dec 25:S2588-9311(20)30212-1. doi: 10.1016/j.euo.2020.12.004. Epub ahead of print. PMID: 33358543.
14. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol.* 2021 Feb;79(2):243-262. doi: 10.1016/j.eururo.2020.09.042. Epub 2020 Nov 7. PMID: 33172724.
15. Mortezaei A, Palsdottir T, Eklund M, Chellappa V, Murugan SK, Saba K et al. Head-to-head Comparison of Conventional, and Image- and Biomarker-based Prostate Cancer Risk Calculators. *Eur Urol Focus.* 2020 May 22:S2405-4569(20)30113-9. doi: 10.1016/j.euf.2020.05.002. Epub ahead of print. PMID: 32451315.

16. Roffman DA, Hart GR, Leapman MS, Yu JB, Guo FL, Ali I, Deng J. Development and Validation of a Multiparameterized Artificial Neural Network for Prostate Cancer Risk Prediction and Stratification. *JCO Clin Cancer Inform*. 2018 Dec;2:1-10. doi: 10.1200/CCI.17.00119. PMID: 30652591; PMCID: PMC6873987.
17. Amparore D, Campi R, Checcucci E, Sessa F, Pecoraro A, Minervini A et al. Forecasting the Future of Urology Practice: A Comprehensive Review of the Recommendations by International and European Associations on Priority Procedures During the COVID-19 Pandemic. *Eur Urol Focus*. 2020 Sep 15;6(5):1032-1048. doi: 10.1016/j.euf.2020.05.007. Epub 2020 May 31. PMID: 32553544; PMCID: PMC7261455.
18. Wallis CJD, Novara G, Marandino L, et al. Risks from deferring treatment for genitourinary cancers: a collaborative review to aid triage and management during the COVID-19 pandemic. *Eur Urol* 2020.

208

209 **CONFLICTS OF INTEREST**

210 None declared.

211

212 **ETHICAL APPROVAL:**

213 The study was conducted in accordance with good clinical practice guidelines, and informed
214 consent was obtained from the patients. According to Italian law (Agenzia Italiana del
215 Farmaco Guidelines for Observational Studies, March 20, 2008), no formal institutional
216 review board or ethics committee approval was required.

217

218

219

220 **FIGURE LEGEND:**

221

222 **Figure 1.** Overview of study results. A): Distribution of 1448 classified patients with negative
223 and positive TB for the 8 prebiopsy variable, according to the thresholds/categories used for
224 PPM construction. B): Confusion matrix reporting the results of our PPM with respect to the
225 TB outcome. C): Distribution of false negative (red) and true positive (green) patients by
226 ISUP. Focusing on the 53 false negative patients, the distribution of ISUP score was: 30.18%
227 (16/53) with ISUP 1, 60.3% (32/53) with ISUP 2, 3.7% (2/53) with ISUP 3, 5.6% (3/53) with
228 ISUP 4, 0% (0/53) with ISUP 5. D): ROC Curve obtained for the 983 classified patients

229