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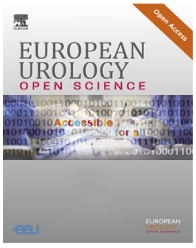

European Association of Urology

Bladder Cancer

The Value of Negative Urinary Dipstick Tests for Haematuria in Patients Undergoing Surveillance for Low-grade Ta Urothelial Cancer: A Two-stage Prospective Clinical Study in 524 Patients

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Abstract

Background and objective: The risk of first recurrence beyond 5 yr for patients with low-grade (LG) Ta non–muscle-invasive bladder cancer (NMIBC) is low enough to consider discontinuing cystoscopic surveillance at that point. However, a positive urinary dipstick test for haematuria (UDH) during and beyond the period of cystoscopic surveillance can disrupt plans to cease surveillance because the association between UDH positivity and recurrence in LG Ta NMIBC is unknown. In a two-stage study, we evaluated this association and explored the role of UDH negativity in predicting the absence of recurrence.

Methods: Because of previously demonstrated changes in recurrence patterns over time, two prospective cohorts were assessed: an "exploratory" cohort (January 2007–March 2008) and a "validation" cohort (November 2017–August 2018). UDH was performed before flexible cystoscopy. Patient, operative, and surveillance data have been recorded prospectively using standard pro forma sheets since 1978 in our institution. Only patients with primary LG Ta pTa NMIBC were included for analysis.

Key findings and limitations: We assessed 231 patients in the exploratory group and 293 in the validation group. The proportion of smokers (67% vs 70%; $p = 0.5$) and mean follow-up (72.2 vs 79.9 mo; $p = 0.2$) were similar between the groups. The recurrence rate was higher in the exploratory group (19% vs 11%; $p = 0.009$), as was the UDH positivity rate (37% vs 11%; $p < 0.001$). The specificity and negative predictive value were 64% and 83% in the exploratory group, and 90% and 90%, respectively, in the validation group. These values increased further for the subgroup with solitary primary tumours the subgroup without recurrence for 3 yr.

Conclusions and clinical implications: UDH negativity has a high probability of being associated with the absence of recurrence in small LG Ta NMIBC and could be an inexpensive adjunct during surveillance. Ongoing validation, which started in

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2019, is being performed in a now-nationalised Scottish protocol in which UDH replaces cystoscopy in years 2 and 4 for patients in the low-risk group.

Patient summary: We investigated the accuracy of a dipstick test for blood in the urine for patients undergoing surveillance for low-grade noninvasive bladder cancer. We found that a negative dipstick test result was highly associated with the absence of tumour recurrence, particularly for patients with the lowest risk. These findings have been introduced into a national protocol designed to reduce the frequency of telescopic inspection of the bladder during surveillance to reduce the burden for patients.

1. Introduction

Urothelial bladder cancer (BC) is the fifth most common malignancy in the Western world [1] and represents a significant economic burden, with findings estimating that it cost the EU almost €5 billion in 2012 and accounted for 5% of overall health care costs for cancer [2].

The resource burden for non–muscle-invasive BC (NMIBC), which accounts for 75% of all BC cases, is high [3,4] across multiple domains. Data from the BOXIT trial [5] showed that the average 3-yr cost for NMIBC patients was £8735, and that progression to high-grade (HG) disease is associated with a significant decrease in health-related quality of life.

Reliance on regular flexible cystoscopy during surveillance contributed to this burden. Cystoscopy is an invasive and uncomfortable procedure that is distressing to the patient and costs approximately £449, not taking into account further expenses if any suspicious lesions are identified [5]. There is debate regarding the duration of surveillance given the low volume of high-level evidence [3] and thus many schemes include surveillance for an indefinite period [6], despite the impact on a patient's quality of life [7].

In the context of the UK National Health Service (NHS), extreme pressures on all health care resources make it essential to find more efficient, safe, and cost-effective solutions. Unfortunately, biomarkers are not yet able to replace cystoscopy in routine clinical practice [8].

Previous Edinburgh-based research allowed a reduction in the cystoscopy burden for patients with low-grade (LG) Ta BC by recommending cessation of surveillance for patients who have been recurrence-free for 5 yr [6,9]. This has since been incorporated into European guidelines [10]. However, a difficulty with this strategy is that the relevance of nonvisible haematuria either during or following cessation of routine surveillance is unknown. While it is acknowledged that up to 16% of patients with a positive urinary dipstick test for haematuria (UDH) have a bladder tumour [11], the implications for patients with LG Ta BC on surveillance is uncertain, which represents a potential barrier to reducing the cystoscopy burden.

The primary aim of this project was to determine the association between UDH positivity and tumour recurrence in patients undergoing surveillance for LG Ta BC. The secondary aim was to investigate whether such an association could be used to increase the efficiency of current surveillance pathways.

2. Patients and methods

The Bladder Cancer Service in Edinburgh introduced a systematic approach to quality improvement in 2006 called the Edinburgh Bladder Cancer Surgery Effectiveness and Efficiency Programme. Its overarching principle was to use prospectively maintained data to evaluate the effectiveness and efficiency of specific interventions in BC care via large multiarm, multistage clinical projects, which were designed to have what were termed "exploratory" and "validation" stages. One of these is SURVEILLANCE-1 (Surveillance, treatment and recurrence protocols using long-term effectiveness and efficiency data with clinical assessments in non-muscle invasive bladder cancer-1). This study is part of SURVEILLANCE-1.

2.1. Patient selection

As a previous study in SURVEILLANCE-1 revealed differing patterns of recurrence in cohorts separated by a decade, with higher odds of delayed first recurrence for the more contemporary cohort [9], we planned to conduct this study over two stages, with an exploratory cohort in 2008 and a validation cohort in 2018 to ensure that this potential difference was factored into the assessment of UDH accuracy.

The initial group comprised all patients undergoing cystoscopy in the Edinburgh Urology Service over the period from January 2007 to March 2008 for the exploratory cohort, and from November 2017 to August 2018 for the validation cohort. This was then limited to patients undergoing surveillance for BC (623 in the exploratory and 518 in the validation cohort). To focus analysis on LG Ta NMIBC, patients were included at the time of surveillance cystoscopy if they were initially diagnosed with either G1 Ta tumour in the exploratory cohort, or LG Ta tumour in the validation cohort. G2 Ta tumours were excluded from the exploratory cohort because of inconsistency in distinguishing LG versus HG disease according to the contemporary classification scheme [12]. Owing to a change in the World Health Organisation (WHO) classification system, low risk was defined as a small, single, grade 1 (G1) Ta primary tumour in the exploratory group, and as a small, single, LG Ta primary tumour in the validation group. We based the sample size on the number of patients in biomarker studies at the time [13], with a prevalence of 40% at 5 yr if free from recurrence up to that point [9]. This led to an estimate of 200 patients in the exploratory and 200 in the validation cohort.

Surveillance patients were excluded from both cohorts if they had HG NMIBC, muscle-invasive BC (MIBC), or upper tract malignancy at diagnosis.

2.2. Data collection and analysis

Patient, operative, and surveillance data have all been prospectively recorded using a standard pro forma sheet since 1978 and transferred into electronic portals (Lothian Surgical Audit and TrakCare). Each patient had only one surveillance cystoscopy during the study period. UDH was performed in all patients just before surveillance cystoscopy, and a value of 1+ or more for the test indicated a positive result. UDH testing was conducted using Siemens Multistix (Siemens Healthineers, Erlangen, Germany) with automated reading on a Siemens Clinitek Status urine analyser. Patients with a symptomatic urinary tract infection did not undergo flexible cystoscopy.

Flexible cystoscopy, including biopsy, was performed by either a supervised urology trainee or a consultant in the same centre using white light cystoscopy. Our protocol for surveillance in patients with low-risk LG Ta [6,9] involves cystoscopy 3 mo after initial transurethral resection of bladder tumour (TURBT), and then annually in recurrence-free cases up to 5 yr, after which surveillance is discontinued. Annual cystoscopies were performed on the anniversary of the initial TURBT. Patients with suspicious lesions on flexible cystoscopy underwent biopsy. Recurrence was defined as a biopsy-proven tumour, as reported by local specialist uropathologists. Urine cytology was not used as part of the surveillance protocol for these patients.

Variables of interest were tumour grade and stage, size and number of initial tumours, UDH result (positive vs negative), and time from the initial diagnosis of LG/G1 tumour to UDH testing. Anticoagulation use and the presence of diabetes were also recorded given their potential influence on UDH testing. Data were analysed using SPSS v25 for Mac (IBM, Armonk, NY, USA). We used simple statistical analysis to calculate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). As data for the presence of haematuria and tumour recurrence were binary, we used the Clopper-Pearson interval to calculate confidence intervals. Comparisons across cohorts were assessed using a χ^2 test for categorical variables and an independent t test for continuous variables. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographics

Of the 1141 patients on surveillance, 231 patients with LG Ta NMIBC were included in the exploratory cohort and 293 in the validation cohort (Fig. 1). Table 1 outlines the patient demographics.

Classification of low risk according to the European Association of Urology (EAU) guidelines (single LG Ta tumour of <30 mm on initial TURBT) [14] yielded a low-risk group of 309 patients (123 in the exploratory and 186 in the validation cohort).

In the validation cohort, 14 patients (14%) taking anticoagulant or antiplatelet medication were UDH-positive, while 17 (9%) not taking these drugs were UDH-positive. Diabetic and nondiabetic patients had similar rates of UDH positivity (13% vs 10%).

3.2. Association between recurrence and UDH

On surveillance cystoscopy, the overall incidence of UDH positivity was greater in the exploratory cohort than in the validation cohort (37% vs 11%; $p < 0.001$). The corresponding recurrence rates were 19% and 11% (44 vs 32 patients; $p = 0.009$).

In the validation cohort, five patients had HG recurrences, all of which were in patients who had at least one previous recurrence within the 2 yr before the current surveillance cystoscopy. The number of HG recurrences could not be accurately identified in the exploratory cohort owing to use of the previous WHO classification.

Of the 145 patients with negative UDH in the exploratory cohort, 125 (83%) had no recurrence. Of the 262 patients with negative UDH in the validation cohort, 235 (90%) had no recurrence (Table 2 and Supplementary Table 1).

The 524 patients were then stratified by factors known to influence recurrence (Table 2) [6,15]. Across almost all strata, the specificity and NPV for UDH negativity were higher in the validation cohort. The highest NPVs were observed when patients had small (<30 mm) and solitary primary tumours across both cohorts, as well as for patients with >3 yr since their last recurrence (Table 2). These findings prompted us to analyse the low-risk group separately.

3.3. Low-risk subgroup

In the low-risk subgroup, the UDH positivity rate was 30% for the exploratory cohort and 11% for the validation cohort ($p < 0.001$); the exploratory cohort had a higher recurrence rate, although the difference was not significant (15% vs 11%; $p = 0.3$).

In the 'Validation' cohort, 21 patients had recurrences; two of these were HG (10% of recurrences) and occurred within 12 mo of initial diagnosis. Both recurrences were stage pTa.

Table 3 and Supplementary Table 2 list results for the low-risk subgroup, and Table 4 and Supplementary Table 3 show results stratified by surveillance duration. These highlight that the NPV was higher for the subgroup with >3 yr since the last recurrence.

4. Discussion

To the best of our knowledge, this is the only study to explore the implications of UDH testing in the surveillance setting. The salient finding from this two-stage clinical study is that there is a high probability that UDH negativity is associated with the absence of recurrence in small LG Ta NMIBC. In particular, high NPVs were seen for patients with low-risk disease and no recurrence for the previous 3 yr (89% in the exploratory cohort vs 94% in the validation cohort). Despite modest sample sizes, NPVs of up to 100% were achieved during years 2–3 and years 4–5 of surveillance in the low-risk group.

Since 2004, WHO has graded bladder malignancy as "high grade" or "low grade" rather than the historical G1, G2, and G3 grades in the 1973 scheme [16]. This has permitted more detailed analysis of factors affecting prognosis [15], leading to the definition of low-risk BC as primary LG Ta tumours that are solitary and <3 cm in size [14]. Most recurrences are small, of low grade, and slow-growing in nature [17].

Owing to the various intervention programmes implemented in our service (including Good Quality White Light TURBT since 2008, Photodynamic Diagnosis–assisted TURBT

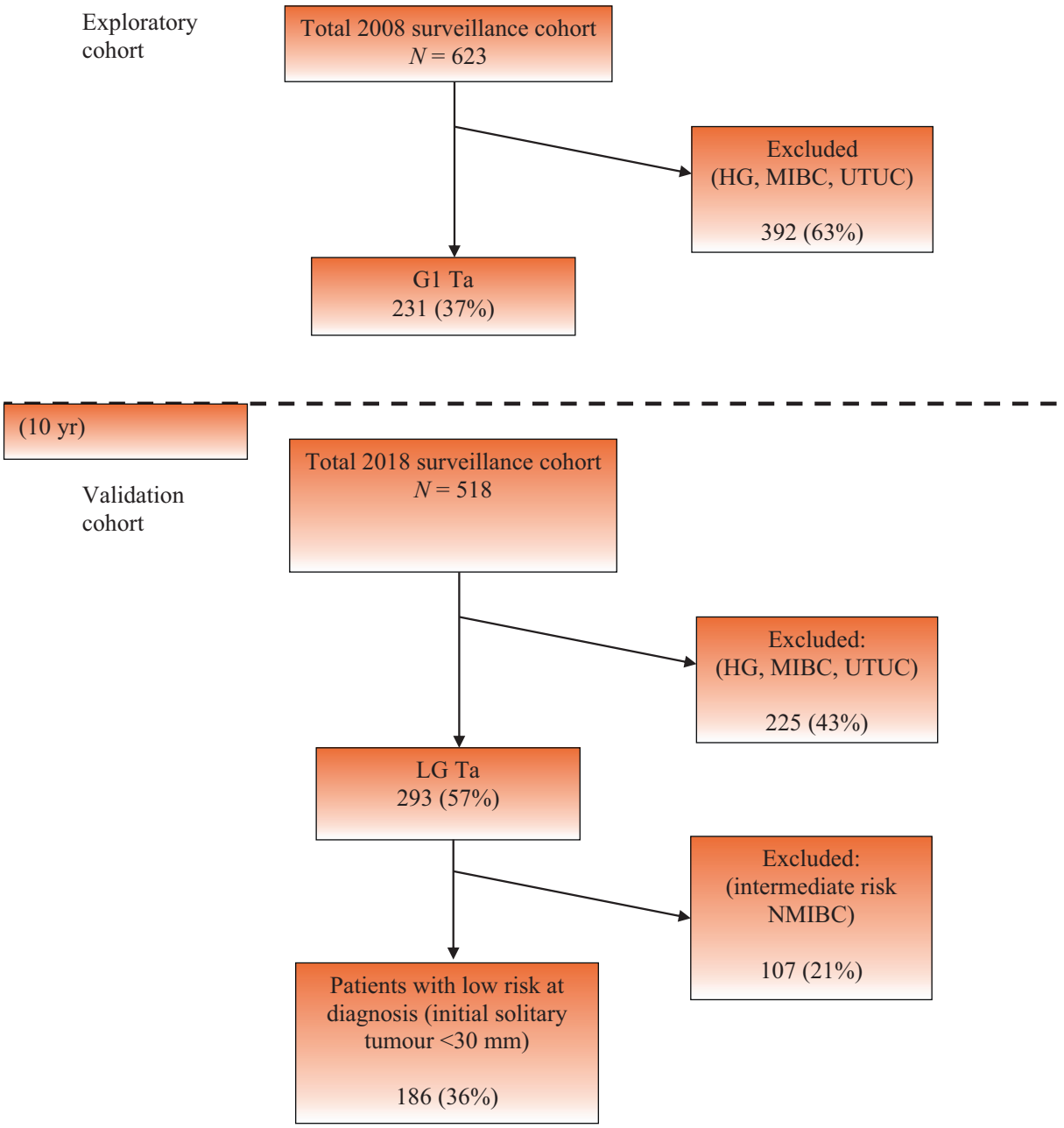

Fig. 1 – Flowchart of patient selection for the exploratory and validation cohorts. HG = high grade; MIBC = muscle-invasive bladder cancer; UTUC = upper tract urothelial carcinoma; LG = low grade; NMIBC = non–muscle-invasive bladder cancer.

since 2009, and the Quality Performance Indicator programme since 2014), the overall recurrence rate in the validation cohort is, as expected, lower than in the exploratory cohort. The apparently higher risk of progression by grade in the validation cohort is likely to be related to the differing WHO classification systems, as we have shown previously [18]. However, recurrence rates in our low-risk subgroup largely reflect the literature [6,19]. Furthermore, our progression rate of 1.1% (HG Ta recurrence identified in 2 cases within 12 mo after initial diagnosis) in the contemporary cohort reflects the 5-yr progression rate of 0.93% reported in international guidelines [14].

To the best of our knowledge, this is the first analysis of the role of UDH negativity in the context of new guidelines [6] for the discharge of patients with LG Ta BC who have been recurrence-free for 5 yr. A meta-analysis by Jubber et al. [11] revealed PPV for UDH of 0–16% for all primary bladder tumours, and <1% for the presence of any first urological malignancy in a group with negative UDH. As expected for a surveillance cohort, our recurrence rates of 17% for the exploratory and 10% for the validation cohort in the UDH-negative group are greater. Notably, the higher NPV for the validation cohort may be attributed to the lower incidence of recurrence and UDH positivity in comparison to the exploratory cohort. Nonetheless, the findings do highlight that UDH negativity is likely to be associated with a high probability of the absence of tumour, particularly in low-risk NMIBC. All recurrences in the validation group

Table 1 – Patient demographics for the exploratory (2008) and validation (2018) cohorts

	Exploratory cohort	Validation cohort
Median age, yr (IQR)	70 (64–78)	73 (65–80)
Median follow-up, mo (IQR)	54.3 (25.3–98.8)	54.9 (20.4–120.4)
Median time from last recurrence, mo (IQR)	20.1 (10.7–47.9)	25.4 (13.7–65.3)
Worst grade, *n* (%)		
Grade 1/low grade	205 (89)	260 (89)
Grade 2	19 (8.2)	N/A
Grade 3/high grade	7 (3.0)	33 (11.3)
Worst stage, *n* (%)		
Ta	225 (97)	283 (97)
T1/Tis	6 (2.6)	6 (2.0)
T2	0 (0)	4 (1.4)
Current/previous smoker, *n* (%)	155 (67)	205 (70)
Taking antiplatelet/anticoagulant, *n* (%)		102 (35)
Diabetes of any type, *n* (%)		48 (16)
Primary tumour multiplicity, *n* (%)		
Single	172 (74)	241 (82)
Multiple	48	52 (18)
Primary tumour size category, *n* (%)		
Small (<30 mm)	154 (67)	212 (72)
Large (≥30 mm)	22	81 (28)
Patients with low-risk disease at diagnosis, *n* (%)	123 (53)	186 (63)

IQR = interquartile range.
[a]Solitary grade 1/low-grade Ta tumour of <30 mm at diagnosis.

were LG Ta tumours of ≤10 mm, and all were either within the first 3 yr of surveillance (47%, 9 patients) or in patients with previous multiple recurrences. Among the 11 patients in the exploratory group, nine had experienced previous recurrences (82%) and the other two recurrences arose during year 2 and year 5 of surveillance. Tumour features on recurrence were unfortunately not noted for these patients.

In addition, the high NPVs for the LG Ta subgroup without recurrence for >3 yr (87% in the exploratory vs 94% in the validation cohort) and the even higher NPVs for the low-risk subgroup (89% vs 94%) may offer some reassurance to both primary care physicians and urologists alike, especially for patients discharged from cystoscopic surveillance after 5 yr free from recurrence [6].

Given all of the above, it was felt that there was scope to reduce annual flexible cystoscopy during surveillance for patients with low-risk disease by incorporating UDH, as these findings reiterate previous work indicating that most recurrences in this group are of minimal risk to the individual and could conceivably even be managed expectantly for a period [17]. We therefore developed a novel surveillance protocol for low-risk BC [20], as shown in Figure 2. Significant changes to previous guidelines include the recommendation to replace flexible cystoscopy with UDH at 24 and 48 mo of recurrence-free surveillance. Patients with a negative

Table 2 – Relationship between dichotomised variables, dipstick haematuria status, and findings at flexible cystoscopy in the exploratory and validation cohorts

Cohort and variable	SSY, % (95% CI)	SPY, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	RR_{UDHN} (%)
Exploratory cohort (*n* = 231)					
Overall	43 (28–59)	64 (57–71)	22 (16–30)	83 (78–86)	17
Primary tumour size					
Small	48 (28–69)	71 (63–79)	24 (17–35)	88 (83–91)	12
Large	50 (12–88)	56 (30–80)	30 (14–53)	75 (55–88)	25
Primary tumour multiplicity					
Single	48 (29–67)	66 (58–74)	23 (16–31)	86 (81–90)	14
Multiple	56 (21–86)	62 (45–77)	25 (14–40)	86 (73–93)	14
Worst grade during surveillance					
Grade 1	42 (26–59)	66 (59–73)	21 (14–29)	84 (80–88)	16
Grade 2	57 (18–90)	50 (21–79)	40 (22–61)	67 (42–85)	33
Grade 3	0 (0–98)	33 (4–78)	0 (N/A)	67 (39–86)	33
Worst stage during surveillance					
pTa	45 (30–61)	64 (57–71)	22 (16–30)	84 (79–87)	16
pT1/pTis	0 (0–84)	75 (19–99)	0 (N/A)	60 (46–73)	40
Time since last recurrence					
≤3 yr	42 (25–61)	67 (58–76)	26 (18–37)	81 (75–85)	19
>3 yr	45 (17–77)	59 (46–71)	15 (8–27)	87 (79–92)	13
Validation cohort (*n* = 293)					
Overall	16 (5.3–33)	90 (86–93)	16 (7.4–32)	90 (88–91)	10
Primary tumour size					
Small	12 (2.6–31)	89 (84–93)	13 (4.4–31)	88 (87–90)	12
Large	29 (3.7–71)	93 (85–98)	29 (8.6–63)	93 (90–96)	7
Primary tumour multiplicity					
Single	13 (2.7–32)	90 (86–94)	13 (4.4–31)	90 (89–92)	10
Multiple	25 (3.2–65)	89 (75–96)	29 (8.5–63)	87 (81–91)	13
Worst grade during surveillance					
Low grade	18 (6.1–37)	92 (88–95)	22 (10–41)	90 (89–92)	10
High grade	0 (0–60)	72 (53–87)	0 (N/A)	84 (81–87)	16
Worst stage during surveillance					
pTa	16 (5.3–33)	92 (87–95)	19 (8.8–37)	89 (88–91)	11
pT1/pTis	N/A	67 (22–96)	0 (N/A)	100 (40–100)	0
pT2	N/A	25 (1.0–81)	0 (N/A)	100 (2.5–100)	0
Time since last recurrence					
≤3 yr	19 (5.4–42)	88 (82–93)	18 (7.7–37)	89 (87–91)	11
>3 yr	14 (0.4–58)	89 (82–94)	7.7 (1.2–36)	94 (92–96)	6

CI = confidence interval; SSY = sensitivity; SPY = specificity; PPV = positive predictive value; NPV = negative predictive value; RR_{UDHN} = recurrence rate for cases with a negative urinary dipstick test for haematuria; N/A = not applicable.

Table 3 – Relationship between the time since last recurrence, dipstick haematuria status, and findings at flexible cystoscopy in patients with low risk in the exploratory and validation cohorts

Cohort and time since recurrence	SSY, % (95% CI)	SPY, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	RR_{UDHN} (%)
Exploratory cohort (*n* = 123)					
Overall	42 (20–67)	72 (62–80)	22 (13–34)	87 (82–91)	13
Time since last recurrence					
≤3 yr	38 (14–68)	72 (60–83)	21 (11–37)	86 (80–91)	14
>3 yr	50 (12–88)	71 (54–85)	23 (10–44)	89 (78–95)	11
Validation cohort (*n* = 186)					
Overall	10 (1.2–30)	88 (83–93)	10 (2.6–30)	88 (87–90)	12
Time since last recurrence					
≤3 yr	6.7 (0.2–32)	88 (79–94)	10 (1.5–45)	83 (80–85)	17
>3 yr	17 (0.4–64)	89 (80–94)	9.1 (1.5–40)	94 (92–96)	6

CI = confidence interval; SSY = sensitivity; SPY = specificity; PPV = positive predictive value; NPV = negative predictive value; RR_{UDHN} = recurrence rate for cases with a negative urinary dipstick test for haematuria.

Table 4 – Relationship between follow-up duration, dipstick haematuria status, and findings at flexible cystoscopy in patients with low-risk grade 1 disease in the exploratory and validation cohorts

Cohort and follow-up	SSY, % (95% CI)	SPY, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	RR_{UDHN} (%)
Exploratory cohort (*n* = 123)					
<1 yr	100 (2.5–100)	79 (49–95)	25 (11–48)	100 (72–100)	0
1–2 yr	50 (1.3–99)	67 (35–90)	20 (4.8–55)	89 (65–97)	11
2–3 yr	N/A	76 (50–93)	0 (N/A)	100 (75–100)	0
3–4 yr	0 (0–84)	78 (40–97)	0 (N/A)	78 (71–83)	22
4–5 yr	0 (0–84)	89 (52–100)	0 (N/A)	80 (76–83)	20
>5 yr	50 (21–79)	65 (49–79)	29 (17–45)	82 (72–90)	18
Validation cohort (*n* = 186)					
<1 yr	0 (N/A)	100 (N/A)	N/A	80 (N/A)	20
1–2 yr	0 (0–60)	93 (66–100)	0 (N/A)	76 (74–79)	24
2–3 yr	N/A	63 (24–91)	0 (N/A)	100 (48–100)	0
3–4 yr	0 (0–84)	100 (48–100)	N/A	71 (N/A)	29
4–5 yr	N/A	88 (62–98)	0 (N/A)	100 (77–100)	0
>5 yr	18 (2.3–52)	88 (78–93)	13 (3.8–37)	91 (89–93)	9

CI = confidence interval; SSY = sensitivity; SPY = specificity; PPV = positive predictive value; NPV = negative predictive value; N/A = not applicable; RR_{UDHN} = recurrence rate for cases with a negative urinary dipstick test for haematuria.

UDH result at these time points can proceed to their next surveillance cystoscopy at 36 and 60 mo, respectively, while patients with a positive UDH result attend for flexible cystoscopy. This has already been incorporated into Scottish guidelines since 2019 and validation is ongoing [20].

The clinical implications of the introduction of UDH are significant. The NHS cost of flexible cystoscopy is £449 [5]. A snapshot of the flexible cystoscopy workload for our validation cohort reveals that of the 88 recurrence-free patients in the low-risk group undergoing flexible cystoscopy, 22 (25%) would not have needed the procedure (18 undergoing cystoscopy at 24 mo, and 4 at 48 mo). Within this group, there were four recurrences: all were detected at 24 mo, all had negative UDH (NPV 73%), and all were LG Ta of ≤10 mm. The NPV at 48 mo was 100%. Without even considering administrative fees and potential costs for complications and medications, omission of flexible cystoscopy in these cases would have saved the health board almost £10 000. Furthermore, it is likely that a reduction in the number of flexible cystoscopy procedures during surveillance would improve patient satisfaction and diagnostic capacity.

Urine cytology is not recommended in LG disease, with sensitivity of just ~16% [21]. The EAU does not currently recommend any biomarkers instead of cystoscopy because of issues that include cost effectiveness [22] and differences in sensitivity and specificity, depending on the BC risk group [8]. Encouragingly, a systematic review has highlighted major marker tests (eg, FISH, ImmunoCyt, NMP22, and microsatellite analysis) that are likely to have greater sensitivity in LG disease than urine cytology, but further studies using these markers to reduce cystoscopy frequency may reveal lower sensitivity values than currently reported [8].

Our study has some limitations. First, it is notable that while we used two cohorts to confirm findings in light of the known variation in recurrence patterns, the results have not yet been validated outside this single centre. This is one of the tasks for the Scot BC Quality OPS project, which is also addressing problems with subgroup undersampling seen in this study [20]. Second, stratified subgroup sizes for some parameters, including surveillance duration, were modest across the exploratory and validation cohorts (n = 11 and n = 7, respectively, for the smallest subgroups), which makes it difficult to confirm the accuracy of NPV from these paired cohorts alone. Further prospective cohort analysis for an external source would help in validating these specific associations. In addition, use of the 1973 WHO classification for tumour grade in the exploration cohort hindered our ability to accurately identify the number of HG recurrences found on surveillance cystoscopy. Therefore, this meant that for analysis relating to progression we relied on results from the validation cohort alone. Information on potential

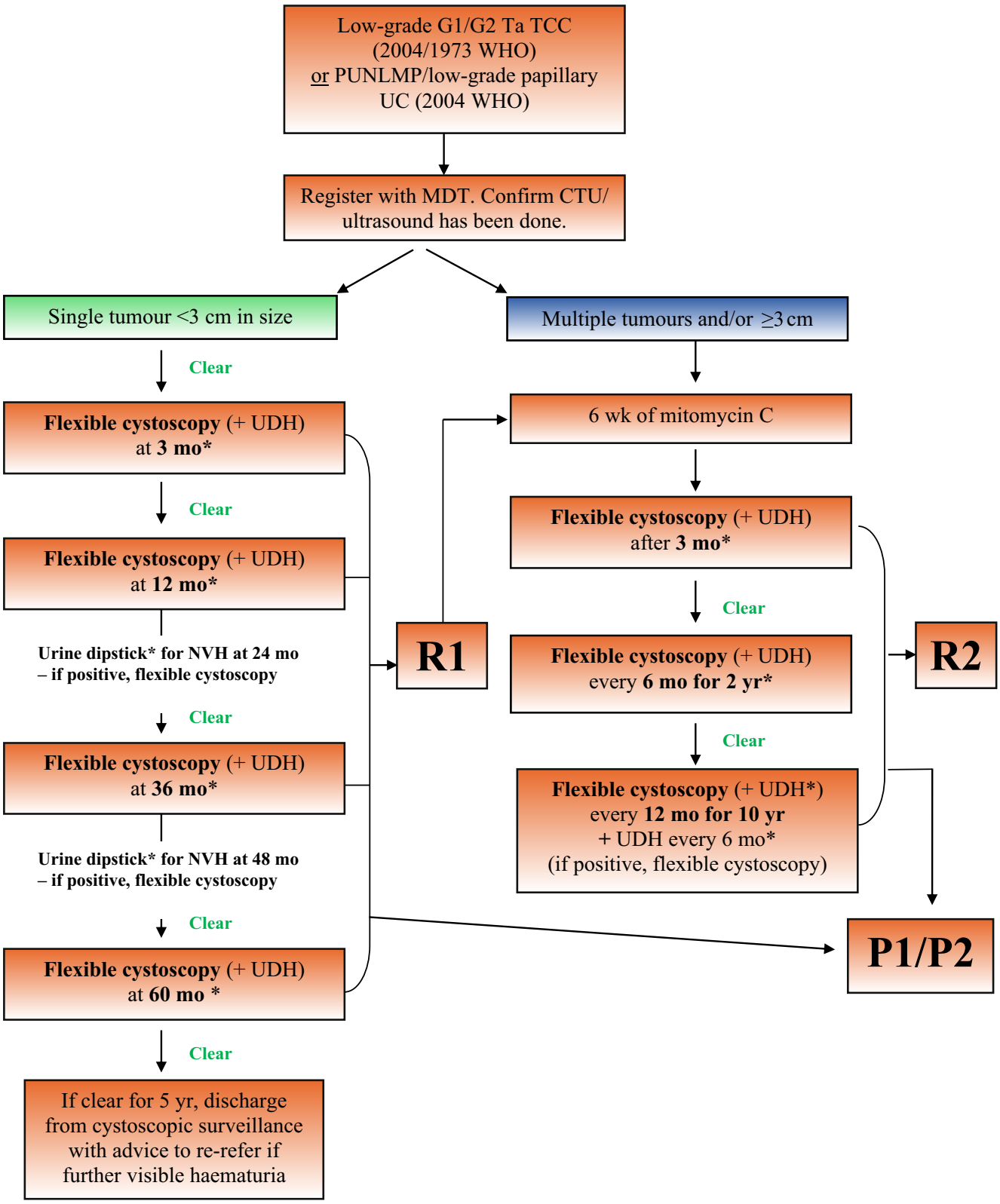

Fig. 2 – Scottish surveillance protocol for low-grade Ta PUC. CTU = computed tomography urography; G1/G1 = grade 1/2; HG = high grade; LG = low grade; MDM = multidisciplinary meeting; MDT = multidisciplinary team; MIBC = muscle-invasive bladder cancer; PUC = papillary UC; PUNLMP = papillary urothelial neoplasm of low malignant potential; TCC = transitional cell carcinoma; UC = urothelial carcinoma; UDH = urinary dipstick for haematuria; WHO = World Health Organisation. R1 = first recurrence with LG Ta PUC; consider an active surveillance protocol. **R2** = further recurrence with LG Ta PUC; MDM and consider the high-risk pathway OR active surveillance protocol. **P1** = recurrence with HG Ta/T1: MDM and follow the high-risk pathway. **P2** = recurrence with MIBC: MDM and follow the MIBC pathway. *Consider adding patient-reported outcome measures, quality of life, and biomarkers. Consider Comprehensive Geriatric Assessment (CGA) where appropriate.

confounders such as anticoagulant use and diabetes as a comorbidity could not be collected for the exploratory cohort, so we cannot exclude the possibility that confounding may have caused discrepancy in the rates of nonvisible haematuria between the cohorts. The UDH tests were essentially snapshots in time for each patient, as they were only tested once; this is being rectified in the larger national evaluation [20]. Work on health economics alongside ongoing validation of the new low-risk protocol will help in clarifying the effectiveness and efficiency of the new recommendations.

5. Conclusions

This two-stage prospective study shows that UDH negativity has a high probability of being associated with the absence of recurrence in small LG Ta NMIBC and in patients who remain recurrence free for >3 yr. This has helped in shaping a novel protocol for patients with low-risk BC that aims to reduce the cystoscopy burden during surveillance. Prospective real-world data collection for validation of this protocol is ongoing.

Author contributions: Paramananthan Mariappan 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: Mariappan.
Acquisition of data: Mariappan, Shah, Lord-McKenzie, Makris, Trail, Gray, Smith.
Analysis and interpretation of data: Mariappan, Shah.
Drafting of the manuscript: Shah.
Critical revision of the manuscript for important intellectual content: Mariappan.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.12.006.

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