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Reducing the Frequency of Follow-up Cystoscopy in Low-grade pTa Non–muscle-invasive Bladder Cancer Using the ADXBLADDER Biomarker

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Abstract

Background: Non–muscle-invasive bladder cancer (NMIBC) is one of the most expensive cancers owing to frequent follow-up cystoscopies for detection of recurrence.
Objective: To assess if the noninvasive ADXBLADDER urine test could permit a less intensive surveillance schedule for patients with low-grade (LG) pTa tumor without carcinoma in situ (CIS) at the previous diagnosis.
Design, setting, and participants: In a prospective, double-blind, multicenter study, 629 patients underwent follow-up cystoscopy, transurethral resection of bladder tumor/biopsy of suspect lesions, and ADXBLADDER testing.
Outcome measurements and statistical analysis: Diagnostic test accuracy and decision curve analysis were used to evaluate the impact of ADXBLADDER on decision-making on whether to perform follow-up cystoscopy. The primary endpoint was the negative predictive value (NPV) of ADXBLADDER for detection of high-grade and/or CIS (HG/CIS) recurrence and its impact on reducing unnecessary cystoscopies.
Results and limitations: ADXBLADDER had sensitivity of 66.7% (95% confidence interval [CI] 34.9–90.1%) and an NPV of 99.15% (95% CI 97.8–99.8%) for detection of HG/CIS recurrence. The probability of HG/CIS recurrence was 5.0% for ADXBLADDER-positive patients and 0.85% for ADXBLADDER-negative patients. For HG/CIS recurrence threshold probabilities between 0.85% and 5.0%, ADXBLADDER yields a net benefit with omission of cystoscopy for ADXBLADDER-negative patients. The corresponding net reduction in unnecessary cystoscopies ranges from 11 to 62 per 100 patients.
Conclusions: Patients with LG pTa tumor at the previous diagnosis, for which the risk of HG/CIS recurrence is low and the ADXBLADDER NPV for ruling out HG/CIS recurrence is 99.15%, are ideally suited for a less intensive, personalized follow-up surveillance strategy using ADXBLADDER, with omission of cystoscopy for ADXBLADDER-negative patients.

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Patient summary: ADXBLADDER is a urine test that can predict the probability of recurrence of bladder cancer. Patients diagnosed with low-grade cancer confined to the bladder mucosa are ideally suited for less intensive follow-up using this test, which could reduce unnecessary cystoscopy procedures for those with a negative result, potentially improve quality of life, and reduce overall health care costs.

1. Introduction

Non–muscle-invasive bladder cancer (NMIBC) is one of the most expensive cancers owing to frequent cystoscopies for detection of disease recurrence and progression [1]. For low-risk disease there is a strong likelihood that any recurrence will also be of low grade (LG) and low stage [2]. Small LG pTa tumors do not present an immediate threat to the patient and early detection offers no benefit regarding the fate of the disease, so there is a strong argument that too many cystoscopies are carried out, leading to overdiagnosis and overtreatment [2,3]. Lower-intensity follow-up schedules in both low- and high-risk disease do not increase the risk of disease progression or death due to bladder cancer when compared to currently recommended schedules [4,5], indicating that a less intensive NMIBC follow-up schedule may be appropriate.

The main objective of a biomarker should be to rule out high-grade (HG) recurrences and carcinoma in situ (CIS) without the need for invasive procedures [6]. The use of a urinary biomarker with a very high negative predictive value (NPV) to predict the absence of both HG recurrence and CIS during follow-up has great utility, providing reassurance that a lower-intensity cystoscopy schedule is safe.

ADXBLADDER is a novel urinary biomarker test that detects MCM5 protein in urine sediment. For HG and/or high-stage disease, ADXBLADDER has high sensitivity (75.6%) and a very high NPV of 99% [7], which are higher than with cytology [8].

The primary objective of this study was to assess the clinical value of ADXBLADDER and determine if a less intensive surveillance schedule could be adopted in LG pTa NMIBC to allow reductions in the number of cystoscopies carried out and associated health care costs.

2. Patients and methods

2.1. Study population

This is a secondary analysis of 1718 patients enrolled in a prospective, double-blind, cohort study carried out at 21 European centers between August 2017 and July 2019. Ethical approval was obtained at all sites (approval references: IRAS ID 224141. REC 17/NE/0174) and all patients provided informed consent [7,8].

Patients were diagnosed with primary or recurrent urothelial NMIBC in the previous 24 mo (positive transurethral resection of bladder tumor [TURBT]/biopsy), were aged ≥18 yr, and were attending the clinic for follow-up flexible cystoscopy.

The following exclusion criteria were applied: presence of prostatitis or calculi within the genitourinary system; use of urological instrumentation within 14 d; a previous or subsequent diagnosis of prostate cancer or renal cancer; and treatment with systemic chemotherapy or radiotherapy.

Patients had to be able to produce 10 ml of urine. Voided urine samples were collected before cystoscopy and processed within 48 h. An ADXBLADDER test was performed as previously described [7].

ADXBLADDER results were compared to the diagnosis obtained via cystoscopy and local pathology of TURBT/biopsy tissue from suspect lesions. Patients were deemed to be recurrence-positive if a lesion detected on cystoscopy was pathologically positive. If cystoscopy was normal or showed only inflammation or erythema, the patient was considered recurrence-negative unless a biopsy was clinically indicated and subsequently determined to be pathologically positive. For ADXBLADDER testing, samples with a result greater than or equal to the assay cutoff according to the manufacturer's instructions were considered MCM5-positive; samples below the assay cutoff were deemed MCM5-negative.

2.2. Statistical analysis

The ADXBLADDER sensitivity, specificity, positive predictive value (PPV), NPV, and area under the receiver operating characteristic curve (AUC) were calculated both for any recurrence and for high-grade (World Health Organization 2004 classification) and/or CIS (HG/CIS) recurrence [9,10].

The prognostic importance of ADXBLADDER positivity for recurrence was assessed in univariate and multivariable logistic regression models and estimated using odds ratios (ORs). Since the tumor number and size at the previous diagnosis were not recorded for half of the patients, these variables were not included in the multivariable analysis. Internal validation was performed by generating 1000 bootstrap random samples with replacement. A nomogram estimating the probability of recurrence was generated from the multivariable logistic regression.

Decision curve analysis (DCA) was used to evaluate the clinical consequences of carrying out or not carrying out cystoscopy across different patient recurrence threshold probabilities by assessing the net benefit of the decision and calculating the net reduction in unnecessary cystoscopies per 100 patients [11].

Statistical analyses were performed with Stata 12.1 using a significance level of 0.05.

3. Results

Among 1718 patients enrolled, 287 were initially excluded, leaving 1431 patients [7]. Only the 629 patients with LG pTa NMIBC without CIS at the previous diagnosis and treated with TURBT alone or TURBT followed by intravesical chemotherapy were included in the analyses (Standards for Reporting of Diagnostic Accuracy diagram, Supplementary Fig. 1).

Patient and tumor characteristics at the previous diagnosis, the most recent treatment, and current ADXBLADDER status are provided in Table 1.

Treatment was TURBT alone in 359 patients (57%) and TURBT + chemotherapy in 270 (43%). In the TURBT + chemotherapy subgroup, 263 (97.4%) received mitomycin C (MMC), of whom 250 had MMC alone (92.6%), 12 (4.4%)

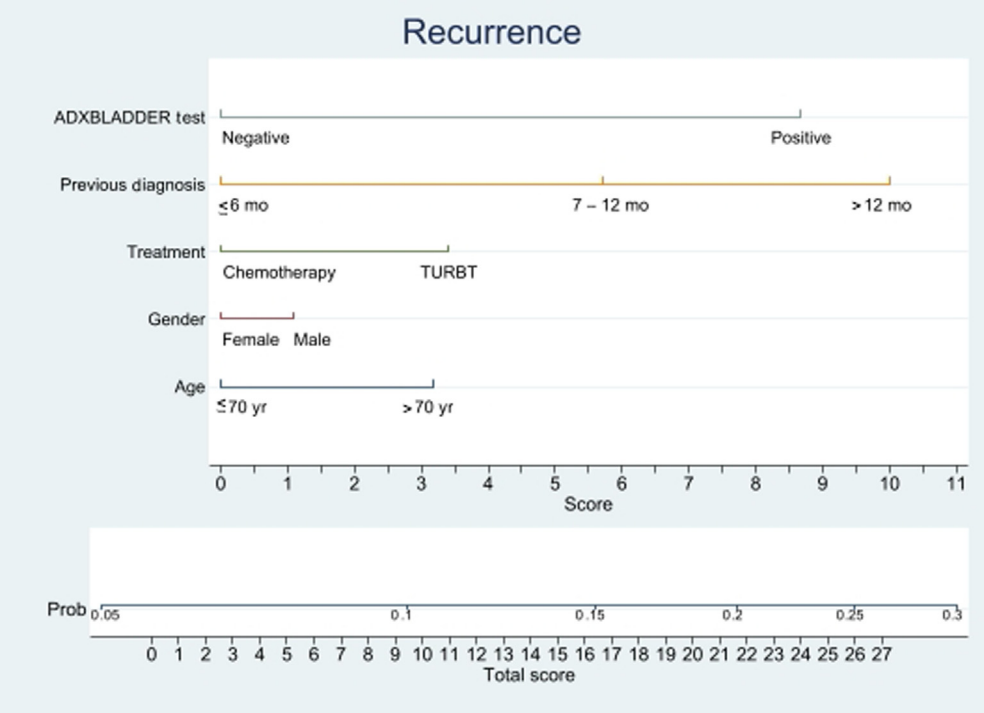

Fig. 1 – Nomogram for calculating the probability of recurrence. Prob = probability; TURBT = transurethral resection of bladder tumor.

had MMC + hyperthermia, and one also received epirubicin. Six patients (2.2%) received epirubicin alone and one had GemRIS. A total of 145 (53.7%) received a single postoperative instillation, while 124 (45.9%) had repeat instillations.

The median times from the previous diagnosis and from the final instillation to ADXBLADDER evaluation were 11.2 and 8.8 mo, respectively. The ADXBLADDER test result was positive in 160 patients (25%) and negative in 469 (75%).

3.1. Any recurrence

Seventy-nine patients (12.6%) had recurrence of any stage and grade, at an interval from previous diagnosis (IFPD) of ≤6 mo for 18 (9.1%), 7–12 mo for 22 (12.0%), and >12 mo for 39 (15.7%) patients (Table 1).

Fifty-one (10.9%) ADXBLADDER-negative patients and 28 (17.5%, PPV) ADXBLADDER-positive patients had recurrence (OR 1.74, 95% confidence interval [CI] 1.01–2.94; $p = 0.029$; Table 1). The difference in recurrence rate between ADXBLADDER-negative and ADXBLADDER-positive patients decreased with increasing IFPD.

Results for the ADXBLADDER sensitivity, specificity, PPV, NPV, and AUC are provided in Table 2. The NPV was 89.1% (95% CI 86.0–91.8%) and decreased from 94.1% for an IFPD of ≤6 mo to 89.3% for an IFPD of 7–12 mo to 85.3% for an IFPD of >12 mo.

Multivariable analysis of recurrence (Table 3) identified ADXBLADDER status (OR 1.78, 95% CI 1.07–2.96; $p = 0.027$) and time from previous diagnosis as significant prognostic factors.

A nomogram predicting the probability of recurrence is given in Figure 1, with nomogram scores provided in Supplementary Table 1. The probability of recurrence varied from 0.056 (age ≤70 yr, female, chemotherapy, IFPD ≤6 mo, and negative ADXBLADDER test: total score = 0) to 0.255 (age >70 yr, male, TURBT alone, IFPD >12 mo, and positive ADXBLADDER test: total score = 26.4).

3.2. HG/CIS recurrence

Twelve patients (1.9%) had a HG/CIS recurrence, accounting for 12 (15.2%) of the 79 recurrences. Of these cases, seven were HG papillary only, three were HG papillary and CIS, and two were CIS only. Six recurrences (2.2%) were after TURBT + chemotherapy and six (1.7%) were after TURBT alone.

HG/CIS recurrence was found for 4/469 (0.85%) ADXBLADDER-negative and 8/160 (5.0%, PPV) ADXBLADDER-positive patients (OR 6.12, 95% CI 1.61–28.1; $p < 0.001$; Table 1).

The ADXBLADDER sensitivity, specificity, PPV, NPV, and AUC for detection of HG/CIS recurrence are provided in Table 2. The sensitivity was 66.7% (95% CI 34.9–90.1%) and the NPV was 99.1% (95% CI 97.8–99.8%).

As there were only 12 HG/CIS recurrences, neither a multivariable prognostic factor analysis nor a nomogram for calculating the probability of HG/CIS recurrence in individual patients was feasible.

3.3. Decision curve analysis

3.3.1. Any recurrence

For recurrence threshold probabilities between 5.6% and 18%, there is a net benefit in using the full model (age + gender + treatment + IFPD + ADXBLADDER status) in deciding

Table 1 – Patient characteristics overall and by recurrence status.

Variable	Overall	Any recurrence	HG/CIS recurrence
Patients, *n* (%)	629	79 (12.6)	12 (1.9)
Median age, yr (IQR)	72 (64–79)		
Age category, *n* (%)			
≤70 yr	266 (42)	29 (10.9)	3 (1.1)
>70 yr	363 (58)	50 (13.8)	9 (2.5)
Gender, *n* (%)			
Female	176 (28)	22 (12.5)	5 (2.8)
Male	453 (72)	57 (12.6)	7 (1.6)
Number of tumors, *n* (%)			
Single	248 (39)	38 (15.3)	5 (2.0)
Multiple	80 (13)	14 (17.5)	2 (2.5)
Unknown	301 (48)	27 (9.0)	5 (1.7)
Maximum diameter, *n* (%)			
<1 cm	177 (28)	30 (17.0	4 (2.3)
1–3 cm	112 (18)	16 (14.3)	2 (1.8)
>3 cm	20 (3)	2 (10.0)	1 (5.0)
Unknown	320 (51)	31 (9.7)	5 (1.6)
Treatment, *n* (%)			
Chemotherapy	270 (43)	30 (11.1)	6 (2.2)
TURBT alone	359 (57)	49 (13.6)	6 (1.7)
Median time to ADXBLADDER test, mo (IQR)			
Since final instillation	8.8 (3.8–14.5)		
Since previous Dx	11.2 (5.0–16.3)		
Previous Dx–ADXBLADDER time, *n* (%)			
≤6 mo	198 (31)	18 (9.1)	3 (1.5)
7–12 mo	183 (29)	22 (12.0)	5 (2.7)
>12 mo	248 (39)	39 (15.7)	4 (1.6)
ADXBLADDER result, *n* (%)			
Negative	469 (75)	51 (10.9)	4 (0.85)
Positive	160 (25)	28 (17.5)	8 (5.0)
ADXBLADDER status by previous Dx time, *n* (%)			
Previous Dx ≤6 mo			
ADXBLADDER negative	136	8 (5.9)	0 (0)
ADXBLADDER positive	62	10 (16.1)	3 (4.8)
Previous Dx 7–12 mo			
ADXBLADDER negative	149	16 (10.7)	2 (1.3)
ADXBLADDER positive	34	6 (17.7)	3 (8.8)
Previous Dx >12 mo			
ADXBLADDER negative	184	27 (14.7)	2 (1.1)
ADXBLADDER positive	64	12 (18.8)	3 (3.1)

CIS = carcinoma in situ; Dx = diagnosis; HG = high grade; IQR = interquartile range; TURBT = transurethral resection of bladder tumor.

Table 2 – ADXBLADDER performance characteristics.

Parameter	Any recurrence	HG/CIS recurrence
Prevalence, % (95% CI)	12.6 (10.0–15.4)	1.9 (0.99–3.3)
Sensitivity, % (95% CI)	35.4 (25.0–47.0)	66.7 (34.9–90.1)
Specificity, % (95% CI)	76.0 (72.2–79.5)	75.4 (71.8–78.7)
AUC (95% CI)	0.56 (0.50–0.61)	0.71 (0.57–0.85)
Positive predictive value, % (95% CI)	17.5 (12.0–24.3)	5.0 (2.2–9.6)
Negative predictive value, % (95% CI)	89.1 (86.0–91.8)	99.1 (97.8–99.8)
Previous diagnosis ≤6 mo	94.1 (88.7–97.4)	100 (97.3–100)
Previous diagnosis 7–12 mo	89.3 (83.1–93.7)	98.7 (95.2–99.8)
Previous diagnosis >12 mo	85.3 (79.4–90.1)	98.9 (96.1–99.9)

AUC = area under the receiver operating characteristic curve; CI = confidence interval; CIS = carcinoma in situ; HG = high grade.

Table 3 – Multivariable analysis of any recurrence.

Variable	Hazard ratio (95% CI)	*p* value
Age		0.40
≤70 yr	Reference	
>70 yr	1.23 (0.75–2.02)	
Gender		0.79
Female	Reference	
Male	1.07 (0.63–1.83)	
Treatment		0.37
Chemotherapy	Reference	
Transurethral resection of bladder tumor	1.25 (0.77–2.05)	
Previous diagnosis		0.09 (2 d.f.)
≤6 mo	Reference	
7–12 mo	1.46 (0.75–2.85)	0.27
>12 mo	1.94 (1.07–3.54)	0.030
ADXBLADDER		0.027
Negative	Reference	
Positive	1.78 (1.07–2.96)	

CI = confidence interval; d.f. = degrees of freedom.

on whether to perform cystoscopy as compared to performing cystoscopy in all patients, not performing cystoscopy in any patient, performing cystoscopy on the basis of age + gender + treatment, or performing cystoscopy on the basis of IFPD + ADXBLADDER status. The difference between the full model and the IFPD + ADXBLADDER model is small and disappears above a recurrence threshold probability of 15% (Fig. 2). Within this range of recurrence threshold probabilities, the largest net reduction in unnecessary cystoscopies is with the full model and ranges from 1 to 30 per 100 patients (Fig. 3 and Supplementary Table 2), although the difference compared to the IFPD + ADXBLADDER model disappears above a recurrence threshold probability of 15%.

3.3.2. *HG/CIS recurrence*

For HG/CIS recurrence threshold probabilities between 0.85% and 5.0%, there is a net benefit in using ADXBLADDER status to decide on whether to omit cystoscopy for ADXBLADDER-negative patients when compared to performing cystoscopy in all patients or not performing cystoscopy in any patient (Fig. 4). Within this range, the net reduction in unnecessary cystoscopies ranges from 11 to 62 per 100 patients (Fig. 5 and Supplementary Table 3).

4. Discussion

Although follow-up cystoscopy is the gold standard for detecting NMIBC recurrence, it is an invasive procedure and does not have 100% sensitivity. A tool that can aid in reducing unnecessary surveillance cystoscopies, especially in patients with low-risk disease, and has a high NPV for ruling out HG/CIS recurrence would be of great benefit.

Among the 79 recurrences in our study, 12 (15.2%) were HG/CIS, confirming that most recurrences among patients with low-risk disease are also of low risk and do not pose an immediate threat to the patient. HG/CIS recurrences, which are at higher risk of progression, need to be diagnosed without delay. The ADXBLADDER PPV for detection of HG/CIS recurrence was greater than the prevalence

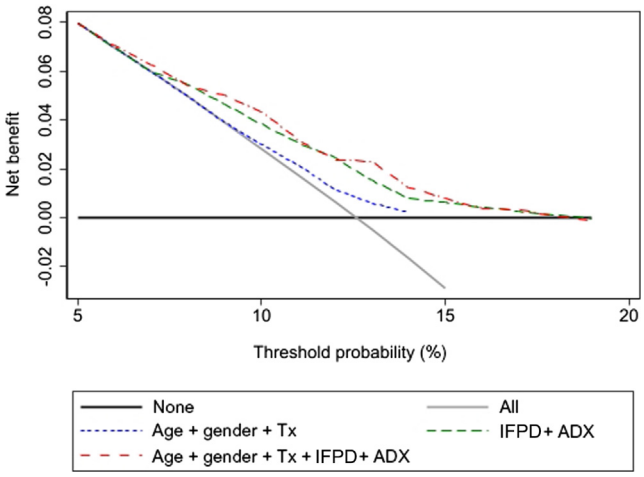

Fig. 2 – Net benefit of models for detecting recurrence. For recurrence threshold probabilities between 5.6% and 18%, there is a net benefit in using the full model to decide whether or not perform cystoscopy as compared to the other models. The difference between the full model and the model using time from previous diagnosis and ADXBLADDER status is small and disappears above a recurrence threshold probability of 15%. ADX = ADXBLADDER test; IFPD = interval from previous diagnosis; Tx = treatment.

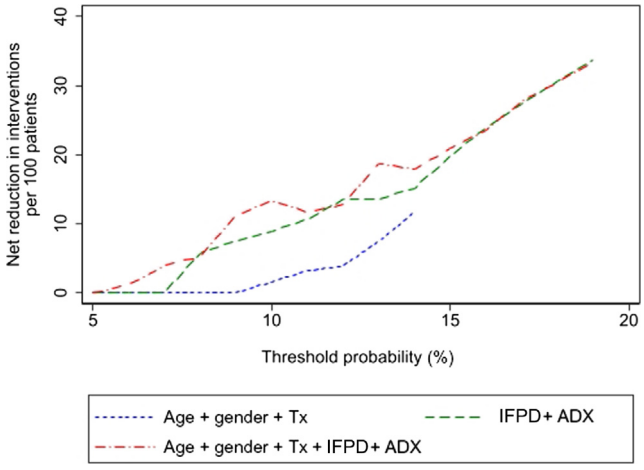

Fig. 3 – Net reduction in unnecessary cystoscopies according to models for detecting recurrence. For recurrence threshold probabilities between 5.6% and 18%, the largest net reduction in unnecessary cystoscopies is with the full model and ranges from 1 to 30 per 100 patients. The difference between the full model and the model using time from previous diagnosis and ADXBLADDER status disappears above a recurrence threshold probability of 15%. ADX = ADXBLADDER test; IFPD = interval from previous diagnosis; Tx = treatment.

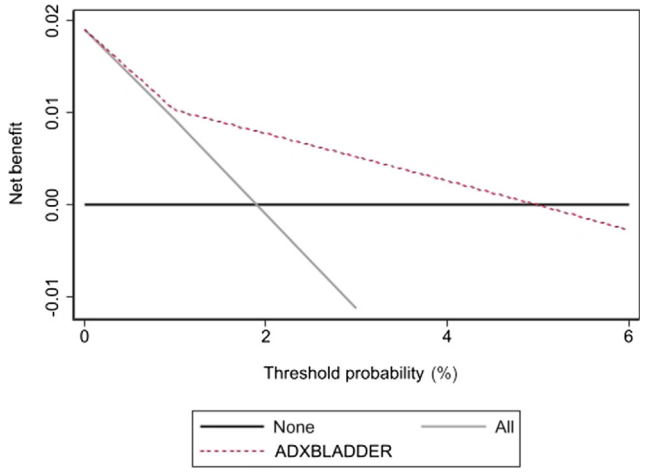

Fig. 4 – Net benefit of using ADXBLADDER for detecting HG/CIS recurrence. For HG/CIS recurrence threshold probabilities between 0.85% and 5.0%, there is a net benefit in using ADXBLADDER status to decide whether or not to perform cystoscopy compared to performing cystoscopy in all patients (threshold probability <0.85%) or not performing cystoscopy in any patients (threshold probability >5.0%). CIS = carcinoma in situ; HG = high grade.

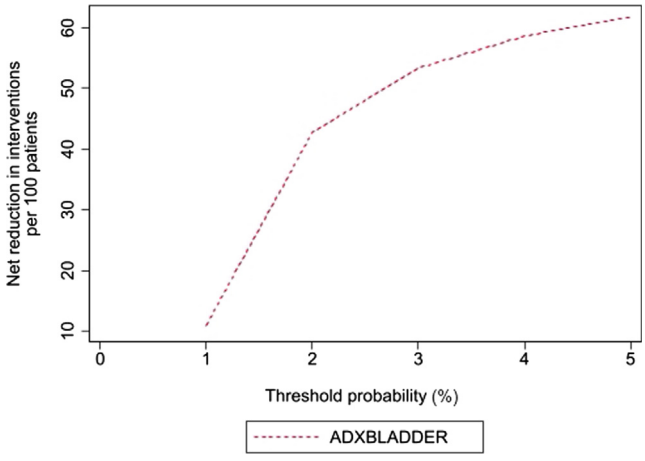

Fig. 5 – Net reduction in unnecessary cystoscopies when using ADXBLADDER for detection of HG/CIS recurrence. For HG/CIS recurrence threshold probabilities between 0.85% and 5.0%, the net reduction in unnecessary cystoscopies when using ADXBLADDER ranges from 11 to 62 per 100 patients. CIS = carcinoma in situ; HG = high grade.

(5.0% vs 1.9%). The sensitivity for detecting HG/CIS recurrence was 66.7%, and the NPV for ruling out HG/CIS recurrence was 99.15%.

Our study has shown that for HG/CIS recurrence threshold probabilities between 0.85% and 5.0%, there is a net benefit and a net reduction in unnecessary cystoscopies when omitting cystoscopy for ADXBLADDER-negative patients. For HG/CIS recurrence threshold probabilities outside of this range, the test has no clinical benefit. For HG/CIS recurrence threshold probability of <0.85%, cystoscopy should be performed. For HG/CIS threshold probability of >5.0%, the optimal decision is to not perform cystoscopy.

For recurrences of any stage and grade and recurrence threshold probabilities between 5.6% and 18%, there is a net benefit and a net reduction in unnecessary cystoscopies when incorporating ADXBLADDER status and IFPD in deciding on whether or not to perform cystoscopy. For the group with IFPD $\leq$6 mo, 8/136 (5.9%) ADXBLADDER-negative patients had a recurrence (NPV 94.1%).

Current European Association of Urology NMIBC guidelines recommend that follow-up should be based on regular cystoscopies, with the first at 3 mo [12]. If this cystoscopy is negative, intervals between subsequent cystoscopies vary according to risk group.

Urinary markers [13] have been proposed as an alternative to reduce the frequency and burden of follow-up cystoscopies and associated health care costs. Newer commercially available biomarkers show similar perfor-

mance for HG recurrences at risk of progression, with sensitivity and NPV of 76% and 99% for ADXBLADDER [7], 79–92% and 99% for EpiCheck [14,15], and 79–100% and ~99% for Xpert Bladder Cancer (Monitor) [16–19], respectively, for detection of HG recurrence.

Despite the high sensitivity and NPV for HG recurrence, none of these newer markers have been accepted in routine clinical practice for patient follow-up or are currently recommended in clinical guidelines. Their true clinical benefit should be assessed using DCA [20].

For a clinically relevant range of HG/CIS recurrence threshold probabilities, our DCA for patients with LG pTa at the previous diagnosis, for which the risk of HG/CIS recurrence is low and the ADXBLADDER NPV for HG/CIS recurrence is 99.15%, demonstrates that these patients are ideally suited for a less intensive, personalized follow-up surveillance strategy using ADXBLADDER, with omission of cystoscopy for ADXBLADDER-negative patients. As in early-stage prostate cancer, active surveillance/watchful waiting is increasingly being recognized as an option for low-risk NMIBC tumors [2,21,22]. Use of the ADXBLADDER test in this setting could help in detecting recurrences before they become aggressive.

Since the cost of performing an ADXBLADDER test is approximately £50, compared to the average cost of white-light flexible cystoscopy in the UK of £937 [23], there is a clear cost benefit for low-risk cases to reduce unnecessary cystoscopies and the burden on patients.

The optimal follow-up schedule incorporating ADXBLADDER remains to be identified. The feasibility of randomizing patients between high- and low-frequency surveillance schedules is problematic [24]. In one study, 14% of patients were willing to replace cystoscopy with a urinary marker, but only if the false-negative rate was <0.5% [25]. The randomized UroFollow trial [26] could not answer the question of the optimal follow-up schedule incorporating markers. Furthermore, the choice of primary endpoint in randomized studies is problematic as the power for detecting differences in HG/CIS recurrence and progression will be low.

Given these difficulties, the next step is to conduct a longitudinal study assessing ADXBLADDER at each follow-up cystoscopy performed according to current recommendations. Besides providing estimates of the NPV over time and data on the safety of reducing follow-up cystoscopies, this will give information about the possible anticipatory positive effect of ADXLADDER in cystoscopy-negative patients [27].

After the 3-mo follow-up cystoscopy, other possibilities exist. For patients with low-risk disease it has been proposed that the next follow-up cystoscopy be performed at 12 mo if the 3-mo cystoscopy is negative [12]. ADXBLADDER could be assessed at 6 and 9 mo to rule out HG/CIS recurrences before 12 mo. Watchful waiting and the absence of cystoscopy could be simulated by not resecting LG recurrences in ADXBLADDER-negative patients. For patients with intermediate- or high-risk disease, ADXBLADDER could be used together with cystoscopy if it is shown to have an anticipatory positive effect and to aid in the detection of lesions missed by cystoscopy. The impact of ADXBLADDER for various follow-up schedules and IFPDs could be assessed in randomized, multiarm, noncomparative screening studies.

Limitations of the study have previously been published [7,8]. In addition, there was no central pathology review. Patients with a positive test and negative cystoscopy did not undergo biopsy/TURBT, but the remaining lysate was retested for MCM5. Cytology results and the tumor number and size at previous diagnosis could not be included in the analysis because of missing data. Prognostic factors for HG/CIS recurrence other than ADXBLADDER status could not be identified. To predict the probability of HG/CIS recurrence in patients with LG pTa disease, institutions should keep an updated database of follow-up data. Health care costs, which vary across countries, and the cost effectiveness of ADXBLADDER have not been considered in detail [28].

The NPV depends on the prevalence of recurrence. In this study of patients with LG pTa without CIS at their previous diagnosis, recurrence rates were low at 12.6% for overall recurrence and 1.9% for HG/CIS recurrence. In other recent studies involving patients with wider variations in stage and grade distributions and follow-up [15–20], recurrence rates were also low, varying from 10.4% to 22.6% for overall recurrence and 3.0% to 10.0% for HG/CIS recurrence; the 95% CIs in individual studies were wide. Larger studies including a cohort with higher prevalence of overall and HG/CIS recurrences are warranted to determine the true clinical applicability and role of ADXBLADDER.

Nevertheless, for patients with LG pTa tumor without CIS at the previous diagnosis, the ADXBLADDER test is a promising tool. Updating guidelines to include ADXBLADDER and other new-generation biomarkers with high NPVs for HG/CIS recurrence would allow a more personalized approach to surveillance, leading to a reduction in unnecessary cystoscopies, a potential improvement in quality of life, and a decrease in associated health care costs.

5. Conclusions

Patients with LG pTa disease at the previous diagnosis, for which the risk of HG/CIS recurrence is low and the ADXBLADDER NPV for HG/CIS recurrence is 99.15%, are ideally suited for a less intensive, personalized follow-up surveillance strategy using the ADXBLADDER test, with omission of cystoscopy for ADXBLADDER-negative patients.

Author contributions: Richard J. Sylvester had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Rouprêt, Gontero, Stockley, Witjes, Palou.
Acquisition of data: Rouprêt, Gontero, McCracken, Dudderidge, Rodriguez, Sieverink, Vanié, Allasia, Witjes, Colombel, Longo, Montanari, Palou.
Analysis and interpretation of data: Sylvester.
Drafting of the manuscript: Sylvester, Stockley.
Critical revision of the manuscript for important intellectual content: Rouprêt, Gontero, McCracken, Dudderidge, Stockley, Kennedy, Rodriguez, Sieverink, Vanié, Allasia, Witjes, Colombel, Longo, Montanari, Palou, Sylvester.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2022.02.006.

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