



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

Morgan Rouprêt^a, Paolo Gontero^b, Stuart R.C. McCracken^c, Tim Dudderidge^d, Jacqueline Stockley^e, Ashleigh Kennedy^e, Oscar Rodriguez^f, Caroline Sieverink^g, Felicien Vanié^a, Marco Allasia^b, J. Alfred Witjes^g, Marc Colombel^h, Fabrizio Longoⁱ, Emanuele Montanariⁱ, Joan Palou^f, Richard J. Sylvester^{j,*}

^aSorbonne Université GRC 5 Predictive Onco-Uro, Urology Department, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France; ^bDepartment of Urology, Ospedale Molinette, Turin, Italy; ^cDepartment of Urology, Sunderland Royal Hospital, Sunderland, UK; ^dDepartment of Urology, University Hospital Southampton, Southampton, UK; ^eArquer Diagnostics, Sunderland, UK; ^fDepartment of Urology, Fundacio Puigvert, Barcelona, Spain; ^gDepartment of Urology, Radboud University Medical Centre, Nijmegen, The Netherlands; ^hDepartment of Urology, Hôpital Edouard Herriot, Lyon, France; ⁱDepartment of Urology, Università Policlinico Milano, Milan, Italy; ^jEuropean Association of Urology Non-muscle-invasive Bladder Cancer Guidelines Panel, Brussels, Belgium

Article info

Article history:

Accepted February 22, 2022

Available online 14 March 2022

Associate Editor: Christian Gatzke

Keywords:

ADXBLADDER
 MCM5 protein
 Urinary biomarker
 Non-muscle-invasive bladder cancer
 Urothelial carcinoma
 Recurrence
 High-grade recurrence
 Follow-up cystoscopy
 Surveillance
 Decision curve analysis

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.

* Corresponding author. EAU Guidelines Office, 500 Avenue Moliere, Brussels 1050, Belgium. Tel. +32 2 3464916.

E-mail address: richard.sylvester@skynet.be (R.J. Sylvester).

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.

© 2022 The Authors. Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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%)

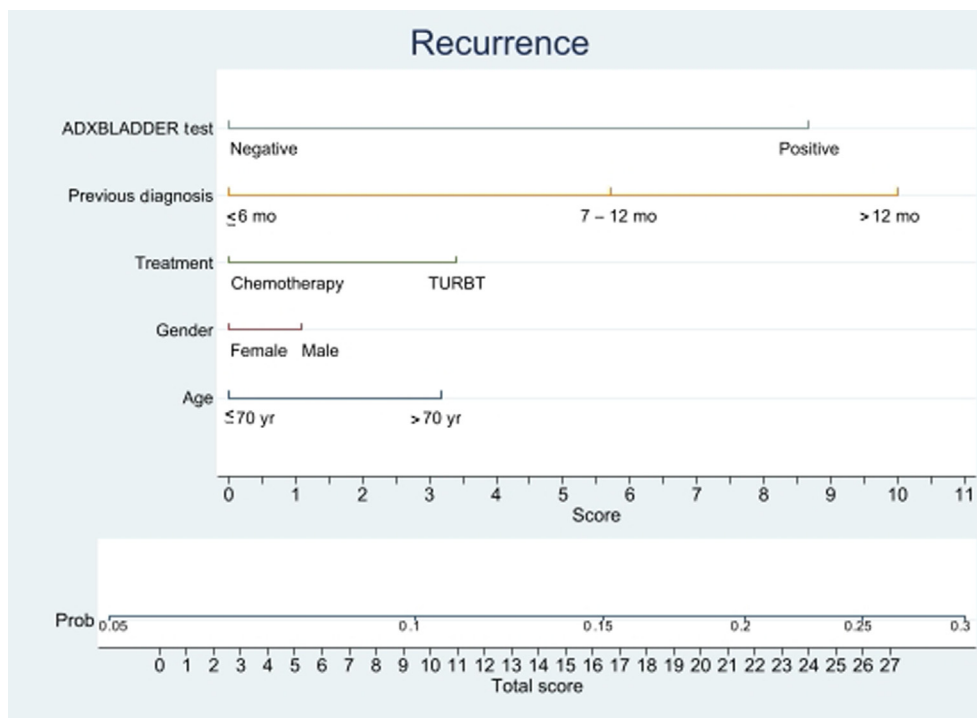


Fig. 1 – Nomogram for calculating the probability of recurrence. Prob = probability; TURBT = transurethral resection of bladder tumor.

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 Sup-

plementary 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 per-

forming 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

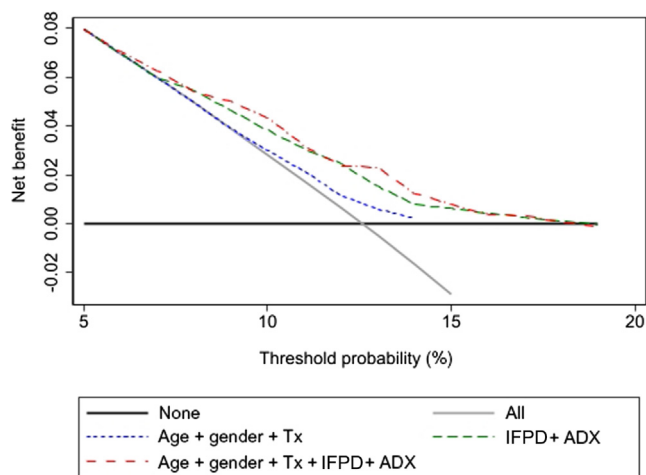


Fig. 2 – Net benefit of models for detecting recurrence. For recurrence threshold probabilities between 5.6% and 18%, there is a net benefit in using the full model to decide whether or not perform cystoscopy as compared to the other models. The difference between the full model and the model using time 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.

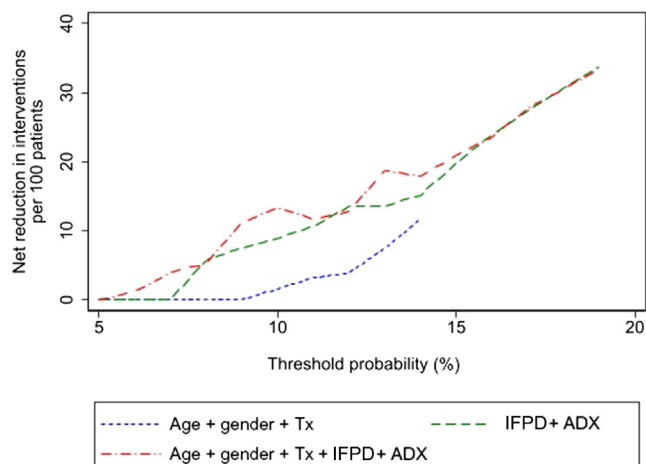


Fig. 3 – Net reduction in unnecessary cystoscopies according to models for detecting recurrence. For recurrence threshold probabilities between 5.6% and 18%, the largest net reduction in unnecessary cystoscopies is with the full model and ranges from 1 to 30 per 100 patients. The difference between the 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.

(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.

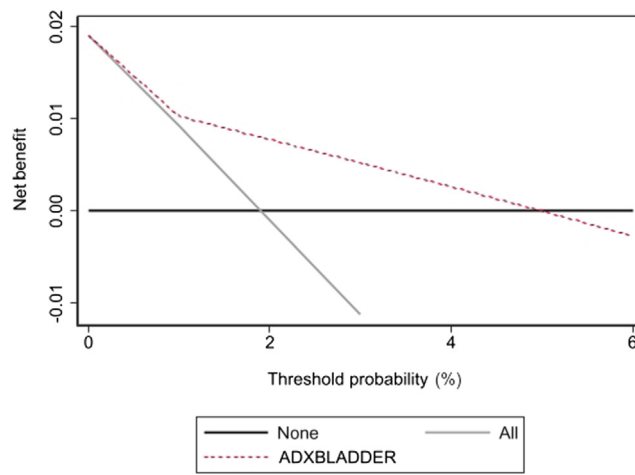


Fig. 4 – Net benefit of using ADXBLADDER for detecting HG/CIS recurrence. For HG/CIS recurrence threshold probabilities between 0.85% and 5.0%, there is a net benefit in using ADXBLADDER status to decide whether or not to perform cystoscopy compared to performing cystoscopy in all patients (threshold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

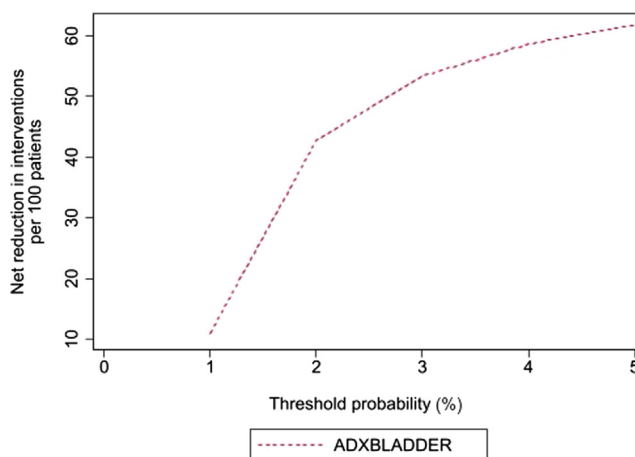


Fig. 5 – Net reduction in unnecessary cystoscopies when using ADXBLADDER for detection of HG/CIS recurrence. For HG/CIS recurrence threshold probabilities between 0.85% and 5.0%, the net reduction in unnecessary cystoscopies when using ADXBLADDER ranges from 11 to 62 per 100 patients. CIS = carcinoma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

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 ≤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 ADXBLADDER 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.

Statistical analysis: Sylvester.

Obtaining funding: Stockley.

Administrative, technical, or material support: Stockley, Kennedy.

Supervision: Stockley, Kennedy.

Other: None.

Financial disclosures: Richard J. Sylvester certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Morgan Rouprêt, Paolo Gontero, Stuart R.C. McCracken, Tim Dudderidge, Marco Colombel, Fabrizio Longo, Emanuele Montanari, Joan Palou, and Richard J. Sylvester are paid consultants for Arquer Diagnostics. J. Alfred Witjes has received lecture honoraria from Nucleix. Jacqueline Stockley and Ashleigh Kennedy are employees of Arquer Diagnostics and hold share options in the company.

Funding/Support and role of the sponsor: This study was sponsored by Arquer Diagnostics. The sponsor played a role in study design; data collection, analysis, and interpretation; and preparation, review, and approval of the manuscript.

Appendix A. Supplementary data

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

References

- [1] Mossanen M, Wang Y, Szymaniak J, et al. Evaluating the cost of surveillance for non-muscle-invasive bladder cancer: an analysis based on risk categories. *World J Urol* 2019;37:2059–65. [10.1007/s00345-018-2550-x](https://doi.org/10.1007/s00345-018-2550-x).
- [2] Hernández V, Llorente C, de la Peña E, Pérez-Fernández E, Guijarro A, Sola I. Long-term oncological outcomes of an active surveillance program in recurrent low grade Ta bladder cancer. *Urol Oncol* 2016;34(165):e19–23. [10.1016/j.urolonc.2015.11.005](https://doi.org/10.1016/j.urolonc.2015.11.005).
- [3] Han DS, Lynch KE, Chang JW, et al. Overuse of cystoscopic surveillance among patients with low-risk non-muscle-invasive bladder cancer – a national study of patient, provider, and facility factors. *Urology* 2019;131:112–9. [10.1016/j.urology.2019.04.036](https://doi.org/10.1016/j.urology.2019.04.036).
- [4] Rezaee ME, Lynch KE, Li Z, et al. The impact of low- versus high-intensity surveillance cystoscopy on surgical care and cancer outcomes in patients with high-risk non-muscle-invasive bladder cancer (NMIBC). *PLoS One* 2020;15:. [10.1371/journal.pone.0230417](https://doi.org/10.1371/journal.pone.0230417)e0230417.
- [5] Schroeck FR, Lynch KE, Li Z, et al. The impact of frequent cystoscopy on surgical care and cancer outcomes among patients with low-risk, non-muscle-invasive bladder cancer. *Cancer* 2019;125:3147–54. [10.1002/cncr.32185](https://doi.org/10.1002/cncr.32185).
- [6] Wolfs JRE, Hermans TJN, Koldewijn EL, van de Kerkhof D. Novel urinary biomarkers ADXBLADDER and bladder EpiCheck for diagnostics of bladder cancer: a review. *Urol Oncol* 2021;39:161–70. [10.1016/j.urolonc.2020.11.014](https://doi.org/10.1016/j.urolonc.2020.11.014).
- [7] Roupret M, Gontero P, McCracken SRC, et al. Diagnostic accuracy of MCM5 for the detection of recurrence in nonmuscle invasive bladder cancer followup: a blinded, prospective cohort, multicenter European study. *J Urol* 2020;204:685–90. [10.1097/ju.0000000000001084](https://doi.org/10.1097/ju.0000000000001084).
- [8] Gontero P, Montanari E, Roupret M, et al. Comparison of the performance of ADXBLADDER test and urinary cytology in the follow up of non-muscle invasive bladder cancer: a blinded prospective multicentric study. *BJU Int* 2021;127:198–204. [10.1111/bju.15194](https://doi.org/10.1111/bju.15194).
- [9] Sitch AJ, Olaf M, Dekkers OM, Scholefield BR, Takwoing Y. Introduction to diagnostic test accuracy studies. *Eur J Endocrinol* 2021;184:E5–9.
- [10] Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. *J Thorac Oncol* 2010;5:1315–6. [10.1097/JTO.0b013e3181ec173d](https://doi.org/10.1097/JTO.0b013e3181ec173d).
- [11] Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Mak* 2006;26:565–74. [10.1177/0272989X06295361](https://doi.org/10.1177/0272989X06295361).
- [12] Babjuk M, Burger M, Capoun O, et al. European Association of Urology guidelines on non-muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ). *Eur Urol* 2022;81:75–94. [10.1016/j.eururo.2021.08.010](https://doi.org/10.1016/j.eururo.2021.08.010).
- [13] Soria F, Droller MJ, Lotan Y, et al. An up-to-date catalog of available urinary biomarkers for the surveillance of non-muscle invasive bladder cancer. *World J Urol* 2018;36:1981–95. [10.1007/s00345-018-2380-x](https://doi.org/10.1007/s00345-018-2380-x).
- [14] Witjes JA, Morote J, Cornel EB, et al. Performance of the Bladder EpiCheck™ methylation test for patients under surveillance for non-muscle-invasive bladder cancer: results of a multicenter, prospective, blinded clinical trial. *Eur Urol Oncol* 2018;1:307–13. [10.1016/j.euo.2018.06.011](https://doi.org/10.1016/j.euo.2018.06.011).
- [15] Trenti E, Pycha S, Mian C, et al. Comparison of 2 new real-time polymerase chain reaction-based urinary markers in the follow-up of patients with non-muscle-invasive bladder cancer. *Cancer Cytopathol* 2020;128:341–7. [10.1002/cncy.22246](https://doi.org/10.1002/cncy.22246).
- [16] van Valenberg FJP, Hiar AM, Wallace E, et al. Prospective validation of an mRNA-based urine test for surveillance of patients with bladder cancer. *Eur Urol* 2019;75:853–60. [10.1016/j.eururo.2018.11.055](https://doi.org/10.1016/j.eururo.2018.11.055).
- [17] Delia C, Pycha A, Folchini DM, et al. Diagnostic predictive value of Xpert Bladder Cancer Monitor in the follow-up of patients affected by non-muscle invasive bladder cancer. *J Clin Pathol* 2019;72:140–4. [10.1136/jclinpath-2018-205393](https://doi.org/10.1136/jclinpath-2018-205393).
- [18] Elsayy AA, Awadalla A, Elsayed A, Abdullateef M, Abol-Enein H. Prospective validation of clinical usefulness of a novel mRNA-based urine test (Xpert® Bladder Cancer Monitor) for surveillance in non muscle invasive bladder cancer. *Urol Oncol* 2021;39(77):e9–e16. [10.1016/j.urolonc.2020.07.013](https://doi.org/10.1016/j.urolonc.2020.07.013).
- [19] Cowan B, Klein E, Jansz K, et al. Longitudinal follow-up and performance validation of an mRNA-based urine test (Xpert® Bladder Cancer Monitor) for surveillance in patients with non-muscle-invasive bladder cancer. *BJU Int* 2021;128:713–21. [10.1111/bju.15418](https://doi.org/10.1111/bju.15418).
- [20] D'Andrea D, Soria F, Zehetmayer S, et al. Diagnostic accuracy, clinical utility and influence on decision-making of a methylation urine biomarker test in the surveillance of non-muscle-invasive bladder cancer. *BJU Int* 2019;123:959–67. [10.1111/bju.14673](https://doi.org/10.1111/bju.14673).
- [21] Hurler R, Lazzeri M, Vanni E, et al. Active surveillance for low risk nonmuscle invasive bladder cancer: a confirmatory and resource consumption study from the BIAS project. *J Urol* 2018;199:401–6. [10.1016/j.juro.2017.08.091](https://doi.org/10.1016/j.juro.2017.08.091).
- [22] Hernández V, Alvarez M, de la Peña E, et al. Safety of active surveillance program for recurrent nonmuscle-invasive bladder carcinoma. *Urology* 2009;73:1306–10. [10.1016/j.urology.2008.12.061](https://doi.org/10.1016/j.urology.2008.12.061).
- [23] Mowatt G, Zhu S, Kilonzo M, et al. Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer. *Health Technol Assess* 2010;14:1–331. [10.3310/hta14040](https://doi.org/10.3310/hta14040).
- [24] Reyes RM, Rios E, Barney S, et al. A randomized feasibility trial comparing surveillance regimens for patients with low and low-intermediate risk non-muscle invasive bladder cancer. *Bladder Cancer* 2021;7:285–95.
- [25] Sayyid RK, Sayyid AK, Klaassen Z, et al. Replacing surveillance cystoscopy with urinary biomarkers in follow up of patients with non-muscle-invasive bladder cancer: patients' and urologic oncologists' perspectives. *Can Urol Assoc J* 2018;12:E210–8. [10.5489/auaj.4922](https://doi.org/10.5489/auaj.4922).
- [26] Enderska-Söder N, Hovanec J, Pesch B, et al. Toward noninvasive follow-up of low-risk bladder cancer – rationale and concept of the UroFollow trial. *Urol Oncol* 2020;38:886–95. [10.1016/j.urolonc.2020.01.006](https://doi.org/10.1016/j.urolonc.2020.01.006).
- [27] Rouprêt M, Gontero P, Montanari E, et al. Anticipatory effects of ADXBLADDER test results in the follow up of cystoscopy negative non muscle invasive bladder cancer patients in a large multicentric European cohort. Poster P0724 presented at the 36th Annual European Association of Urology Congress, 2021.
- [28] Witjes JA. Follow-up in non-muscle invasive bladder cancer: facts and future. *World J Urol* 2021;39:4047–53. [10.1007/s00345-020-03569-2](https://doi.org/10.1007/s00345-020-03569-2).