

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

GENERICO -- 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)

28 **ABSTRACT:**

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

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

38 **Results:** A total of 1448 patients were included. Using the Frequent-Pattern growth
39 algorithm we extracted 875 rules and used to build the fuzzy classifier. 963 subjects were
40 classified whereas for the remaining 484 subjects were not classified since no rules matched
41 with their input variables. Analyzing the classified subjects we obtained a specificity of
42 59.2% and sensitivity of 90.8% with a negative and the positive predictive values of 81.3%
43 and 76.6%, respectively. In particular, focusing on ISUP ≥ 3 PCa, our model is able to
44 correctly predict the biopsy outcomes in 98.1% of the cases.

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

48

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

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

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

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

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

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

91 Our Personalized Predictive Model (PPM) was tested on the entire dataset and the results
92 are summarized in Figure 1.B. 963 subjects were classified whereas for the remaining 484
93 subjects were not classified. Focusing on the classified subjects, 231 out of 390 patients
94 (specificity; Sp = 59.2%) were correctly classified as negative and 520 out of 573 patients
95 (sensitivity; Se = 90.8%) were correctly recognized as positive. The negative and the positive
96 predictive values (NPV and PPV) of the PPM were 81.3% and 76.6%, respectively. The
97 distribution of the ISUP score among the positive patients is showed in Figure 1.C. The ROC
98 curve obtained for the 963 classified patients, corresponding to an AUC value of 0.77 (Figure
99 1D).

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

102 Our findings are particularly noteworthy if we focus on more aggressive PCa, defined as
103 $ISUP \geq 3$, for which our PPM is able to correctly predict the biopsy outcomes in 98.1% of the
104 cases. These results outclass the performance of PSA and its derivatives such as PSA density
105 or free PSA, which Sp ranging from 30-40% and Se between 70% and 80%. Similarly,
106 considering the indication to perform TB with respect to mp-MRI findings [12], the PPV of
107 suspicious mpMRI for csPCa was 40% (95% confidence interval 36–43%), with large
108 heterogeneity between the studies analyzed in a recent metanalysis (I^2 94%, $p < 0.01$) [13].
109 If these are the findings that analyzed one single variable (serum markers or images) alone,
110 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.

141

142 **REFERENCES**

- 143 1. Checcucci E, Amparore D, De Luca S, Autorino R, Fiori C, Porpiglia F. Precision
144 prostate cancer surgery: An overview of new technologies and techniques. *Minerva*
145 *Urol e Nefrol.* 2019;71(5):487–501.
- 146 2. Checcucci E, Autorino R, Cacciamani GE, Amparore D, De Cillis S, Piana A, et al.
147 Artificial intelligence and neural networks in Urology: Current clinical applications.
148 *Minerva Urol e Nefrol.* 2020;72(1):49–57.
- 149 3. Giannini V, Rosati S, Regge D, Balestra G. Specificity improvement of a CAD system
150 for multiparametric MR prostate cancer using texture features and artificial neural
151 networks. *Health Technol (Berl).* 2017;7(1):71–80.
- 152 4. Rosati S, Balestra G, Giannini V, Mazzetti S, Russo F, Regge D. ChiMerge
153 discretization method: Impact on a computer aided diagnosis system for prostate
154 cancer in MRI. In: 2015 IEEE International Symposium on Medical Measurements and
155 Applications (MeMeA) Proceedings. IEEE; 2015. p. 297–302.
- 156 5. Bhandari M, Reddiboina M. Building artificial intelligence-based personalized
157 predictive models. *BJU Int.* 2019;124(2):189–91.
- 158 6. Hung AJ. Can machine-learning algorithms replace conventional statistics? *BJU Int.*
159 2019;123(1):1.
- 160 7. Checcucci E, De Cillis S, Granato S, Chang P, Afyouni AS, Okhunov Z; Uro-
161 technology and SoMe Working Group of the Young Academic Urologists
162 Working Party of the European Association of Urology. Applications of neural
163 networks in urology: a systematic review. *Curr Opin Urol.* 2020 Nov;30(6):788-
164 807. doi: 10.1097/MOU.0000000000000814. PMID: 32881726.

- 165 8. Rosati S, Agostini V, Balestra G, Knaflitz M. Basographic gait impairment score: A
166 fuzzy classifier based on foot-floor contact parameters. In: 2014 IEEE International
167 Symposium on Medical Measurements and Applications (MeMeA). 2014. p. 1–5.
- 168 9. Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. *Eur*
169 *Radiol.* 2012;22(4):746-757. doi:10.1007/s00330-011-2377-y
- 170 10. Barentsz JO, Weinreb JC, Verma S, et al. Synopsis of the PI-RADS v2 Guidelines for
171 Multiparametric Prostate Magnetic Resonance Imaging and Recommendations for
172 Use. *Eur Urol.* 2016;69(1):41-49. doi:10.1016/j.eururo.2015.08.038
- 173 11. Han J, Pei J, Yin Y, Mao R. Mining frequent patterns without candidate generation: A
174 frequent-pattern tree approach. *Data Min Knowl Discov.* 2004;8:53–87.
- 175 12. Checcucci E, de Cillis S, Piramide F, Amparore D, Kasivisvanathan V, Giganti F, et al.
176 The role of additional standard biopsy in the MRI-targeted biopsy era. *Minerva Urol*
177 *e Nefrol.* 2020;72(5):637–9.
- 178 13. Mazzone E, Stabile A, Pellegrino F, Basile G, Cignoli D, Cirulli GO et al. Positive
179 Predictive Value of Prostate Imaging Reporting and Data System Version 2 for the
180 Detection of Clinically Significant Prostate Cancer: A Systematic Review and Meta-
181 analysis. *Eur Urol Oncol.* 2020 Dec 25:S2588-9311(20)30212-1. doi:
182 10.1016/j.euo.2020.12.004. Epub ahead of print. PMID: 33358543.
- 183 14. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De
184 Santis M, et al EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020
185 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur*
186 *Urol.* 2021 Feb;79(2):243-262. doi: 10.1016/j.eururo.2020.09.042. Epub 2020 Nov 7.
187 PMID: 33172724.
- 188 15. Mortezaei A, Palsdottir T, Eklund M, Chellappa V, Murugan SK, Saba K et al.
189 Head-to-head Comparison of Conventional, and Image- and Biomarker-based
190 Prostate Cancer Risk Calculators. *Eur Urol Focus.* 2020 May 22:S2405-
191 4569(20)30113-9. doi: 10.1016/j.euf.2020.05.002. Epub ahead of print. PMID:
192 32451315.

- 193 16. Roffman DA, Hart GR, Leapman MS, Yu JB, Guo FL, Ali I, Deng J. Development and
194 Validation of a Multiparameterized Artificial Neural Network for Prostate Cancer Risk
195 Prediction and Stratification. *JCO Clin Cancer Inform.* 2018 Dec;2:1-10. doi:
196 10.1200/CCI.17.00119. PMID: 30652591; PMCID: PMC6873987.
- 197 17. Amparore D, Campi R, Checcucci E, Sessa F, Pecoraro A, Minervini A et al. Forecasting
198 the Future of Urology Practice: A Comprehensive Review of the Recommendations
199 by International and European Associations on Priority Procedures During the
200 COVID-19 Pandemic. *Eur Urol Focus.* 2020 Sep 15;6(5):1032-1048. doi:
201 10.1016/j.euf.2020.05.007. Epub 2020 May 31. PMID: 32553544; PMCID:
202 PMC7261455.
- 203 18. Wallis CJD, Novara G, Marandino L, et al. Risks from deferring treatment for
204 genitourinary cancers: a collaborative review to aid triage and management during
205 the COVID-19 pandemic. *Eur Urol* 2020.
206
207

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