



Study of diagnostic accuracy of Fagan's two-step nomogram in increasing the value of predictive tools for prostate cancer: application of specific spatial distribution of positive/negative bioptic cores to predict extracapsular extension

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Received: 12 January 2018 / Accepted: 7 April 2018
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Abstract

Background Prostate cancer (PC) represents the second most frequent cancer in the male population worldwide. It is mandatory to have a very accurate staging to choose the best possible treatment.

Aims To test the possibility of improving the performance of Partin's tables in predicting the pathological staging of PC by introducing bioptic parameters through an innovative statistic tool (Fagan's two-step nomogram).

Methods We prospectively collected data of all 1048 consecutive patients undergoing saturation 24-core transrectal prostate biopsy. Then, in eligible 94 patients, we compared the prediction of presence/absence of extracapsular extension of neoplasm (EPE+/-), with pathological assessment of invasion through (pseudo)capsule in the prostatectomy specimens. Starting from the probability of EPE- (pre-test probability, calculated with formula "100%-risk of EPE+"), we used Fagan's nomogram to examine the diagnostic sensitivity (DSe) and specificity (DSp) of negative "lateral" bioptic cores.

Results We specifically analyzed the status of "lateral" cores in each side (94 patients × 2 sides = 188 sides). "Lateral" cores were negative in 42.5% of sides (80/188) with a DSe and DSp of 91.7 and 45.4%, respectively. In these sides, the mean probability of EPE+ according to Partin's tables was 21.6%. With Fagan's nomogram, the post-test probability of EPE+ when all "lateral" cores were negative was 14.1%, with a substantial gain of 7.5%.

Discussion The spatial distribution of bioptic positive cores allowed us to demonstrate the role Fagan's nomogram in increasing the accuracy of already existing, predictive tools for PC.

Conclusions This pioneering study may justify the use of the above nomogram in testing "local" predictive parameters in combination with pre-existing nomograms.

Keywords Prostate cancer · Staging · Prostate biopsy

Introduction

Prostate cancer (PC) represents the second most frequent cancer in the male population worldwide; its impact on quality of life depends on the treatment chosen, as recently

demonstrated by a multicentric Italian study. For this reason, it is mandatory to have a very accurate staging to choose the best possible treatment [1].

When PC is suspected, a 10/12-core prostate biopsy (PBx) under transrectal sonographic (TRUS) guidance is routinely performed [2]. This diagnostic technique has a cancer detection rate of 42.1 and 48.3% using a transperineal and transrectal approach, respectively [3]. Because a negative PBx does not exclude the possibility of PC and the false-negative rate may approach 50% [4], a saturation PBx (SPBx) is also used, significantly improving the PC detection rate in patients with suspicious clinical findings following the previous negative standard PBx [5, 6].

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When the presence of PC is demonstrated, there are many tools, such as nomograms or tables, available to predict the correct extent and staging of the disease [7]. However, some histologic parameters are rarely evaluated: one of these is the spatial distribution of positive bioptic cores.

Intuitively, positive cores involving more than one prostatic zone at biopsy may be associated with a larger and/or multiple tumor or foci, which may denote less favourable tumor characteristics, as documented by several investigators who found significant differences in treatment outcomes between unifocal and multifocal lesions [8, 9].

Knowledge of the precise spatial distribution of cancer is one of the most important problems, particularly as regards two aspects: one is its role in planning and performing focal therapies, in view of the fact that almost one in five candidates treated with radical prostatectomy is amenable to focal therapy targeting one side of the prostate, as reported by some authors [10]. Another problem of the precise definition of spatial distribution of prostate tumors is planning nerve-sparing surgery, especially in low- and intermediate-risk patients: the presence/absence of an extracapsular extension of the neoplasm (EPE+/-) is in fact a critical pathological variable which can significantly cause disease-free recurrence in patients undergoing mono/bilateral preservation of neurovascular bundles [11, 12]. Precise knowledge of the side-specific hazard of EPE+ is obviously crucial in low- and intermediate-risk patients, more often candidates for nerve-sparing treatment.

The aim of this study was to test the possibility of improving the performance of the most widely used validated system (Partin's tables [13]) in predicting the pathological staging of PC by introducing a bioptic parameter (number and site of positive/negative cores at SPBx) through an innovative statistic tool (Fagan's two-step nomogram [14]).

From the point of view of clinical practice, the aim was to increase the prediction of EPE- in low-intermediate-risk patients to perform a complete nerve-sparing with no (or very low) risk to have a PSM.

Fagan's two-step nomogram (Fig. 1) is a modification of Fagan's original nomogram [15], including the calculation step for the likelihood ratio (LR) through previously determined diagnostic sensitivity (DSe) and specificity (DSp), to ascertain the final probability of EPE- (post-test probability).

A line is drawn connecting the appropriate DSe and DSp values for the test, and the intersection of the line with the central axis provides the LR of the test result.

The LR represents the direction and strength of evidence provided by a test result. It is calculated by dividing the likelihood of the test result among patients by the likelihood of the same test result among patients without it [16].

For this test with a binary outcome, only a positive test result (LR+) is reported. LR+ may be computed directly from the DSe and DSp [$LR+ = DSe/(1 - DSp)$].

A specific freely available iOS app allows easy and precise calculation of each patient's post-test probability.

Materials and methods

We first prospectively collected demographic, pre-operative (pre-biopsy and pre-surgery) pathologic data of all 1048 consecutive patients undergoing saturation 24-core transrectal and transperineal PBx for suspected PC after a previous negative standard PBx, between January 2010 and December 2016 in our department. To maintain data homogeneity, we consider eligible only patients undergoing transrectal biopsy.

These procedures were performed by several urologists, using standardised techniques ('normal clinical practice').

To perform transrectal saturation PBx, we used a Trans Rectal Ultra Sound end-fired probe (TRUS) at a variable frequency of 5–7.5 MHz to guide the 18-gauge transrectal needle.

The biopsy patterns targeted six sectors (apex, lateral, and base, bilaterally) and the transition zone (TZ) to ensure a broad sampling area: the 24-core biopsy scheme is shown in Fig. 2.

All cores were immediately stretched and placed in 24 labeled tissue cassettes between two nylon sponges, without orientation of the biopsy specimen [17].

All slides were analyzed by a single experienced uropathologist (MPG) using contemporary diagnostic criteria for High-Grade Prostatic Intraepithelial Neoplasia (HGPIN), Atypical Small Acinar Proliferation (ASAP), and PC.

Pathology assessment of the biopsy cores included core length, number and location of positive cores, percent of cancer involvement in any positive core, presence of perineural invasion, and the Gleason score.

From this group of transrectal SPBx, we considered "eligible" patients diagnosed for PC (excluding those with clinical locally advanced or metastatic neoplasms) and treated with radical prostatectomy (open or robotic) in our centre. Pre-operative staging was performed by computerized tomography scan (CT) or abdominal magnetic resonance imaging (MRI), and bone scan. The D'Amico criteria were used to identify the specific class of risk [18].

Whole prostatectomy specimens were processed in the same laboratory. In the case of EPE+ and/or positive surgical margins, the specific site was identified. All pathological prostatectomy specimens were assessed by the same expert uropathologist (MPG).

Using these homogeneous data, we compared the prediction of EPE+ by choosing the pre-operative

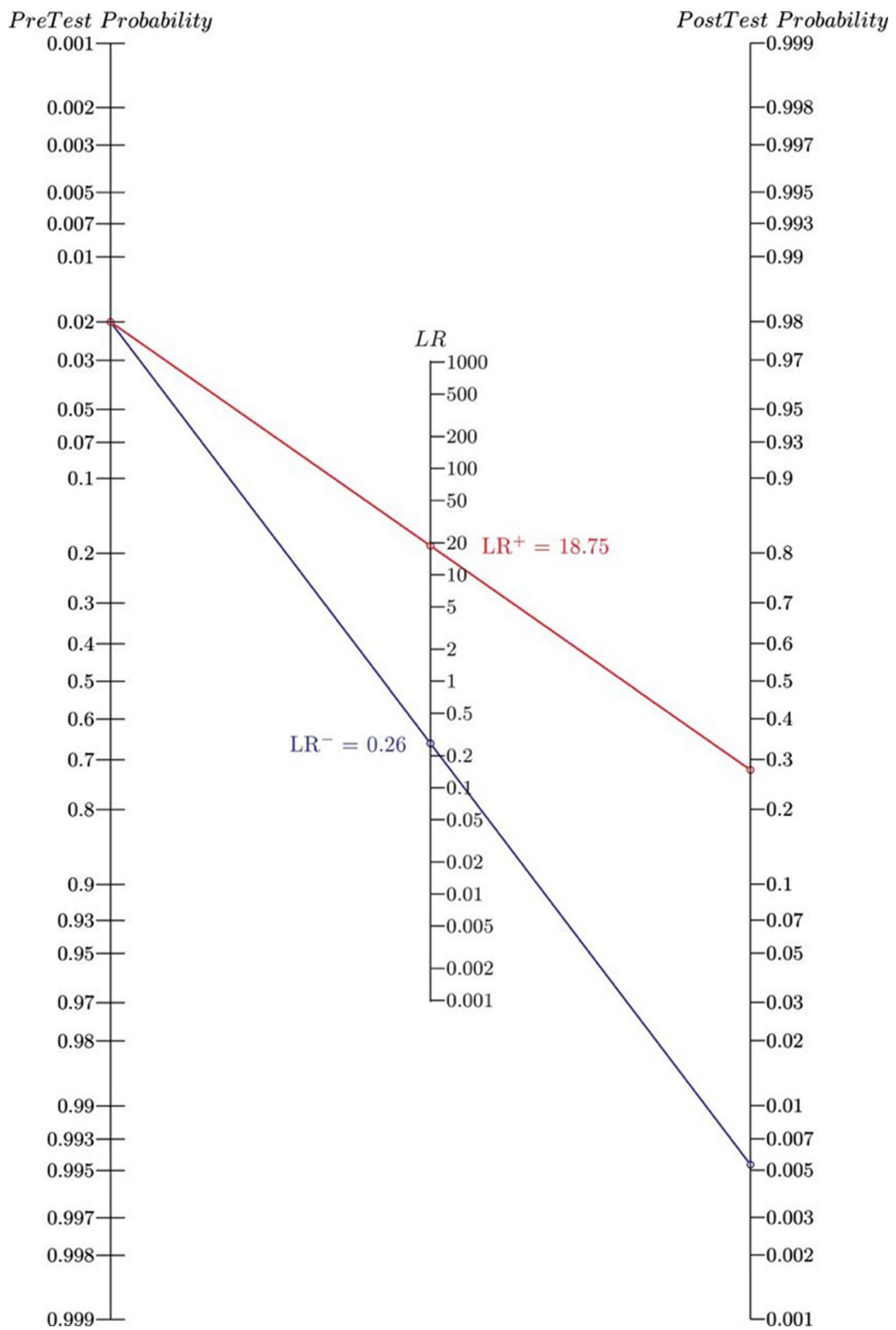


Fig. 1 Fagan's two-step nomogram

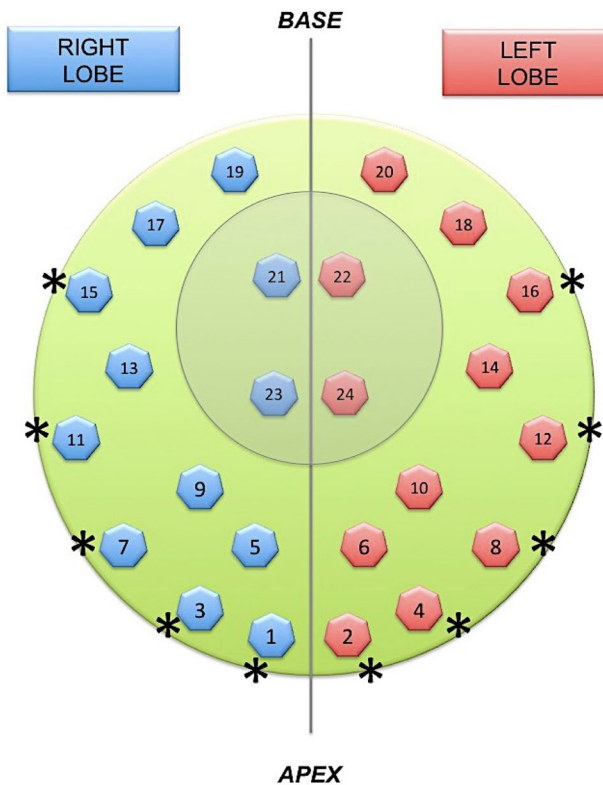


Fig. 2 24-core biopsy scheme. Asterisks indicate the lateral cores

biochemical, clinical, and pathological features used in Partin's tables, with pathological assessment of invasion through (pseudo)capsule in the prostatectomy specimens.

Then, we calculated the DSe and DSp of the positive "lateral" bioptic cores in each prostate and compared these findings with the presence of a tumor in the corresponding sites at the final slides from prostatectomy, noting EPE+ or EPE- in these sites.

Starting from the probability of EPE- calculated with Partin's tables (pre-test probability, calculated with formula "100%-risk of EPE+"), we used Fagan's two-step nomogram to examine the DSe and DSp of negative "lateral" bioptic cores.

Categorical data were reported as counts and percentages, whereas continuous variables with a normal distribution were reported as means and standard deviations (SD); if the data did not follow a normal distribution, we reported as median and interquartile range. We tested the concordance between different categorical data using the Cohen's Kappa test.

Results of this diagnostic test evaluation (DTE) study are reported according to internationally accepted standards for reporting DTE (STARD 2015 checklist—<http://www.equator-network.org/reporting-guidelines/stard/>).

Results

From the initial 1083 "potentially eligible patients" undergoing saturation PBx in the period of analysis, we selected 148 cases treated with radical prostatectomy out of whom were included in this study 94 "low-intermediate"-risk patients. See STARD diagram to report flow of participants through this study—Fig. 3.

Demographic characteristics, indications for SPBx, and the bioptic and definitive pathologic data showed that our series can be compared with others reported in the literature in terms of the accuracy of SPBx and sample homogeneity (see Table 1).

There was a poor concordance between bioptic and definitive Gleason score ($K: 0.3823$).

We found 54 cases of EPE+ (36.5%), while, in 25% of patients (37), a positive surgical margin (PSM). A significant correlation between EPE+ and PSM was noted ($p = 0.001$, OR 3.62). This correlation was also noted in low-risk patients (78 cases) with a $p = 0.03$ (OR 3.57).

We then examined the "lateral" bioptic cores (identified as numbers 1, 3, 7, 11 and 15 in our template), and these cores did turn out to be closer to the (pseudo)capsule at the level of the lateral margin, where neurovascular bundles approach the prostatic (pseudo)capsule.

Stratifying patients according to D'Amico classes, we decided to exclude both high-risk and hormonally treated patients, focusing only on the 94 low- or intermediate-risk patients: we specifically analyzed the status of "lateral" cores in each side, for a total of 188 sides analyzed.

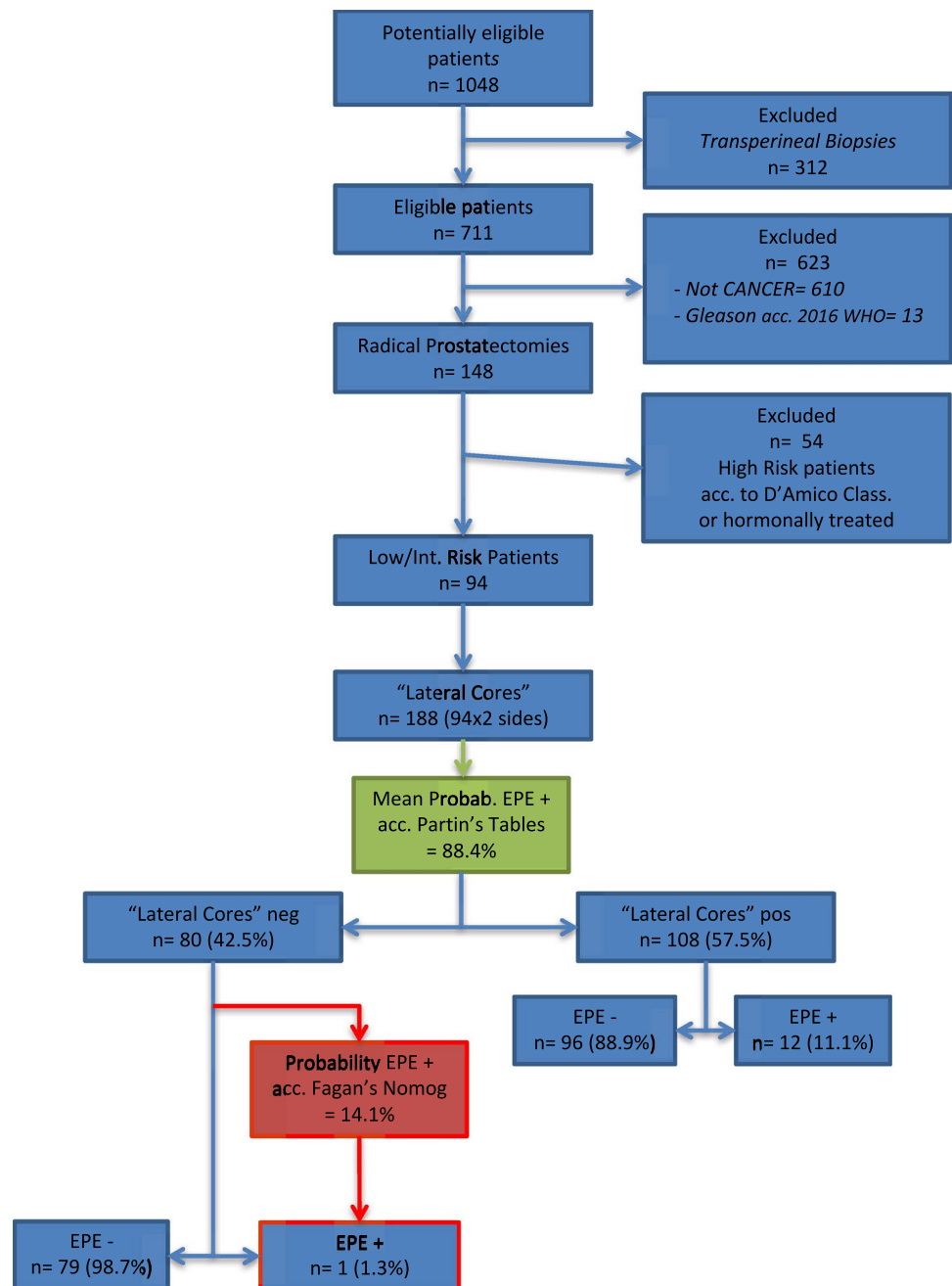
At least one of the "lateral" cores was positive in 57.5% of sides (108/188); in this group, 12 (11.1%) EPE+ was found in analysis of slides from prostatectomy. According to Partin's table, the mean probability of EPE+ was 23.6%.

Using the Cohen's Kappa test, we found a discrete concordance between the positive side at biopsy and laterality of cancer at prostatectomy specimen ($K: 0.487$); moreover, using this test, we demonstrated only a poor concordance between presence of at least one positive "lateral" core and presence of EPE+ ($K: 0.0834$).

Considering that our aim was to predict EPE- in low-intermediate-risk patients to perform a complete nerve-sparing with zero (or very low risk) to have a PSM, we focused our attention on the sides in which all the "lateral" cores were negative (42.5% of sides – 80/188): in this group, only one EPE+ was found in analysis of slides from prostatectomy; all the other cases (98.7%) were EPE-. In the latter cases, the DSe and DSp of negative "lateral" cores were 91.7 and 45.4%, respectively. In these sides, the mean probability of EPE+ according to Partin's tables was 21.6%.

With Fagan's two-step nomogram, the post-test probability of having EPE+ when all "lateral" cores were

Fig. 3 STARD diagram to report flow of participants through this study



negative in low/intermediate-risk patients was 14.1%, with a substantial gain of 7.5% in comparison with the probability calculated with Partin's tables alone.

Discussion

The presence of EPE+ increases the local stage of tumors and, in patients without systemic disease, can influence anticipated prognoses by altering therapeutic decisions such as whether to perform nerve-sparing radical prostatectomy or not, especially in patients with low-/

intermediate-risk PC. As reported by Ohori et al. [11], EPE+ was identified as a unilaterally frequent event (only 15% were bilateral) usually occurring near the neurovascular bundle: knowledge of the precise location of EPE+ can help treatment planning, to preserve the neurovascular bundle at least on one side.

Some studies have associated biopsy findings with the location of EPE+: Taneja et al. concluded that labeling biopsy cores as right side or left side was not justified, because of the low PPV (12.9 and 8.9%, respectively), but only 16% of their patients had EPE+ [19]. Nevertheless, Ohori et al. [11] demonstrated that the PPV of a PBx (any

Table 1 Patients' characteristics

| Parameter | Value |
|---|------------------------------|
| Age (mean \pm SD)—range | 64.2 \pm 6.4 (45–76) years |
| PSA median (interquartile range) | 6.45 (4.45) ng/ml |
| Pr. volume median (interquartile range) | 37.6 (33.6) cc |
| N. positive core median (interquartile range) | 4 (1–24) |
| Gleason score (biopsy)* | |
| 6 | 91 (61.5%) |
| 7 | 39 (26.4%) |
| 8 | 15 (10.1%) |
| 9–10 | 3 (2%) |
| Gleason score (definitive)* | |
| 6 | 49 (33.1%) |
| 7 | 71 (48%) |
| 8 | 18 (12.2%) |
| 9–10 | 10 (6.7%) |

SD standard deviation

*K test concordance: 0.3823

number of cores) for EPE+ on the same side was only 22%, but the dSe was high (88%).

Conversely, in our DTE study, we demonstrated higher PPVs (24.7%/42.2%/65.4% in low/intermediate-/high-risk patients, respectively). This difference may be due to the method of analysis, because, whereas other authors used only “number of positive cores”, “percentage of positive cores”, and “percentage of cancer” to predict side-specific EPE+, we used a more accurate approach, evaluating the presence of cancer in the specific “lateral” cores (those closest to the capsule in the lateral region).

To improve the accuracy of local staging, several studies [20] have demonstrated that magnetic resonance imaging (MRI) is the reference standard test for local staging of PC [21] because of its high diagnostic accuracy. MRI combined with MRI-ultrasound fusion techniques could potentially enhance or even replace template prostate biopsies in the future [22], but will not be available everywhere for a few years to come. For this reason, many validated predictive tools are available, precisely to be able to predict PC staging.

Partin's tables represent one of the most widely used tools, since they can pre-operatively quantify the risk of EPE+ or nodal involvement. However, the probability of EPE+ cannot be predicted in a side-specific fashion, a limitation which has been addressed by several authors [19].

Many other nomograms reveal poor spatial definition of PC extent, particularly as regards the side of a possible EPE+ [23]. The spatial distribution of positive cores is in fact rarely considered in these predictive cases.

This lack may be due to the fact that, although SPBx templates are usually standardised, PBx techniques differ

(can we think of transrectal versus transperineal PBx?). Consequently, data from the spatial distribution of positive/negative cores (when rigidly standardised) seem to be homogeneous only in single Centers, which means that this parameter cannot be successfully introduced in any predictive nomogram.

It was to emphasize this parameter that we performed this multistep study: we first collected homogeneous data from our TR SPBx.

Although, in clinical practice, it is usually accepted a first prostate biopsy of 10–12 cores, we decided to use only data from 24-core PBx, because the number of “lateral” cores is higher than in standard biopsies: considering that our aim was to test the ability of Fagan's nomogram to predict the extracapsular invasion or not, it was more logical to consider a group of patients with a greater number of “lateral” cores. Moreover, we consider that, in daily routine, a more accurate prediction of EPE+/- is more useful in planning the surgical strategy in patients that, for example, after a first standard biopsy demonstrating a very low-risk cancer (suitable for active surveillance), after a SPBx are demonstrated to have a cancer to be treated: in these cases, it is of great help to have an accurate prediction of capsular status to propose to the patient the best possible surgical strategy, for example, planning to preserve or not, completely or partially, and bilaterally or monolaterally the neurovascular bundles.

As we knew that neither sample size (creating a nomogram involves having available data from hundreds to thousands of patients and subjecting those data to logistic regression models and artificial neural networks) nor the characteristics of those data (as mentioned previously) would allow us to create a specific predictive tool exportable to other centers, we decided to use a specific statistic tool, Fagan's two-step nomogram.

Recent experiences reported in the literature demonstrate the role of this nomogram in improving diagnostic accuracy [14]. From the probability of the patient having the target disorder (in this case, the specific side risk of EPE-) (pre-test probability) estimated with other nomograms (i.e., Partin's tables), this graphic tool uses the results of ‘local’ data of a diagnostic ‘test’ (in this case, DSe and DSp for negative “lateral” cores at SPBx in predicting EPE-) and calculates the probability of the patient having the target situation (EPE-) after running the test (post-test probability).

In our experience, comparison of bioptic and final pathologic data demonstrates that Fagan's nomogram can allow a substantial decrease in predicting side-specific EPE- (from 21.6 to 14.1%).

The strengths of our approach are the possibility of using “local” data from any centre (stressing the value of an internal univocal anatomo-pathological evaluation, where possible), while maintaining the role of already existing, well-known, validated tools (not only Partin's

tables, but also any other nomogram) with the aim of improving their predictive value.

We tested this tool by focusing on EPE status using the spatial distribution of bioptic cores, but this method can be applied to any other bioptic, biochemical, or imaging parameter predicting the pathologic features of PC [24].

The prime reason for using Fagan's nomogram was to obtain further information which can modify the pre-test probability of disease estimated with validated predictive tools. One major advantage of LHs is that they can be used to help clinicians to adapt the dSe and dSp of any "locally calculated" parameter to individual patients. When surgeons examine their patients, they may decide to perform that test, because, based on their personal experience or on "local" data, they suspect a certain diagnosis and would like to increase its specific probability, without having to create their own nomograms.

The results of clinical tests are generally used not to make or exclude a diagnosis categorically (i.e., EPE+ or EPE-?), but to modify pre-test probability, to generate post-test probability.

Our study has several limitations: (a) the sample size is low, which did not allow the creation of a nomogram (which, however, was not our main aim); (b) we used the Partin's tables, although there are more recent and accurate nomograms.

Further external studies are needed to validate the use of this tool.

The strengths of this DTE study are: (a) the homogeneity of the prospective analyzed data, which allows accurate evaluation of the influence of location of positive cores in predicting EPE+ (with a PPV superior to that reported in similar studies); (b) the novelty of applying Fagan's nomogram to increase diagnostic accuracy by using not a "test", but dSe and dSp from "local" data; (c) the possibility of using this method with other locally identified parameters. The availability of some online tools, such as iOS apps (e.g., DocNomo®) allows a daily bedside interpretation of a 'diagnostic' test result.

Conclusions

Homogeneous data of the spatial distribution of positive cores at SPBx allowed us to confirm not only the statistic value of Fagan's two-step nomogram, but also to demonstrate its role in increasing the accuracy of already existing, validated, predictive tools for PC. This pioneering study may justify the use of the above nomogram (even with simplified digital versions, e.g., iOS apps) in testing "local" predictive parameters in combination with pre-existing nomograms.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable standards.

Informed consent Informed consent was obtained from individual participants included in this study.

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