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Advances in Brief

The Fibroblast Growth Factor Receptor 3 (*FGFR3*) Mutation Is a Strong Indicator of Superficial Bladder Cancer with Low Recurrence Rate[1]

Bas W. G. van Rhijn, Irene Lurkin, François Radvanyi, Wim J. Kirkels, Theodorus H. van der Kwast, and Ellen C. Zwarthoff[2]

Department of Pathology, Josephine Nefkens Institute, Erasmus University, 3000 DR Rotterdam, the Netherlands [B. W. G. v. R., I. L., T. H. v. d. K., E. C. Z.]; Department of Urology, Erasmus University and University Hospital, 3000 CA Rotterdam, the Netherlands [B. W. G. v. R., W. J. K.]; and Laboratoire de Morphogenèse Cellulaire et Progession Tumorale, UMR 144, Centre National de la Recherche Scientifique, Institut Curie, 75248 Paris Cedex 05, France [F. R.]

Abstract

We analyzed the possible prognostic value of the recently discovered fibroblast growth factor receptor 3 (*FGFR3*) mutations in bladder cancer. A *FGFR3* mutation was found in 34 of 53 pT_aG_{1-2} bladder cancers, whereas none of the 19 higher-staged tumors had a mutation ($P < 0.0001$). In 57 patients with superficial disease followed prospectively by cystoscopy for 12 months, 14 of 23 patients in the wild-type *FGFR3* group developed recurrent bladder cancer compared with only 7 of 34 patients in the mutant group ($P = 0.004$). The recurrence rate per year was 0.24 for the *FGFR3* mutant tumors and 1.12 for tumors with a wild-type *FGFR3* gene. In addition, *FGFR3* mutation status was the strongest predictor of recurrence when compared with stage and grade ($P = 0.008$). This is the first mutation in bladder cancer that selectively identifies patients with favorable disease characteristics. Our results suggest that the frequency of cystoscopic examinations can be reduced considerably in patients with *FGFR3*-positive tumors.

Introduction

Urinary bladder cancer is the fifth most common neoplasm in western society with ~54,400 new cases in the United States per year (1). In the majority of patients, bladder cancer is superficial (*i.e.*, pT_a-pT_1) at first presentation. After TUR[3] of superficial bladder cancer, patients are monitored by cystoscopy at regular intervals because the recurrence rate of superficial bladder cancer is up to 70% (2–4). Progression to invasive disease occurs in around 15–20% of patients (2, 3). Clinical and histopathological factors for prediction of tumor recurrence and progression of bladder cancer have been studied extensively (2–4). Tumor grade, stage, and recurrence rate are especially important. In addition, it has appeared that mutations in the tumor suppressor genes *TP53* and *RB* are of additional value to assess aggressive tumor behavior (5). The FGFR3 is a glycoprotein composed of three extracellular immunoglobulin-like domains, a transmembrane domain, and a split tyrosine-kinase domain. Several reports have shown that constitutive activation of the *FGFR3* gene by specific point mutations leads to congenital anomalies such as achondroplasia and thanatophoric dysplasia (6, 7). A frequent t(4;14)(p16.3;q32.3) chromosomal translocation with the breakpoint near *FGFR3* in multiple myelomas suggested an oncogenic role for the *FGFR3* gene (8). However, an activating mutation in the *FGFR3* gene occurred rarely in multiple myeloma (9). The same missense mutations (R248C, S249C, G372C, and K652E) that were observed in thanatophoric dysplasia were recently found in 9 of 26 bladder carcinomas and 3 of 12 cervix carcinomas (10). It has been shown that mutated *FGFR3* can transform NIH 3T3 cells when targeted to the cell membrane (11). Because the *FGFR3* gene is expressed in bladder cancer and normal urothelium (10), it is likely that the mutant gene has an oncogenic role in bladder cancer pathogenesis. The present study assesses the possible prognostic value of the *FGFR3* mutation in bladder cancer.

Materials and Methods

Patients. Seventy-two consecutive patients who underwent TUR at the University Hospital Rotterdam in 1998–1999 were entered into this study. The patients were not selected on any clinical or other parameter. All of the patients signed written informed consent. The Medical Ethical Committee of the Erasmus University and the University Hospital Rotterdam approved the study (MEC 168.922/1998/55). Median age at time of diagnosis was 65.4 years (range, 30–89); male:female ratio was 4.2:1. We examined each patient's history and obtained 12-months clinical follow-up on a prospective basis, including a cystoscopic examination every 3 months, from all of the patients that were diagnosed with superficial bladder cancer at the time of *FGFR3* mutation analysis. Grading of cancers was performed according to the WHO classification and staging according to the 1997 TNM classification guidelines (UICC 1997). A recurrence was defined as the presence of histologically proven bladder cancer at a positive cystoscopy after a complete previous TUR. The recurrence rate per year was defined as the number of recurrences divided by the total number of months of follow-up. The result was then multiplied by 12. Hence, the recurrence rate takes into account the clinical course of patients during a longer interval and not only the time to first recurrence.

Sample Collection and DNA Extraction. The bladder tumors were subjected to careful microdissection after confirmation of the histopathological diagnosis. Venous blood (7 ml) was obtained from every patient to be used as control. DNA from paraffin-embedded, formalin-fixed neoplastic tissue was extracted using DNeasy Tissue kit (Qiagen GmbH, Hilden, Germany) according to enclosed protocol. DNA from venous blood was isolated using one-step DNAzol BD Reagent (Life Technologies, Inc., Grand Island, NY). We checked the accuracy of the microdissection procedure by LOH analysis in 18 of the 19 patients with $\geq pT_1$ tumors comparing the allele intensities of normal and tumor DNA of the same samples that were used for the *FGFR3* mutation analysis. A 50% reduction of allele intensity was considered LOH. We used 23 microsatellite markers on 9 different chromosomes as described previously (12). Every LOH was confirmed in a second PCR.

***FGFR3* Mutation Analysis.** *FGFR3* mutation analysis was performed by PCR-SSCA on tumor- and control blood DNA of all of the patients. Three regions of interest containing the four previously identified mutations were amplified by PCR. The primer sequences were the same as used by Capellen *et al.* (10). The following primer pairs were used: for exon 7, 5′-AGTGGCGGTGGTGGTGAGGGAG-3′ and 5′-TGTGCGTCACTGTACACCTTGCAG-3′; for exon 10, 5′-CAACGCCCATGTCTTTGCAG-3′ and 5′-CGGGAAGCGGGAGATCTTG-3′; and for exon 15, 5′-GACCGAGGACAACGTGATG-3′ and 5′-GTGTGGGAAGGCGGTGTTG-3′. All of the tumors with an aberrant band at SSCA were sequenced with T7 Sequenase v2.0 (Amersham life Science, Inc., Cleveland, OH) on both strands to check the identity of the

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[2] To whom requests for reprints should be addressed, at Department Pathology, Josephine Nefkens Institute, Erasmus University, P. O. Box 1738, 3000 DR Rotterdam, the Netherlands. Phone: 31-104087929; Fax: 31-104089487; E-mail: zwarthoff@path.fgg.eur.nl.

[3] The abbreviations used are: TUR, *trans*-urethral resection; RB, retinoblastoma; FGFR3, fibroblast growth factor receptor 3; LOH, loss of heterozygosity; SSCA, single-strand conformation analysis.

mutations. Analysis of all of the samples was carried out in a blinded fashion, without knowledge of clinical or histopathological status.

Statistical Analysis. Statistical package for social sciences 8.0 (SPSS Inc., Chicago, IL) and StatXact version 2 (Cytel Software Corporation, Cambridge, MA) computer software were used for data documentation and analysis. Fisher's exact test was used to analyze the *FGFR3* mutation in relation to stage, grade, highest stage, and prediction of tumor recurrence. Logistic regression analysis with the backward elimination method was used for comparison of variables to predict recurrence. All of the *P*s are two sided. Statistical significance was assumed if $P < 0.05$.

Results

We performed a mutation analysis of the *FGFR3* gene in a group of 72 bladder carcinomas from 72 consecutive patients. Thirty-seven patients were diagnosed with bladder cancer for the first time. All of the 72 bladder cancers were transitional cell carcinomas except for one squamous cell carcinoma that was pT_2, grade 3.

SSCA detected aberrant bands (Fig. 1) in DNA samples from 34 tumors but not in DNA from corresponding venous blood, indicating the somatic nature of *FGFR3* mutations in bladder cancer. Thirty mutations concerned the already described codon 249 mutation (S249C). Codon 248 (R248C) and 372 (G372C) mutations were found once and twice, respectively (Fig. 1, *A*, *C*, and *D*). An additional mutation, not observed in bladder cancer previously, was also detected (Fig. 1*E*). DNA sequence analysis revealed the point mutation leading to A393E, previously known in a hereditary skeletal syndrome (13). The two mutations, R248C and S249C, can be found in one amplification region. This region represented 91% of the observed *FGFR3* mutations in our group of bladder cancers. The identity of all of the mutations was confirmed by DNA sequence analysis. Five samples from blood DNA were also sequenced as negative controls. No mutations were found in these samples. Fig. 1 shows that the five detected mutations can easily be identified by SSCA.

All of the 34 mutations were found in the 53 pT_a bladder cancers

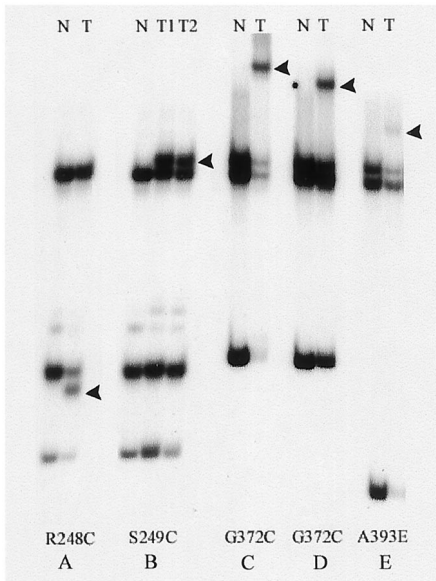

Fig. 1. PCR-SSCA of the *FGFR3* gene. The figure shows examples of the *FGFR3* gene mutations in our population. Paired lanes are normal blood DNA (*N*) and tumor DNA (*T*) from the same patient. *Solid arrowheads*, mutations leading to R248C (patient *A*), S249C (patient *B*), G372C (patient *C*), G372C (patient *D*), and A393E (patient *E*). In patient B, the same activating point mutation (*S249C*) was found in the original (*T1*) and the recurrent tumor (*T2*). In patient C, an additional silent mutation (G to T transition) at nucleotide position 1113, adjacent to codon 372, was observed. The codon and nucleotide numbering corresponds to the cDNA open reading frame of the *FGFR3b* isoform. This isoform is expressed in epithelium and contains two amino acids more than the *FGFR3c* isoform expressed in bone.

Table 1 *Tumor stage and FGFR3 mutation status*

	FGFR3 mutation analysis		
	Wild type	Mutation	P^a
A. Relation between the tumor stage and the *FGFR3* mutation status ($n = 72$)			
Stage			
pT_a	19	34	<0.0001
pT_1	4	0	
$\geq pT_2$	15	0	
Total	38	34	
B. Relation between the highest stage throughout patient's history and the *FGFR3* mutation status ($n = 72$)			
Highest stage			
Only pT_a	12	33	<0.0001
$\geq$Once pT_1	11	1	
$\geq$Once pT_2	15	0	
Total	38	34	

[a] *P*s were determined by two-sided Fisher's exact test calculated for 3 × 2 tables.

Table 2 *Relation between disease recurrence within 12 months in superficial (i.e., pT_a, pT_1) bladder cancer patients and the FGFR3 mutation status ($n = 57$)*

	FGFR3 mutation analysis		
	Wild type	Mutation	P^a
12 months follow-up			
Recurrence-free	9	27	0.004
Recurrence	14	7	
Total	23	34	

[a] *P* was determined by two-sided Fisher's exact test calculated for a 2 × 2 table.

(64%), whereas none of the 4 pT_1 and 15 higher-staged tumors had a mutation in the gene (Table 1A). Furthermore, all of the tumors with a mutation in the *FGFR3* gene were grade 1 or 2. The mutation did not occur in 19 grade 3 tumors ($P < 0.0001$). The stages of these 19 G_3 tumors were pT_a in 3, pT_1 in 1, and $\geq pT_2$ in 15 cases, respectively. When we compared the patient's history (median history of 5.4 years; range, 0.8–26.9 years) with histopathological and *FGFR3* mutation status, we observed that patients with only a pT_a history, had a mutation in 33 (73%) of 45 cases. In patients whose history revealed at least 1 pT_1 tumor, the *FGFR3* mutation occurred in only 1 (8%) of 12 tumors ($P < 0.0001$; Table 1B). These results suggest that the *FGFR3* mutations are linked with a disease course in which lower-staged (*i.e.*, pT_a) tumors prevail.

To further investigate the link between *FGFR3* mutations and stage, we performed a prospective follow-up analysis. Twelve months follow-up after mutation analysis revealed that bladder cancer recurrence was far more frequent in the group of patients whose initial tumors were wild type with respect to the *FGFR3* gene ($P = 0.004$; Table 2). It should be noted that only patients ($n = 57$) diagnosed with superficial bladder cancer (*i.e.*, pT_a, pT_1) at time of mutation analysis were included in this follow-up analysis because patients with invasive tumors underwent cystectomy or radiotherapy. Moreover, in logistic regression analysis with the backward elimination method, using recurrence as a dependent variable and tumor stage, grade, highest stage, and *FGFR3* mutation status as independent variables, the *FGFR3* mutation status remained as the only significant ($P = 0.008$) predictor of recurrence.

We also determined the number of recurrent tumors per patient. In 14 of the 23 patients that were wild type for the *FGFR3* gene, 24 TURs revealed recurrent bladder cancer during the 12 months of follow-up. In 17 of the removed tumors *FGFR3* mutation analysis was performed. No mutations were found. Two patients, both with a wild-type *FGFR3* gene, had already progressed to invasive (*i.e.*, $\geq pT_2$) disease after 3 months. They were removed from subsequent cystoscopical follow-up. On the other hand, in 7 of the 34 patients

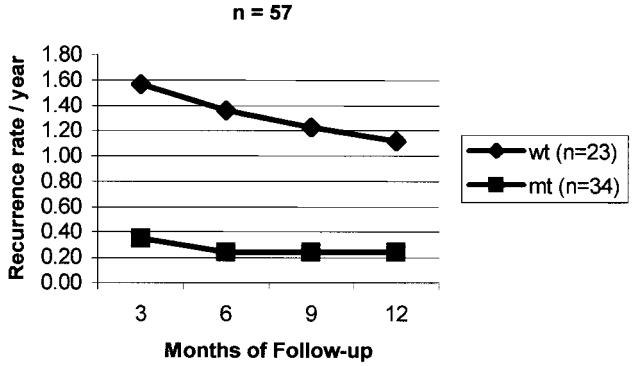

Fig. 2. Recurrence rate of superficial bladder cancer for patients with wild-type and mutant tumors. The recurrence rate per year was calculated at the 3, 6, 9, and 12 months cystoscopical evaluation points. After 12 months, 24 (28%) of 86 cystoscopies were positive in the *FGFR3* wild-type group. This was only 8 (6%) of 136 in the *FGFR3* mutant group. *wt*, wild type *FGFR3* gene; *mt*, mutated *FGFR3* gene; *n*, number of patients who entered cystoscopical follow-up.

with a mutation in their initial tumor, only 8 TURs revealed recurrent bladder cancer (pT_aG_1 in 6 and pT_aG_2 in 2). All of the eight analyzed tumors retained the *FGFR3* mutation that was initially observed. Consequently, 24 (28%) of 86 cystoscopies were positive in the *FGFR3* wild-type group, resulting in a recurrence rate per year of 1.12. In the *FGFR3* mutant group, only 8 (6%) of 136 cystoscopies were positive after 12 months of follow-up, resulting in a recurrence rate per year of 0.24. The recurrence rate per year was calculated at the 3-, 6-, 9-, and 12-month cystoscopical evaluation points (Fig. 2). We also performed a subset analysis of primary and recurrent superficial tumors. The recurrence rates were higher shortly after TUR (3 months) for both patient groups (Fig. 2). The recurrence rates per year were similar if the patients were divided into cases with primary and recurrent cancers (results not shown). In addition, we observed a difference in mutation frequencies between primary and recurrent superficial tumors; when 18 (72%) of 25 primary superficial tumors had a mutation in the *FGFR3* gene, the mutation frequency was only 16 (50%) of 32 for the recurrent tumors.

Discussion

Bladder cancer is a common type of cancer that has a high incidence but, more importantly, requires major clinical attention after initial treatment. Nowadays, patients are monitored intensively by cystoscopy for possible recurrence. Standard practice after TUR of bladder cancer is to screen patients with a cystoscopic examination every 3–4 months for 2 years and every 6–12 months thereafter. On the basis of incidence numbers and recurrence rate (1–4), it can be calculated that >500,000 cystoscopies per year are performed in the United States alone.

Our results show that *FGFR3* mutations occur in nearly 50% of bladder cancers. The mutations were exclusively observed in superficial tumors and absent from invasive carcinomas. Moreover, bladder cancer recurrence rates were dramatically lower for tumors with a mutant *FGFR3* gene. We, therefore, conclude that the *FGFR3* mutations identify a large cohort of bladder cancer patients with favorable disease characteristics. As a consequence, molecular *FGFR3* mutation analysis represents a novel, technically simple, and potentially powerful tool for the adjustment of clinical management in bladder cancer. Nowadays, all patients undergo frequent cystoscopy to monitor their disease. Our results suggest that the frequency of this uncomfortable, invasive, and expensive diagnostic procedure can be reduced considerably in patients with *FGFR3*-positive tumors.

We observed a difference in mutation frequencies between primary and recurrent superficial tumors in our study. It has been noted by others that patients who already have recurrent disease continue to develop recurrences more often than patients with a primary tumor (2, 4). We suggest that this difference in mutation percentage is caused by the fact that patients who are cured after a single TUR, ~30%, do not, by definition, take part in the group of patients with recurrent disease. Combining these observations, we feel that it is likely that the group of patients with primary bladder cancer containing a *FGFR3* mutation encompasses patients who will not develop a recurrence at all. Thus, the *FGFR3* mutation itself, being an indicator of superficial bladder cancer with a low recurrence rate, is at least part of the explanation of the differences between these groups. Capellen *et al.* (10) were the first to report on somatic *FGFR3* mutations in bladder cancer. They found 9 mutations in 26 tumors. Three of the nine mutations occurred in invasive (*i.e.*, $\geq pT_2$) tumors. The stage distribution of the wild-type tumors was not given in their study. In contrast, we found no mutations in invasive tumors. In addition, the correlation between the presence of a mutation and low stage was highly significant in our study. To ensure that no mutations were missed by contamination of benign cells in the invasive tumors, we also performed LOH analysis on these DNA samples. Multiple allelic losses were observed in 17 of 18 evaluable tumors (results not shown). These losses supported the hypothesis that the DNA samples used for mutation and LOH analysis indeed contained DNA that was derived mainly from tumor cells. Thus, the apparent discrepancy between our study and that of Capellen *et al.* (10) remains difficult to explain. It may be attributable to the relatively small number of tumors examined by Capellen *et al.* (10).

The finding that tumors with *FGFR3* mutations are less likely to lead to recurrences can be explained by the hypothesis that such tumors shed cells with a lower frequency than those tumors that do not carry a *FGFR3* mutation. In the seven patients with recurrence in the mutant *FGFR3* group, six of eight tumors occurred at the same region in the bladder, and six of eight recurrent lesions were single growths. In contrast, in most of the 14 patients who had recurrence in the nonmutant group, multiple tumors were found, and these tumors occupied several different sites in the bladder. These preliminary data indeed suggest that superficial bladder tumors without a *FGFR3* mutation shed cells more easily and/or that these cells are better equipped to reimplant into the bladder epithelium. In addition, it may be possible that the *FGFR3*-mutated tumors proliferate not as fast as the nonmutated tumors. Additional experiments are required to test these hypotheses.

Molecular markers for bladder cancer may provide information to be used in clinical decision making. The incidence of *TP53* gene mutations and an altered expression of the *RB* gene product appeared to be much higher in invasive, high-grade bladder cancers than in superficial low-grade ones (14, 15). These reports suggest that these molecular markers are relatively late events in disease pathogenesis and identify tumors with aggressive biological behavior. The clinical value of these two tumor suppressor genes is of importance to patients presenting with invasive bladder cancer (15, 16) and for prediction of progression in patients with high-grade superficial bladder cancer. Barton Grossman *et al.* (5) advocated stratification of pT_1 bladder cancer patients based on *TP53* and *RB* status. Their results suggest that patients with normal protein expression for both genes can be managed conservatively, whereas patients with alterations in one, and particularly in both genes, require more aggressive treatment to prevent progression to invasive disease (5). In contrast, chromosome 9q deletions, determined by LOH analysis, are found with similar frequency in superficial and invasive bladder cancer (17, 18) and, therefore, cannot be used for prognostic purposes. The *FGFR3* gene is the first gene identified in bladder cancer to be mutated selectively in

those cancers that are characterized by favorable clinical parameters. Future studies should determine whether a combination of *TP53*, *RB*, and *FGFR3* gene analyses could lead to a more accurate prediction of the disease course with regard to recurrence and progression. Furthermore, treatment strategies may also be determined based on these molecular markers.

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