Non-muscle-invasive bladder cancer surveillance for which cystoscopy is partly replaced by microsatellite analysis of urine: a cost-effective alternative?

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Study Type – Economic (Markov model with sensitivity analysis)
Level of Evidence   2b

OBJECTIVE

To determine how good microsatellite analysis (MA) markers in voided urine samples should be to make a surveillance procedure cost-effective in which cystoscopy is partly replaced by MA for patients with non-muscle-invasive urothelial carcinoma (NMI-UC).

PATIENTS AND METHODS

We constructed a semi-Markov model with a time horizon of 2 years, and a man aged 65 years as reference case. Data were used from a randomized trial (including 448 patients with NMI-UC from 10 hospitals), and from other data sources. The costs and effects (probability of being in a specific health state) were compared for two surveillance strategies: (i) cystoscopy of the urinary bladder every 3 months (conventional arm), and (ii) semi-automated MA of voided urine samples to identify loss of heterozygosity every 3 months, with a control cystoscopy at 3, 12 and 24 months (test arm). Various sensitivity analyses were used to determine the sensitivity, specificity, and costs of MA of urine for which the test arm was as cost-effective as the conventional arm.

RESULTS

The probability of being without recurrence after 2 years of surveillance was similar (86.6% conventional arm vs 86.3% test arm) with currently available MA markers (sensitivity of 58% and specificity of 73%). However, the test arm led to higher costs (€4104 vs €3433 per head). The test arm would be as effective and cost the same as the conventional arm if the sensitivity of the currently available MA markers was increased at ≥61%, had a specificity of 73%, and decreased the costs of the MA test per follow-up sample from €158 to <€70.

CONCLUSIONS

Over 2 years, surveillance in which cystoscopy is partly replaced by currently available urinary MA to reduce patient burden can only provide a cost-effective alternative to the conventional surveillance if the MA urine test had a slightly higher sensitivity and its costs could be reduced.

KEYWORDS

cost-effectiveness, urine test, Markov decision model, microsatellite analysis, surveillance, urothelial carcinoma
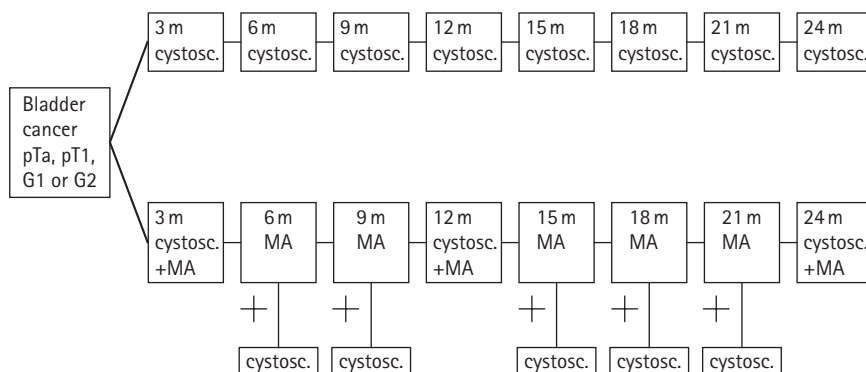
INTRODUCTION

In the Western world bladder cancer is the fourth most common malignancy among men, after prostate, lung and colon cancers [1]. Histologically, 90–95% of bladder cancers in the western world are urothelial carcinoma (UC). UC not only originate from the urothelial lining of the bladder, but they can also occur in the pyelum, the ureters or the urethra. Clinically, a distinction is made between non-muscle-invasive (NMI) and muscle-invasive (MI) UC. NMI-UC are generally treated surgically by a transurethral resection (TUR). Although these NMI-UC are generally rather indolent, their recurrence rate is high (up to 75%). Close monitoring of patients with a NMI-UC is warranted as 10–20% of recurrent tumours can show progression to MI UC; the latter is a life-threatening disease, with a 5-year survival of ≈50%, even after curative surgery (i.e. cystectomy). Surveillance of patients with NMI-UC is by regular cystoscopy (combined with cytological examination for high-risk NMI-UC). Although cystoscopy is considered as the reference standard for detecting tumour recurrences, a disadvantage of the method is its inability to detect recurrences in the upper urinary tract (UUT, pyelum, ureter). Moreover, cystoscopy is an invasive procedure, that can be associated with subsequent complaints of anxiety, dysuria and UTI, adversely influencing the quality of life of the patients [2–4]. Thus substantial efforts have been undertaken to design strategies that could reduce the frequency of cystoscopy in patients with NMI-UC [5,6]. One of these strategies is to replace cystoscopy partly by microsatellite

FIG. 1. Interventions in the conventional and test arm of the randomized study, in which the plus sign indicates a positive MA test.

FIG. 2. The core of the model for bladder cancer surveillance: monitoring patients with NMI-UC can prevent progression to MI-UC by detecting and treating recurrent tumours first (i.e. it is possible to prevent progression). This figure was used for the construction of the Markov model.

analysis (MA) to identify loss of heterogosity in urine samples; published reports show that MA is a highly sensitive and specific marker for diagnosing and monitoring UC, especially in patients with low-stage and low-grade tumours [7]. Van der Aa *et al.* [8] showed, in a randomized controlled trial, that MA can be used to detect tumours earlier and to detect tumours in the UUT that might be missed by cystoscopy. However, the sensitivity (58%) and specificity of MA (73%) for detecting recurrences in the bladder were both worse than for cystoscopy (98% and 88%, respectively) [8].

In the present study we determined the requirements in terms of sensitivity, specificity and real costs of MA markers on voided urine samples to achieve cost-effectiveness of a surveillance procedure of patients with NMI-UC whose cystoscopy is partly replaced by MA. We used data from the randomised controlled Cost-effectiveness of Follow-up of urinary Bladder Cancer (CEFUB) trial.

PATIENTS AND METHODS

We conducted the randomized controlled CEFUB trial (including 448 patients with NMI-UC, recruited by 10 Dutch hospitals; registration ClinicalTrials.gov NCT00126958) to evaluate the efficacy of MA on voided urine for detecting tumour recurrences in the follow-up of patients. Patients included had a primary or recurrent NMI-UC (pTa, pT1, G1 or G2) of the urinary bladder, based on histopathological examination of the surgically removed tumour. Figure 1 shows the interventions in the conventional and test

arm of the randomized study over 2 years. The conventional arm consisted of cystoscopy of the urinary bladder every 3 months. The test arm consisted of semi-automated MA of DNA (for 20 polymorphic microsatellite markers on 10 chromosomes) extracted from voided urine samples from patients with a NMI-UC every 3 months. A blood sample was taken as a control for the MA of the subsequent urine samples, and was used during the entire study period. A control cystoscopy was done at 3, 12 and 24 months after TUR, and if the MA was positive. If a tumour recurrence was found by cystoscopy, irrespective of conventional or test arm, it was removed by TUR. If there was progression to MI-UC or G3 NMI-UC after adjuvant intravesical treatment, a cystectomy was considered. Additional radio-imaging was used to examine the UUT for the presence of UC, if the clinical performance was suspect or if the outcome of MA and cystoscopy were discordant, i.e. MA was positive but no tumour was detected by cystoscopy during two subsequent visits (i.e. a persistently positive MA). The UUT radio-imaging was not done immediately for a positive MA and negative cystoscopy, as previous studies showed that a positive MA test frequently antedates cystoscopically detectable recurrences [8,9]. Finally, 80 radio-imaging procedures showed seven tumours in the UUT (five in the test arm and two in the control arm). If there was suspected UC in the UUT, a unilateral nephroureterectomy was considered.

We constructed a semi-Markov decision model to assess costs and effects (probability of being in a specific health state) of both bladder cancer surveillance methods (i.e. the test and conventional arm). The model was
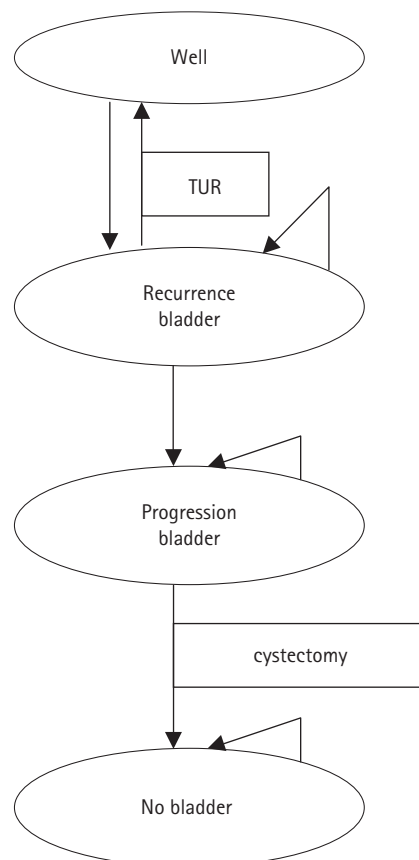
implemented in DATA software (Version TreeAge PRO 2007, TreeAge Software, Boston, MA, USA). Figure 2 highlights the core of the surveillance model; monitoring patients with NMI-UC can prevent progression to MI-UC by detecting and treating recurrent tumours first (i.e. it is possible to prevent progression). Appendix 1 shows the underlying conceptual model; missing those patients with recurrent tumours can lead to cystectomy and a higher probability of death due to progressive tumours. Poor health states indicate dead, no bladder, progression (i.e. MI-UC or G3 NMI-UC) and recurrent UC, and all other health states indicate 'well'. Notably, after a detected recurrent UC, the patient will go back to the health state 'well' again. Transition probabilities for each 3 months were used to correspond with the follow-up times. The reference case was a man aged 65 years, and the time horizon was 2 years. To retain some

TABLE 1 *The baseline assumptions of the Markov model*

Description	Sensitivity/specificity, % or P or costs, €	Note	Source
Sensitivity MA, bladder	58		study
Sensitivity MA, UUT	58		study
Specificity MA, bladder	73		study
Specificity MA, UUT	73		study
Sensitivity cystoscopy, bladder	98		study
Sensitivity cystoscopy, UUT	0		study
Specificity cystoscopy, bladder	88		study
Specificity cystoscopy, UUT	100		study
Sensitivity IVU	60		http://www.guideline.gov
Specificity IVU	100	False positives not possible	
3–month, P			
Dead after progression	0.12	3-month risk year 1	Dutch comprehensive cancer centres
	0.085	3-month risk year 2	Dutch comprehensive cancer centres
Progression after recurrence	0.157		study
Recurrence	0.058	Selection primary tumour + counted for 3 recurrences	study
Recurrence UUT	0.1	Given there is a recurrence	Dutch comprehensive cancer centres
Recurrence bladder after NU	0.12		[10]
Costs			
MA blood analysis	357		Department of Pathology, Erasmus MC
MA urine analysis	158		Department of Pathology, Erasmus MC
Cystoscopy	168		Department of Finance, AMC
IVU	165		Department of Finance, AMC
TUR	1409		Department of Finance, AMC
Cystectomy	7997		Department of Finance, AMC
Nephroureterectomy	3333		Department of Finance, AMC

memory in the Markov model some health states were constructed with a 'sub-health' state, indicating whether the MA was positive and the cystoscopy negative at the last visit of surveillance. When this was also the case in the subsequent visit, an IVU was assumed to be done.

Table 1 shows the variables used in the Markov model to provide insight into the current effects and costs of both strategies [10]. Data from the trial (448 patients) were used to determine the 3-month probabilities of recurrence ($P_{rec} = .058$) and progression after recurrence of NMI bladder cancer ($P_{prog} = 0.157$) [8]. Also, the 3-month probabilities of undergoing a cystoscopy, sensitivity (58%) and specificity (73%) of MA, and sensitivity and specificity of cystoscopy in the bladder (98% and 88%, respectively) were determined by our trial data. Detailed, integral cost data of the MA analysis (blood and urine analysis) were obtained from the Department of Pathology of the Erasmus Medical Centre Rotterdam. Cost data for cystoscopy, IVU, TUR, cystectomy, and unilateral

nephroureterectomy were obtained from the Department of Finance of the Academic Medical Centre Amsterdam. Unit prices were determined by following the microcosting method [11], which is based on comprehensive 'bottom-up' analyses and included costs of employment, material and equipment. A societal perspective was adopted. Costs of one cystoscopy procedure were calculated as €168 per patient (the including personal costs were relatively low (€63.4 per patient) due to the short diagnostic time and efficient organization in the participating hospitals). We compared these costs with the determined unit prices of the Department of Finance of Erasmus Medical Centre Rotterdam. The costs were about the same. Confidentiality agreements did not allow us to give more detailed information. Costs of a single MA blood analysis and MA urine analysis were, respectively, €357 and €158. MA of the blood acted as reference value for MA urine analysis. Therefore, during 2 years of surveillance, costs of MA blood analysis were estimated only once (i.e. all costs were at the beginning of the

surveillance). However, the costs of MA urine analysis were incurred at every follow-up.

We made the following assumptions in the present study: (i) progression takes place after recurrence; (ii) only one recurrence can take place at the same time; (iii) the health state 'recurrence in UUT after nephroureterectomy' does not exist; this prevents a second possible nephroureterectomy in the model; (iv) only patients who had progression of the tumour at a specific time have a higher probability of death than the background mortality; (v) a cystoscopy never reveals a progressive recurrence, which originated in the UUT and invades the bladder; (vi) UUT imaging has a specificity of 100%; (vii) in case of progression to MI-UC the next step was a cystectomy; (viii) after cystectomy the surveillance stops; and (ix) if the IVU was positive the next step was a nephroureterectomy.

One-way sensitivity analyses were used to evaluate the effects of varying costs, recurrence rate, progression rate, sensitivity rates, and specificity rates. All point estimates

TABLE 2 Detailed overview of costs and effects in the conventional and test arms

Stage, months	Costs, €		%							
	/stage	Cumulative	Dead	No bladder	Progression UUT	Progression bladder	Recurrence UUT	Recurrence bladder	Well
Conventional									
3	451	451	0.37	0.80	0.09	0.02	0.49	0.09	98.15
6	447	897	0.75	1.61	0.25	0.02	0.89	0.09	96.40
9	440	1337	1.15	2.40	0.44	0.02	1.21	0.09	94.69
12	433	1769	1.57	3.18	0.66	0.02	1.48	0.08	93.01
15	426	2195	1.99	3.94	0.92	0.02	1.70	0.08	91.35
18	419	2615	2.43	4.68	1.19	0.02	1.87	0.08	89.73
21	412	3027	2.89	5.41	1.47	0.02	2.01	0.08	88.13
24	406	3433	3.37	6.12	1.74	0.01	2.12	0.08	86.57
Test									
3	964	964	0.37	0.80	0.09	0.02	0.49	0.09	98.15
6	336	1300	0.75	1.27	0.21	0.36	0.76	1.91	94.75
9	355	1655	1.18	2.05	0.34	0.60	0.98	3.37	91.47
12	713	2367	1.66	3.81	0.46	0.04	1.11	0.11	92.81
15	323	2690	2.06	4.26	0.59	0.35	1.21	1.85	89.68
18	346	3036	2.50	5.02	0.70	0.58	1.27	3.22	86.72
21	366	3402	2.97	6.00	0.79	0.76	1.29	3.93	84.27
24	702	4104	3.45	7.94	0.86	0.04	1.30	0.11	86.29

of these variables were halved or doubled, except the point estimates of the sensitivity and specificity rates, which were increased and decreased based on previous reports [8,12].

Finally, by using a two-way sensitivity analysis between the sensitivity and specificity of MA, we determined a threshold line at which both surveillance strategies were equally effective. Various combinations of MA sensitivity, specificity, and costs of MA urine analysis were determined in which the test arm was as effective and cost the same as the conventional arm.
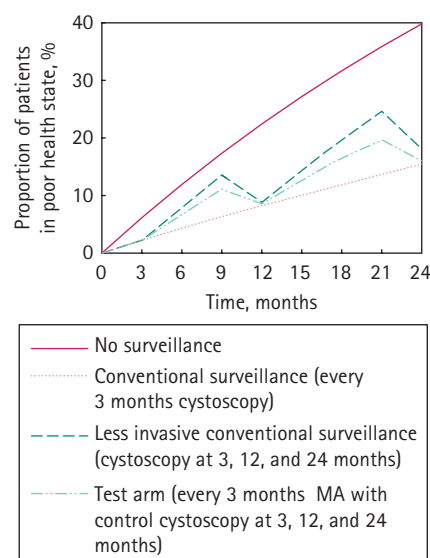
RESULTS

Table 2 shows the current costs and effects based on the Markov model for the conventional and test arm, respectively, for different follow-up samples. Over 2 years the total costs of surveillance were lower (€3433 per head, €1283 diagnostic and €2150 therapeutic costs) for the conventional arm, than for the test arm (€4104 per head, €2347 diagnostic and €1757 therapeutic costs; column 3, stage 24 months). For the conventional arm the cost per head decreased by every subsequent stage (column 2), because the probability to be in health states 'Dead' (column 4) or 'No bladder' (column 5)

increased over the time. For the test arm the costs per head at stage 3 months were more than twice as high as the conventional arm. At stage 3 months not only was there MA urine analysis, but also a MA blood analysis and cystoscopy. Stages 12 and 24 months were more expensive than the conventional arm due to the control cystoscopy.

Over the 2 years there was a probability of 6.1% of losing the bladder in the conventional arm and 7.9% in the test arm (see column 5, stage 24 months). The probability of having a progressive tumour in the bladder was very low, but higher (0.04%) in the test arm than the conventional arm (0.01%; column 7, stage 24 months). However, the test arm resulted in better outcomes for UC originating in the UUT due to using IVU after twice-discordant outcomes between MA and cystoscopy in subsequent visits. Although the test arm detected tumours earlier and in the UUT, more tumours in the bladder were missed. Therefore, the current conventional and the test arm were similarly effective over the 2 years (Fig. 3). Thus, the Markov model suggested, as expected, that the conventional arm dominated the test arm in terms of cost-effectiveness. The conventional arm had lower costs and a slightly more patients in a good health state (86.6% vs 86.3%; Table 2, column 10, stage 24 months). Figure 3 also showed that (i) if patients had only MA with

FIG. 3. The probability (%) of being in a poor health state in either surveillance strategy (conventional or test arm) for different times of follow-up. Poor health states indicate dead, no bladder, progression and recurrence of UC.

No surveillance

Conventional surveillance (every 3 months cystoscopy)

Less invasive conventional surveillance (cystoscopy at 3, 12, and 24 months)

Test arm (every 3 months MA with control cystoscopy at 3, 12, and 24 months)

no control cystoscopy at stage 3, 12 and 24 months, the probability of being in a poor health state would increase steeply; and (ii) if patients had only a cystoscopy at stage 3, 12 and 24 months with no MA, fewer would be in a good health state than in the test arm.

TABLE 3 *Sensitivity analysis of costs and effects for both surveillance arms over 2 years*

Variable	Variability	Cumulative costs, €		Difference	Probability, % of being 'well'		Difference
		Test	Conventional	test – con	Test	Conventional	test – con
Recurrence rate	0.029	3629	3053	576*	91.48	91.69	−0.21
	0.116	4954	4135	819*	77.04	77.08	−0.04
Progression rate	0.079	3905	3276	629*	90.17	89.52	0.65†
	0.314	4440	3731	709*	79.65	80.94	−1.29
Costs cystoscopy, €	84	3745	2792	953*	86.29	89.57	−3.28
	336	4823	4716	107*	86.29	86.57	−0.28
Costs MA blood, €	179	3926	3433	493*	86.29	89.57	−3.28
	714	4460	3433	1027*	86.29	86.57	−0.28
Costs MA urine, €	79	3502	3433	69*	86.29	89.57	−3.28
	316	5308	3433	1875*	86.29	86.57	−0.28
Sensitivity MA	0.29	4079	3433	646*	83.87	86.57	−2.70
	0.70	4111	3433	678*	87.27	86.57	0.70†
Specificity MA	0.69	4181	3433	748*	86.30	86.57	−0.27
	0.76	4048	3433	615*	86.28	86.57	−0.29
Sensitivity cystoscopy	0.84	4093	3432	661*	84.63	85.31	−0.68
	0.98	4104	3433	671*	86.29	86.57	−0.28
Specificity cystoscopy	0.79	4583	4327	256*	86.29	86.57	−0.28
	0.98	3572	2439	1133*	86.29	86.57	−0.28

*Test arm is more expensive than conventional arm over 2 years; †Test arm is more effective than conventional arm over 2 years.

FIG. 4. *The threshold analysis for surveillance strategies. Sensitivity and specificity combinations in the white area indicate that the conventional arm is more effective; sensitivity and specificity combinations in the light green area means that the test arm is more effective.*
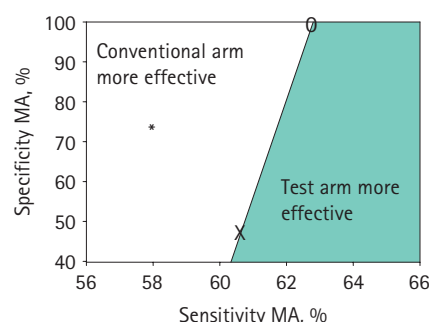
* = current assumption for MA test (MA sensitivity 58%, MA specificity 73%)

x = if MA–urine test has a sensitivity of 60.5%, a specificity of 47%, and will be free of charge, the test arm will be as effective and cost the same as the conventional arm

0 = if MA–urine test has a sensitivity of 62.8% and a specificity of 100%, and will cost €130.5, the test arm will be as effective and cost the same as the conventional arm

Table 3 shows various one-way sensitivity analyses of costs and effects for both surveillance arms over the 2 years. Changing the variables over plausible ranges did not

TABLE 4 *Combinations of MA sensitivity, specificity, and costs of MA urine in which the test arm is as effective and costs the same as the conventional arm*

Sensitivity MA, %	Specificity MA, %	Costs of MA urine, €
60.5	47	0.0
60.7	53	17.0
61.4	73	69.6
62.8	100	130.5

make the test arm cheaper than the conventional arm. Only if the progression rate was halved (i.e. 0.079) was the probability of being 'Well' (i.e. being without a recurrence or progressive UC) larger in the test arm than the conventional arm (90.2% vs 89.5%, respectively) over the 2 years. This was also the case if the sensitivity of MA was increased to 70% (i.e. probability of being 'Well' was 87.3% in the test arm vs 86.6% in the conventional arm). Obviously, changing the costs did not influence the health effect side.

Figure 4 shows that the test arm was equally effective as the conventional arm, if the MA had a sensitivity of 60.3% in combination with a specificity of 39.8%, or if the MA had a sensitivity of 62.8% in combination with a specificity of 100%, or all linear combinations of MA sensitivity and specificity in between. Table 4 shows that, for instance, if the

sensitivity was increased to 61%, the specificity of MA remained at 73%, and the costs of MA urine tests will decrease to €70, then the test arm is as effective and costs the same as the conventional arm.

DISCUSSION

Currently available MA markers are not sensitive enough (sensitivity of 58%) or specific (specificity of 73%) to use as a replacement for cystoscopy in the surveillance of bladder cancer. The probability of being without recurrence after 2 years of surveillance was similar for both surveillance strategies (86.6% conventional arm vs 86.3% test arm), but the test arm led to higher costs (€4104 vs €3433 per head). The conventional arm hence dominated the test arm (less costs, similar effects). However, the test arm will be

as effective and cost the same as the conventional arm if the sensitivity of the current available MA markers increased to ≥61%, the specificity of MA remained at 73% and the costs of MA urine test per follow-up sample decreased from €158 to <€70.

Lotan and Roehrborn [13] used a decision tree to evaluate the cost-effectiveness of substituting cystoscopy by other bladder tumour markers than MA markers. They showed that using a urine-based tumour marker alternating with cystoscopy is cost-effective for a wide range of marker sensitivities, specificities and costs, a 20–80% yearly recurrence and a 2–40% yearly progression rate. Although the sensitivity and specificity of their tumour markers and our MA markers were almost the same as in the present study (respectively, 50% vs 58%, and 70% vs 73%), the costs of diagnostic and therapeutic interventions used in both studies differed, especially for the costs of the tumour markers. Ignoring the inflation rate, the costs of the tumour markers were assumed as $50 [13], in contrast to €158 for our MA urine analysis and €357 for the one-time MA blood analysis. It is plausible that genetic analysis (i.e. MA markers) are more expensive than urine-sediment diagnosis. However, for a fair comparison of costs we should use the same costing method. The costs in the present study were based on unit prices determined by following the microcosting method [11], while the costs in Lotan and Roehrborn [13] were according to the listing of the manufacturers. Another important difference between both studies is that in the present study at stage 3, 12 and 24 months there was a control cystoscopy in addition to MA urine analysis, which increased the costs.

Our Markov model did not explicitly account for the burden (i.e. quality of life, e.g. pain, infection rate) associated with cystoscopy. Cystoscopy would take place 7.6 times in the conventional arm and just 4.3 times in the test arm over the 2 years. However, we assumed that this difference is not enough to compensate for the more frequent cystectomies or greater risk of dying from cancer. Further, in the test arm at stage 3, 12 and 24 months MA urine analysis took place in addition to cystoscopy. Cystoscopy has by definition a high sensitivity. Therefore, at these stages the MA urine analyses might be superfluous and its costs can be saved here, i.e. in practice urologists should use MA as a substitute rather than as an adjunct for

bladder cancer detection and follow-up. Another point is that MA blood analysis was required to provide reference values for MA urine analyses. The cost of MA blood analysis was incurred only once, at the start of surveillance. Over the course of, e.g. 10 years instead of 2 years of surveillance, there will hence be less difference in total costs between the arms.

Our study had some further limitations, primarily related to various assumptions that had to be made in the model to make the model manageable. For example, we assumed that progression only takes place after recurrence. However, it is conceivable that progression occurs directly from the health state 'Well'. Based on data from the present study, we can assume that MA is more sensitive for progression than for recurrence. In all, this would make the cost-effectiveness for MA worse. Finally, it is not immediately clear how to exactly translate our cost estimates in other countries or clinical practice routines. The costs might vary from one area to another in Europe, and in the USA, and the panel of tested markers can be improved. Further prospective studies in a larger international population are therefore necessary.

Some recommendations can be made. The costs of MA (blood and urine analysis) were higher than the costs of cystoscopy. The large difference in cost is caused by material as well as personnel costs. Further automation of MA testing might lead to mass production and cost reduction. Research is needed to find out how much the cost per head will decrease due to automation. According to the model, the current MA markers were not sensitive enough compared with cystoscopy. Better MA markers should be found to obtain better cost-effectiveness. Sensitive markers of particular interest are those that do not require comparison with a blood sample of the patient for reference values. Notably, based on data from the present study, it is conceivable that awareness of a positive MA outcome might have prompted a higher detection rate of UC recurrences by cystoscopy. Indeed, separate analysis of the patients of the MA arm showed an improved cross-sectional sensitivity (70%) of the MA test [8]. Recent developments suggest other DNA-based tests as alternatives, such as detection of *FGFR3* mutations (present in most NMI-UC) and assays for detecting tumour-associated methylation of genes of

interest [14–18], as these tests are cheaper than MA in material and personnel costs.

In conclusion, over the 2 years of surveillance in which cystoscopy was partly replaced by currently available urinary MA to reduce patient burden, it can only provide a cost-effective alternative to conventional surveillance if the MA urine test had slightly better sensitivity and its costs were reduced.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **UC**, urothelial carcinoma; **(N)MI**, (non-) muscle-invasive; **TUR**, transurethral resection; **UUT**, upper urinary tract; **MA**, microsatellite analysis; **CEFUB**, Cost-effectiveness of Follow-up of urinary Bladder Cancer.

APPENDIX 1

Decision-analytic model for bladder cancer surveillance.