FGFR3 Mutation Analysis in Voided Urine Samples to Decrease Cystoscopies and Cost in Nonmuscle Invasive Bladder Cancer Surveillance: A Comparison of 3 Strategies

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Abbreviations and Acronyms

CT = computerized tomography

FGFR3 = fibroblast growth factor receptor 3

NMIBC = nonmuscle invasive bladder cancer

TUR = transurethral resection

UC = urothelial carcinoma

UUT = upper urinary tract

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Purpose: We determined whether *FGFR3* mutation analysis of voided urine samples would be cost-effective to partly replace cystoscopy in the surveillance of patients treated for nonmuscle invasive urothelial carcinoma.

Materials and Methods: In this decision analytical study we analyzed data on 70 Dutch patients with *FGFR3* positive primary tumors and a median followup of 8.8 years. Surveillance strategies were compared in a Markov model. Modified surveillance consisted of *FGFR3* mutation analysis of voided urine samples every 3 months, and cystoscopy at 3, 12 and 24 months. Standard surveillance was defined as cystoscopy every 3 months and minimal surveillance was defined as cystoscopy at 3, 12 and 24 months. Analysis was stratified for 3 risk profiles, including surveillance after 1) the primary tumor, 2) the first to third recurrence and 3) the fourth recurrence or more. Sensitivity analysis was performed to evaluate the impact of variations in cost, sensitivity and specificity.

Results: The probability of no recurrence after 2 years of surveillance after a primary tumor was higher for modified surveillance than for standard and minimal surveillance, eg after primary tumors (95.7% vs 95.0% and 93.9%, respectively). The total cost of surveillance after the primary tumor was lower for minimal and modified surveillance (€2,254 and €2,558, respectively) than for standard surveillance (€5,861). Results were robust to changing inputs over plausible ranges and consistent for each of the 3 risk profiles.

Conclusions: Surveillance in which cystoscopy is partly replaced by *FGFR3* mutation analysis of urine seems a safe, effective and cost-effective surveillance strategy. Further validation in larger cohorts is required.

Key Words: urinary bladder; urinary bladder neoplasms; receptor, fibroblast growth factor, type 3; cystoscopy; cost-benefit analysis

ALTHOUGH the 5-year survival rate of NMIBC is high at 80% to 90%,[1] surveillance for recurrent disease places a major burden on patients and the health care system in general. More than half of these patients have 1 or more recurrences and must be monitored for the rest of their lives to detect recurrence and progression to muscle invasive cancer (10% to 20%).[2] Progressive disease leads to bladder loss via cystectomy and possibly to death. Therefore, an intensive surveillance protocol is generally followed.

Surveillance relies on regular cystoscopy, which is an invasive procedure associated with anxiety, dysuria, urinary tract infection and financial

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costs.[3–6] Moreover, cystoscopy can only detect recurrence inside the bladder and not in the kidneys or ureters, where these UCs may also recur. Thus, the diagnosis of such upper urinary tract recurrences may be delayed since they are only detected if symptoms occur. Therefore, substantial efforts have been made to design surveillance strategies that could decrease the frequency of cystoscopy in patients with NMIBC without compromising early detection.

Approximately two-thirds of NMIBCs are *FGFR3* mutants. These mutant tumors grow less aggressively and only few progress to muscle invasive disease.[7–10] A decrease in cystoscopy frequency in these patients is an attractive option with cystoscopy replaced by *FGFR3* mutation analysis of voided urine samples. We determined the cost-effectiveness and safety of such a surveillance strategy compared to those of standard surveillance and a minimal surveillance variant.

MATERIALS AND METHODS

Patient Data

We studied a consecutive series of 70 patients with primary nonmuscle invasive UC (pTa or pT1) treated at our medical center in The Netherlands, as previously described in detail.[11] All patients had a *FGFR3* positive primary tumor and were retrospectively examined for recurrence and progression between 1983 and 2007 (see table). Recurrence was defined as a tumor removed at TUR with histopathological confirmation and without muscle invasion. Progression was defined as muscle invasive UC, ie pT2 or greater. All tumors were staged and graded according to the 1997 TNM[12] and 1973 WHO[13] classifications.

Characteristics of 70 patients

No. gender (%):		
M	46	(65.7)
F	24	(34.3)
Median age at primary tumor (range)	66	(32–84)
No. primary tumor stage (%):		
Ta	61	(87.1)
T1	9	(12.9)
No. primary tumor grade (%):		
G1	36	(51.4)
G2	30	(42.9)
G3	4	(5.7)
No. CIS (%):		
Yes	2	(2.9)
No	68	(97.1)
Median mos followup (range)	106.1 (42.7–270.9)	
Recurrence:		
No.	207	
No. pts without (%)	19	(27.1)
No. pts with (%)	51	(72.9)
Median No./pt (range)	3	(1–18)
No. progression	4	
No. death (%):		
Yes	21	(30)
No	49	(70)
Disease	8	(11.4)
Other cause	13	(18.6)
No. cystectomy (%):		
Yes	4	(5.7)
No	66	(94.3)

Decision Model

We adapted a Markov decision model from a previously published model used to evaluate the cost-effectiveness of partly replacing cystoscopy by microsatellite analysis in the followup of patients with NMIBC.[14] Patients started in the well health state and eventually died (dead state). Other states related to recurrence and progression in the bladder or UUT (fig. 1). The Markov model had a time horizon of 2 years with 3 monthly cycles. Patients were modeled by tumor, that is for each detected recurrence a new surveillance course began. Markov cohort analysis of 1,000 cases was performed to compare the surveillance strategies.

Model outcomes included the fraction of patients per health state, including a well state for those without recurrence, progression or a bladder, and cumulative financial costs for up to 2 years.

Surveillance Strategies

We modeled 3 strategies (fig 2). 1) A standard surveillance arm included cystoscopy every 3 months. 2) A minimal surveillance arm was defined as a lower end reference and included cystoscopy at 3, 12 and 24 months. 3) A modified surveillance arm consisted of *FGFR3* mutation analysis of voided urine samples every 3 months. Followup cystoscopy was scheduled at 3, 12 and 24 months. Additional cystoscopy was performed when *FGFR3* mutation analysis had a positive outcome.

If recurrence was found at cystoscopy, it was assumed to be removed by TUR. This patient then restarted surveillance. In cases of progression to muscle invasive bladder cancer, the bladder was removed via cystectomy. If the outcome of *FGFR3* mutation analysis was positive but followup cystoscopy remained negative for 2 subsequent visits, CT of the abdomen was performed to rule out any UUT recurrence. When a UUT tumor was detected, unilateral nephroureterectomy was performed.

Transition Probabilities and Cost Data

We determined the 3-month probability of recurrence and progression using data on 70 patients in a Dutch cohort by Cox proportional hazards regression analysis with SPSS®, version 15. We analyzed 207 recurrences and 4 progressions that occurred during a median followup of 8.8 years. The 3-month probability of progression was subsequently estimated, conditional on recurrence. Three sets of transition probabilities for recurrence and progression were analyzed, ie after 1) the primary tumor, 2) the first to third recurrence and 3) the fourth recurrence or more.

Sensitivity and specificity of the included tests were obtained from the literature, as were all remaining transition probabilities (supplementary table 1, http://jurology.com/).[1,14,15] The specificity of *FGFR3* mutation analysis was set at 100% because mutations do not occur in the urine samples of nonpatients.

Cost data were based on Dutch sources (supplementary table 1, http://jurology.com/). Costs were deter-