

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

*Original*

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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  $\geq 3$  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.

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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