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Utility of digital rectal examination in a population with prostate cancer treated with active surveillance

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Abstract

Introduction: Digital rectal examination (DRE) is part of the clinical evaluation of men on active surveillance (AS). The purpose of the present study is to analyze the value of DRE as a predictor of upgrading in a population of men with prostate cancer (PCa) treated with AS.

Methods: We used the prostate biopsy (PBx) database from an academic center, including PBx from 2006–2018, and identified 2029 confirmatory biopsies (CxPBx) of men treated with AS, of which 726 men had both diagnostic (initial) and CxPBx information available. We did a descriptive analysis and evaluated sensitivity, specificity, and predictive values of DRE for the detection of clinically significant PCa (csPCa). Multivariable regression analysis was done to identify predictors of csPCa. The primary outcome was to evaluate DRE as a predictor of the presence of csPCa at CxPBx.

Results: Among the 2029 patients with a CxPBx, 75% had PCa, and of these, 30.3% had upgrading to International Society of Urologic Pathologists (ISUP) grade ≥2. Thirteen percent of men had a suspicious DRE (done by their treating physician). Sensitivity, specificity, negative and positive predictive values of DRE to detect csPCa were best with a prostate-specific antigen (PSA) <4 ng/ml (27%, 88%, 31%, and 87%, respectively). A suspicious DRE at CxPBx, particularly if the DRE at diagnosis was negative, was a predictor of csPCa (odds ratio [OR] 2.34, p=0.038). The main limitation of our study is the retrospective design and the lack of magnetic resonance imaging.

Conclusions: We believe DRE should still be used as part of AS and can predict the presence of csPCa, even with low PSA values. A suspicious nodule on DRE represents a higher risk of upgrading and should prompt further assessment.

Introduction

Active surveillance (AS) has become the standard of care for men with low-risk prostate cancer (PCa).[1,2] One of the criteria used for including patients in AS protocols is the digital rectal examination (DRE). Most guidelines allow for cT2 patients to be offered AS as long as the rest of the low-risk criteria are fulfilled.[3,4]

AS followup protocols vary between institutions.[4-7] The followup usually includes periodical prostate-specific antigen (PSA) measurements, DRE, and prostate biopsies (PBx).[4] Most centers mandate a confirmatory PBx within 6–18 months from the initial diagnostic PBx, as the initial PBx can miss clinically significant prostate cancers (csPCa).[5]

Large AS series have reported a consistent rate of pathological progression (upgrading and/or upstaging) at the confirmatory PBx of 19.9–28.1%.[5] Accurate and timely detection of patients with csPCa who require treatment is crucial, although we also struggle to determine who may safely avoid or delay a confirmatory PBx. Risk factors for upstaging/upgrading include high-volume International Society of Urologic Pathologists (ISUP) grade 1, suspicious lesions on magnetic resonance imaging (MRI), PSA density, race, and age.[8-12]

DRE is widely considered a component of clinical evaluation in men with PCa, although in AS, the value of DRE is uncertain. Nonetheless, DRE involves mild discomfort and may require an additional patient visit. The objective of the present study was to analyze the value of DRE as a predictor of upgrading in a population of patients on AS.

Methods

After research ethics board approval, we used the prospectively maintained PBx database from a large tertiary center and retrieved patients treated with AS between 2006 and

2018. We included patients who were initially diagnosed with ISUP grade 1 PCa (in our center or somewhere else), were started on AS, and had at least one followup PBx in our center. For patients who had more than one followup PBx, we included only the first confirmatory PBx for the analysis, as the time to the following PBx is widely variable. As part of our AS protocol, all men initially managed with AS undergo a confirmatory PBx 6–18 months from the diagnostic PBx. We also looked into patients who had both diagnostic PBx and confirmatory PBx done in our center, of whom we had complete data to account for changes between the two time points. Data collected included age, number of PBx, number of cores in the confirmatory PBx, PSA before the PBx, number of cores taken, prostate volume (PV), suspicious transrectal ultrasound results (TRUS), referral DRE (rDRE), DRE done by the radiologist at the time of the PBx (bxDRE), presence of PCa (any), and presence of csPCa (defined as ISUP grade ≥2). The rDRE was performed by the treating physician. The great majority of these DRE were done by urologists (either uro-oncologist or general urologists), but some were done by radiation oncologists and a small proportion were performed by family physicians before the diagnostic PBx. These were done in clinic as part of the routine physical examination, both prior to the diagnostic PBx and during AS before the confirmatory PBx. Some men were referred to our center for the diagnostic PBx and then continued the AS by the group of urologists in our center, and some were referred after the PCa diagnosis was made, with a biopsy done outside of our center. All of these men were being treated in our center after the diagnosis was made. We defined "suspicious DRE" as the presence of a palpable nodule compatible with PCa, judged by the treating physician in clinic (rDRE) or the radiologist right before the biopsy (bxDRE). In our center, we routinely do a systematic biopsy taking 12 cores (six from each prostate lobule) for the first and subsequent PBx. Suspicious nodules on DRE or ultrasound are targeted obtaining extra cores (2–3 from each suspicious lesions), and in case of suspicious lesion on MRI, we use a targeted fusion technique.

Statistical analysis

We did a descriptive analysis with median and interquartile ranges (IQR) for continuous variables and proportions for discrete variables. We then calculated a Cohen kappa value between rDRE and bxDRE, as well as sensitivity, specificity, and predictive values for the detection of csPCa, stratified by PSA values (PSA<4 ng/ml, PSA 4–10 ng/ml, and PSA>10 ng/ml).

Finally, we used univariable and multivariable logistic regression analysis to obtain the odds ratio (OR) of a positive rDRE to detect a csPCa in the confirmatory PBx. rDRE was used for the inferential analyses, as it represent the current practice in which the initial or diagnostic DRE can be done by a variety of physicians with varying levels of expertise, as opposed to an physician who has done multiple biopsies and DREs, having constant feedback from pathological results for many years (bxDRE). The other predictors included into the models were chosen based on factors commonly used to guide decisions in patients on AS, such as PSA, PV, number of cores taken at the biopsy, TRUS results, and age. The multivariable model included all predictors that were statistically significant in the univariable analysis.

We repeated the analyses using only the population of patients who had both diagnostic PBx and confirmatory PBx done in our center. In these groups, we analyzed potential changes in PSA ("deltaPSA") and DRE from diagnostic PBx to confirmatory PBx. In this population, we also categorized the changes in PSA, defined as:

- PSA decrease (PSAd) as a decrease in PSA from diagnostic PBx to confirmatory PBx ≥2 ng/ml;
- PSA increase (PSAi) as an increase ≥2 ng/ml; and
- Stable PSA (PSAs) if the PSA variability was <2 ng/ml from one biopsy to the other.

DRE dynamics were classified as:

- DRE-/- if DRE was non-suspicious at both diagnostic and confirmatory PBx;
- DRE+/+ if DRE was suspicious at both diagnostic and confirmatory PBx;
- DRE+/- if DRE was suspicious at diagnostic PBx but non-suspicious at confirmatory PBx; and
- DRE-/+ if DRE was non-suspicious at diagnostic PBx and suspicious at confirmatory PBx.

All analyses were done using R version 3.4.3.

Results

A total of 19 821 PBx were performed in our center between 2006 and 2018. Of these, 2029 were first confirmatory PBx of unique patients initially diagnosed with low-risk PCa treated under AS. The population of patients with complete information on both diagnostic PBx and confirmatory PBx in our center consisted of 726 patients. Table 1 shows the patients and their associated PBx characteristics, showing an upgrading of 30.3% in all the confirmatory PBx and 21.9% in the cohort of patients who had both diagnostic and confirmatory PBx in our center.

Among all men with a confirmatory PBx (n=2029), the rDRE was suspicious in 263 (12.96%) and bxDRE in 463 (22.82%). The agreement between rDRE and bxDRE was 82.8%, with a Cohen kappa of 0.426. Regarding the detection of csPCa at confirmatory PBx, rDRE led to 497 false-negative diagnoses (non-suspicious DRE with csPCa at the confirmatory PBx), of which bxDRE detected 120 (24.1%). Conversely, bxDRE led to 407 false-negative diagnoses, of which rDRE detected only 30 (7.4%). For those with both

Table 1. Patient and prostate biopsy (PBx) characteristics

	All confirmatory PBx (n=2029)	Diagnostic PBx (n=726)	Confirmatory PBx in men with diagnostic PBx available (n=726)
Age in years, median (IQR)	65 (60–71)	63 (58–68)	65 (60–70)
Number of cores, median (IQR)	16 (14–17)	12 (10–12)	16 (15–17)
Prostate-specific antigen in ng/ml, median (IQR)	5.83 (3.80–8.40)	5.82 (3.85–6.92)	5.30 (3.39–7.70)
Prostate volume in cc, median (IQR)	44 (33–60)	43 (34–56)	44 (34–58)
Suspicious TRUS, n (%)	893 (44%)	232 (32%)	298 (41%)
Suspicious rDRE, n (%)	263 (12.96%)	184 (25.34%)	81 (11.16%)
Suspicious bxDRE, n (%)	463 (22.82%)	185 (25.48%)	156 (21.49%)
Any cancer, n (%)	1 531 (75.5%)	726 (100%)	536 (73.8%)
Upstaging to csPCa, n (%)	614 (30.3%)	NA	159 (21.9%)

bxDRE: digital rectal examination done right before the biopsy by the person performing the biopsy; csPCa: clinically significant prostate cancer (ISUP grade 2 or higher); IQR: interquartile ratio; PBx: prostate biopsy; rDRE: digital rectal examination done in clinic by the treating physician prior to the biopsy; TRUS: transrectal ultrasound.

diagnostic and confirmatory PBx, DRE agreement at diagnostic PBx was 79.2%, with a Cohen kappa of 0.451; at confirmatory PBx, it was 82.2%, with a Cohen kappa of 0.362.

Table 2 shows the sensitivity, specificity, positive, and negative predictive values of rDRE and bxDRE in all the confirmatory PBx (n=2029) for the detection of csPCa categorized by PSA values. We can see some differences between rDRE and bxDRE, mainly in terms of sensitivity. In Table 3, we present our inferential analysis for the prediction of Gleason upgrading in the whole cohort of men with confirmatory PBx. The predictors for upgrading were a suspicious rDRE, an elevated PSA, lower PV, a suspicious TRUS, and older age.

For the 726 patients in whom we had both diagnostic and confirmatory PBx, we found that most had DRE-/- (512, 70%), 51 (7%) had DRE+/+, 133 (18%) had DRE+/-, and only 30 (4%) had DRE-/+. We did a univariable and multivariable analysis, including the variation of PSA (deltaPSA) and DRE (deltaDRE) in this subpopulation of patients (Table 4). The predictors for upgrading were DRE -/+, an elevation in the PSA (deltaPSA), PV, older age, and a suspicious TRUS.

Of the men who had PSAd, PSAs, and PSAi, 89 (18%), 38 (18%), and 68 (29%) had csPCa, respectively. As expected, PSAi (increase ≥2 ng/ml) had the higher rate of Gleason upgrading, but PSAd and PSAs did not rule out the presence of csPCa. Grouped by deltaDRE, of the men who had DRE-/-, DRE+/+, DRE+/-, and DRE-/+, 104 (20%), 15 (29%), 29 (22%), and 11 (37%) had csPCa, respectively.

Discussion

This study was conducted in a large population of AS patients undergoing their first confirmatory PBx. There was a slightly higher prevalence of suspicious DRE (13%) compared to a screening population (9.2%).[13] This can be explained by the fact that these men are a selected population who already have a diagnosis of PCa, although it seems to be a minor difference.

The rDRE has a low sensitivity (19%) in the overall population, but a good specificity (90%). This suggests that a suspicious rDRE can reliably signal presence of csPCa indicating the need for a PBx or other studies (molecular biomarkers or MRI). Table 2 shows that sensitivity of rDRE for the detection of csPCa in men undergoing a confirmatory PBx is higher with a lower PSA. Similarly, negative predictive value is high, comparable to MRI, particularly with a PSA <4 ng/dl.[8,14,15] The latter could be in relation to a low prevalence of csPCa in men with low PSA values. In contrast to reports in undiagnosed patients,[16] in the AS population, DRE was most useful in patients with a lower PSA. One explanation is that patients with a suspicious DRE and confirmed csPCa at diagnostic PBx had already been selected

Table 2. Sensitivity, specificity, PPV, and NPV of rDRE and bxDRE in all the confirmatory biopsies (n=2029), stratified by PSA for the prediction of csPCa

	rDRE				bxDRE			
	Overall	PSA<4 ng/ml	PSA 4–10 ng/ml	PSA >10 ng/ml	Overall	PSA<4 ng/ml	PSA 4–10 ng/ml	PSA >10 ng/ml
Sensitivity	19%	27%	18%	17%	34%	35%	32%	37%
Specificity	90%	88%	91%	85%	82%	80%	83%	79%
PPV	44%	31%	48%	56%	45%	23%	46%	66%
NPV	72%	87%	71%	49%	74%	87%	73%	54%

bxDRE: digital rectal examination done right before the biopsy by the person performing the biopsy; csPCa: clinically significant prostate cancer (ISUP grade 2 or higher); NPV: negative predictive value; PPV: positive predictive value; PSA: prostate-specific antigen; rDRE: digital rectal examination done in clinic by the treating physician prior to the biopsy.

out of the AS cohort (as a number of these suspicious DRE from the initial assessment have already been targeted in the diagnostic biopsy and represented csPCa that led to a treatment with curative intent as opposed to AS); thus, a new nodule represents real disease progression. With these findings, we can interpret that in case of finding a nodule on DRE, we should do further testing (especially if this was not present in previous visits), but a normal or non-suspicious DRE does not rule out the presence of csPCa; the decision to pursue a new PBx should be based on other clinical factors (PSA dynamics, time from previous biopsy, tumor volume, MRI, etc.). In Table 2, we can observe a marked difference between rDRE and bxDRE, which may be a reflection of the experience or even the setting (the position of the patient, the constant review/feedback from pathological results, among others) in which physicians are doing biopsies on a regular basis. Such difference shows a clinical correlation, since bxDRE was suspicious in 24.1% of the csPCa that were not detected on rDRE.

By looking into the population for which we had information on both diagnostic and confirmatory PBx, we were able to study the changes from one to another. As expected, those patients with an elevation of PSA ≥2 ng/ml had a higher frequency of csPCa in the confirmatory PBx (29%). The deltaPSA was a predictor of upgrading in both univariable and multivariable analyses. This supports the current monitoring strategies. Regarding the DRE, Table 3 shows that in the case of not having information on the diagnostic PBx (all confirmatory PBx cohort), a suspicious DRE is a predictor of upgrading at confirmatory PBx. With more granularity, in the cohort of patients with information on both diagnostic and confirmatory PBx (Table 4), a "newly" suspicious DRE (DRE-/+) had a higher likelihood of upgrading, while the presence of a persistently suspicious DRE (DRE +/+) did not reach statistical significance. In the univariable and multivariable analyses, only DRE-/+ was a predictor of the presence of csPCa at confirmatory PBx, despite modest numbers (30 patients, with 11 patients found with csPCa at confirmatory PBx). The lack of statistical significance of DRE+/+ as a predictor of upgrading may be related to the sample number (51 patients, with 15 of them upgraded to csPCa) but also to the fact that if they had a suspicious DRE from the beginning, it has likely been sampled in the diagnostic PBx and those with csPCa have already been detected and treated accordingly.

We present evidence supporting the use of DRE as part of AS, adding information to decide whether to do a confirmatory PBx or not. Currently, even with the new technology (MRI, biomarkers) available, it is still recommended to always do at least one confirmatory PBx.[17] Nonetheless, all information that could be obtained to predict the presence of a more aggressive cancer (csPCa) can be used in clinic to decide upon performing further biopsies or even to risk-stratify and consider a more conservative management for certain patients. We believe these results offer valuable evidence for the clinician, supporting further investigations in case of finding a positive DRE, regardless of the PSA dynamics. The need for a DRE in men with access to MRI

Table 3. Univariable and multivariable regression analyses predicting upgrading in all confirmatory PBx (n=2029)

	Clinically significant prostate cancer		
	OR	95% CI	p
Univariable			
rDRE	2.05	1.57–2.66	<0.001
PSA, ng/ml*	1.14	1.11–1.16	<0.001
PV, c	0.99	0.98–0.99	<0.001
Number of cores taken	1.03	0.99–1.06	0.165
TRUS	2.44	2.01–2.97	<0.001
Age, years	1.06	1.05–1.08	<0.001
Multivariable			
rDRE	1.54	1.14–2.07	0.004
PSA (ng/ml)*	1.15	1.12–1.18	<0.001
PV, cc	0.98	0.97–0.98	<0.001
Suspicious TRUS	2.05	1.66–2.53	<0.001
Age (year)	1.06	1.04–1.07	<0.001

*The OR was calculated using PSA as a continuous variable, representing each 1.0 ng/ml increase. CI: confidence intervals; OR: odds ratio; PBx: prostate biopsy; PSA: prostate-specific antigen; PV: prostate volume; rDRE: digital rectal examination done in clinic by the treating physician prior to the biopsy; TRUS: transrectal ultrasound.

Table 4. Univariable and multivariable analyses to predict csPCa in the population of men who had diagnostic PBx and confirmatory PBx in our center (n=726)

	OR	95% CI	p
Univariable analysis			
rDRE -/- (n=512)	Ref	Ref	Ref
rDRE +/+ (n=51)	1.63	0.84–3.05	0.132
rDRE +/- (n=133)	1.09	0.78–1.72	0.705
rDRE -/+ (n=30)	2.27	1.02–4.85	0.038
deltaPSA	1.09	1.04–1.16	<0.001
PV in cc	0.99	0.98–1.00	0.09
Age in years	1.06	1.03–1.08	<0.001
Suspicious TRUS	1.88	1.32–2.68	<0.001
Multivariable analysis			
DeltaDRE			
rDRE-/-	Ref	Ref	Ref
rDRE+/+	1.11	0.54–2.16	0.769
rDRE+/-	1.06	0.65–1.70	0.811
rDRE-/+	2.34	1.02–5.17	0.038
deltaPSA	1.10	1.05–1.17	<0.001
PV in cc	0.99	0.98–1.00	0.004
Age in years	1.06	1.03–1.09	<0.001
Suspicious TRUS	1.75	1.21–2.53	0.003

CI: confidence intervals; csPCa: clinically significant prostate cancer (ISUP grade 2 or higher); deltaPSA: variation of prostate-specific antigen from the diagnostic prostate biopsy to the confirmatory prostate biopsy; OR: odds ratio; PBx: prostate biopsy; PV: prostate volume; rDRE: digital rectal examination done in clinic by the treating physician prior to the biopsy; TRUS: transrectal ultrasound.

has not been studied and could not be evaluated in the present study. The transformation from a non-suspicious DRE to a suspicious DRE should lead to closer surveillance and should be discussed with the patient.

Limitations

The limitations of the study include the retrospective design and the missing information on the diagnostic PBx, given that many of these were not done in our center. This design limited the available details on the DRE and had to be classified as suspicious vs. non-suspicious, as this is how it was recorded on the database. Similarly, since the rDRE was performed by a more heterogeneous group of physicians (particularly for the diagnostic PBx), rDRE had more interobserver variability compared to the bxDRE, which was performed by a limited number of physicians specialized in doing PBx. Likewise, the number of cores taken in each biopsy varied according to clinical criteria. Comparing the PSA changes over time or the PSA reported at diagnosis in the whole population would be useful and would allow better characterization of these variables, although we were able to do this in a significant number of patients (n=726). Another limitation is the lack of MRI in this cohort. MRI has currently been incorporated into the followup of AS men in many centers.[17,18] In this cohort, MRI was not employed routinely. It is plausible that some cancers may be palpable without restricted diffusion, but this data is lacking. Further studies of the accuracy of DRE in the context of MRI are warranted. Also, the study was limited to the first followup biopsy in an attempt to control for the time-to biopsy (time to subsequent PBx is much more variable after the first confirmatory biopsy), focusing the study on the initial period of AS.

Conclusions

Even though it cannot be used to exclude the presence of csPCa, we believe DRE should still be used in the clinical evaluation of men being managed with AS, regardless of the PSA value. A suspicious nodule on DRE is associated with a higher risk of upgrading, adding information that should be considered in the diagnostic workup and treatment decision.

Competing interests: The authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed

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