ORIGINAL RESEARCH
Urooncology

Doi: 10.4274/jus.galenos.2025.2025-9-6
J Urol Surg

TRK Expression in Urothelial Bladder Cancer: A Single-center Cohort Study

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What's known on the subject? and What does the study add?

Neurotrophic receptor tyrosine kinase (NTRK) gene fusions represent rare but actionable alterations across solid tumors, with tropomyosin receptor kinase (TRK) inhibitors showing high efficacy in fusion-positive cases. However, the prevalence and clinical impact of TRK expression and NTRK fusions in bladder cancer are poorly defined, with existing reports providing inconsistent results. This study demonstrates that TRK expression is very uncommon and that NTRK fusions are absent in a cohort with metastatic urothelial carcinoma. These findings suggest limited relevance of TRK-targeted therapies in unselected bladder cancer populations, while underscoring the importance of systematic molecular profiling.

Abstract

Objective: Urothelial carcinoma is an aggressive malignancy with limited therapeutic options in the metastatic setting. Neurotrophic receptor tyrosine kinase (NTRK) gene fusions are actionable alterations in several solid tumors; however, their prevalence and clinical relevance in bladder cancer remain unclear.

Materials and Methods: A retrospective analysis was performed on cystectomy specimens from 60 patients with metastatic urothelial carcinoma who were treated between 2009 and 2021 at a single tertiary center. Tropomyosin receptor kinase (TRK) protein expression was evaluated by immunohistochemistry using a pan-TRK antibody. Positive cases were further analyzed for NTRK1/2/3 fusions using a real-time polymerase chain reaction assay detecting 109 known variants. Clinicopathological parameters and survival outcomes were reviewed.

Results: The cohort included 55 males (91.7%) and 5 females (8.3%), with a median age of 62 years. At cystectomy, all tumors were high-grade, with pathological stages ranging from pT1 to pT4a. Median overall survival was 49.5 months, and median survival after progression to metastatic disease was 19.5 months. Pan-TRK positivity was observed in 2 of 60 cases (3.3%). Molecular analyses of these samples revealed no NTRK fusions, indicating isolated TRK protein overexpression without gene rearrangements.

Conclusion: TRK expression was rare, and NTRK fusions were absent in this cohort with metastatic urothelial carcinoma. These results suggest that TRK-targeted therapies are unlikely to benefit unselected bladder cancer populations. Nonetheless, systematic molecular profiling remains essential for identifying patients with rare targetable alterations, while TRK signaling does not appear to represent a major oncogenic driver in urothelial carcinoma.

Keywords: Bladder cancer, urothelial carcinoma, tropomyosin receptor kinase, TRK

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Received: 18.09.2025 **Accepted:** 28.10.2025 **Epub:** 19.06.2026

Cite this article as: Akar E, Baytekin HF, Gemci ÖD, Şahin S, Altınay S, Yararbaş K, Tural D. TRK expression in urothelial bladder cancer: a single-center cohort study. J Urol Surg. [Epub Ahead of Print]

Introduction

Urothelial carcinoma is the ninth most common cancer worldwide (1). Although only 5% of patients present with metastatic disease at diagnosis, approximately 40% of those initially diagnosed at an early stage eventually progress to metastatic disease during the course of their disease (2). Platinum-based chemotherapy remains the standard first-line treatment for stage IV bladder cancer, with a median overall survival (OS) of approximately 15 months (3). Among patients who experience disease progression after initial chemotherapy, the expected survival is markedly poor, ranging from 5 to 7 months (4). In recent years, the introduction of immune checkpoint inhibitors into routine clinical practice has expanded treatment options in both the first- and second-line settings for stage IV bladder cancer. Particularly among patients who achieve a response, these agents have been associated with durable remissions and prolonged survival (5). However, the objective response rates (ORRs) observed in clinical trials of immunotherapeutics have been relatively modest, ranging from 17% to 28% (6-9). Consequently, elucidating alternative molecular mechanisms in patients who do not respond to checkpoint inhibition or develop secondary resistance is essential for developing new therapeutic strategies (10). The tropomyosin receptor kinase (TRK) family (TRKA, TRKB, and TRKC) comprises neurotrophin receptors that play key roles in neural development, but they also function as oncogenic proteins implicated in carcinogenesis. Genetic alterations, most notably neurotrophic receptor tyrosine kinase (NTRK) gene fusions, lead to ligand-independent activation of TRK receptors, thereby promoting cellular proliferation and survival (11). Clinical trials investigating TRK-targeted tyrosine kinase inhibitors, such as larotrectinib and entrectinib, have demonstrated striking response rates (ORR approximately 75%) in tumors harboring NTRK fusions (12). The prevalence and biological relevance of NTRK fusions and TRK expression in bladder cancer remain poorly characterized. In one study evaluating TRK expression in bladder cancer, TRKB positivity was observed at relatively high frequencies, ranging from 46.7% to 76.9% (13). Another study of upper tract urothelial carcinoma reported TRKC expression in 54.2% of cases (14). In light of these data, the present study aimed to investigate TRK expression and NTRK gene fusions in cystectomy specimens from patients with metastatic (stage IV) bladder cancer.

Materials and Methods

Patients

This study used archived cystectomy specimens from patients diagnosed with metastatic bladder cancer who were followed at the Medical Oncology Department of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital between January 1, 2009, and January 1, 2021. Demographic and clinical data were obtained by reviewing patient files and digital medical records.

Immunohistochemistry and Pathological Evaluation

Archived formalin-fixed paraffin-embedded (FFPE) tumor tissues and slides from cystectomy specimens were re-evaluated to confirm the diagnosis, the pathological T-stage, and the histological grade. All histopathological and immunohistochemical evaluations were performed independently by two pathologists blinded to clinical data. For each patient, the paraffin block that best represented the morphological characteristics of the tumor and had the highest T-stage was selected. 4-µm-thick sections were cut, mounted on lysine-coated slides, and processed for immunohistochemistry (Figure 1). All immunohistochemical procedures were performed using the fully automated Ventana Benchmark XT system (Ventana Medical Systems, Tucson, AZ, USA). Following standard deparaffinization, rehydration, and antigen retrieval (CCV1 antigen retrieval solution, 64 minutes at 100 °C), sections were incubated for 1 hour at 37 °C with a recombinant immunoglobulin G anti-pan-TRK antibody (ab181560, clone EPR17341, Abcam, Cambridge, MA, USA) at a 1:500 dilution. Detection was performed using the OptiView DAB Immunohistochemistry Detection Kit (Roche Diagnostics/Ventana Medical Systems, Tucson, AZ, USA) for 10 minutes, followed by amplification with the OptiView Amplification Kit (Roche Diagnostics/Ventana Medical Systems, Tucson, AZ, USA) for 30 minutes. Slides were then counterstained with hematoxylin, dehydrated through graded alcohols and xylene, and mounted for microscopic evaluation. The immunohistochemical staining results were independently assessed by two pathologists blinded to clinical data. An external positive control was established using cerebellar tissue, whereas an internal positive control was verified using ganglion cells.

NTRK Fusion Analysis

The presence of NTRK gene fusions in tumor tissue was assessed using the AmoyDx® NTRK Gene Fusions Detection Kit (Amoy Diagnostics Co., Ltd., Xiamen, China). Analyses were performed on total RNA isolated from FFPE tumor samples, using kits optimized for FFPE material, in accordance with the manufacturer's instructions. Extracted RNA was reverse transcribed into cDNA during the kit's reverse transcription step. Real-time polymerase chain reaction amplification was subsequently carried out using specific primers and fluorescent probes targeting 109 known fusion variants of NTRK1, NTRK2, and NTRK3. Reactions were performed in a 40 µL volume under the manufacturer's recommended conditions (initial denaturation at 95 °C followed by 47 three-step cycles).

Each run included manufacturer-supplied positive controls and no-template controls. Amplification curves were analyzed using fusion-specific signal and reference gene signal fluorescence channels. Samples with Ct ≤25 were considered positive for the corresponding NTRK fusion, whereas samples with Ct >25 were classified as negative or below the limit of detection. RNA quality was verified through amplification of the internal control gene provided in the kit.

Statistical Analysis

Descriptive statistics and frequency analyses were performed. Survival analyses, including OS and progression-free survival (PFS), were conducted using the Kaplan-Meier method. Statistical analyses were performed using SPSS version 23.0 (IBM Inc.). Two-sided p-values <0.05 were considered statistically significant.

Ethical Approval and Funding

The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2019-18, date: 16.09.2019). The study was supported by the scientific research fund of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital.

Results

A total of 60 patients were included in the study, comprising 55 men (91.7%) and 5 women (8.3%). The median age at diagnosis was 62 years (range: 35-81). Based on the initial transurethral resection (TUR), the pathological stage was pTa in 8 patients (13.3%), pT1 in 23 patients (38.3%), pT2a in 18 patients (30%), and pT2b in 11 patients (18.3%). At diagnosis, 14 patients (23.3%) had low-grade tumors, whereas 46 (76.7%) had high-grade disease. Cystectomy was performed for different clinical indications. These included palliative or salvage surgery (7 patients, 11.7%), invasive disease detected at diagnostic TUR (28 patients, 46.7%), radiologically identified invasive tumors, ≥pT2 (5 patients, 8.3%), and progression to invasive disease during TUR follow-up (20 patients, 33.3%). Pathological evaluation of cystectomy specimens revealed pT1 in 4 patients (6.7%), pT2a in 3 patients (5%), pT2b in 7 patients (11.7%), pT3a in 10 patients (16.7%), pT3b in 9 patients (15%), and pT4a in 27 patients (45%). All cystectomy specimens demonstrated high-grade tumors. Sites of recurrence or metastasis included pelvic masses in 9 patients (15%), lymph node metastases in 7 patients (11.7%), bone metastases in 21 patients (35%), lung metastases in 24 patients (40%), liver metastases in 15 patients (25%), and intracranial lesions in 3 patients (5%). Clinical and pathological

Table 1. Clinical and pathological characteristics of the patients

Variable	n	%
Sex		
Male	55	91.7
Female	5	8.3
Age		
<65	36	60.0
≥65	24	40.0
Pathological T-stage at diagnosis (TUR)		
pTa	8	13.3
pT1	23	38.3
pT2a	18	30.0
pT2b	11	18.3
Grade at diagnosis		
Low grade	14	23.3
High grade	46	76.7
Indication for cystectomy		
Palliative/salvage	7	11.7
Invasive tumor at TUR	28	46.7
Invasive tumor on imaging	5	8.3
Progression during follow-up	20	33.3
Pathological T-stage at cystectomy		
pT1	4	6.7
pT2a	3	5.0
pT2b	7	11.7
pT3a	10	16.7
pT3b	9	15.0
pT4a	27	45.0
Pathological grade at cystectomy		
High grade	60	100
Nodal stage at cystectomy		
N0	41	68.3
N1	6	10.0
N2	12	20.0
N3	1	1.7
Sites of recurrence/metastasis		
Pelvic mass	9	15.0
Distant lymph node	7	11.7
Bone	21	35.0
Lung	24	40.0
Liver	15	25.0
Intracranial	3	5.0

TUR: Transurethral resection

characteristics of the patients are summarized in Table 1. The median OS for the entire cohort was 49.5 months. In patients who underwent cystectomy for reasons other than primary metastatic disease (excluding those who underwent palliative or salvage surgery), the median PFS was 19 months (range: 1-81 months). After progression to metastatic disease, the median OS was 19.5 months. Immunohistochemical evaluation with the anti-pan-TRK antibody revealed no staining in 58 patients (96.7%), while positive staining was observed in 2 patients (3.3%) (Figures 1c and 1d). Both positively stained specimens exhibited a cytoplasmic staining pattern; one showed approximately 1% positivity, while the other showed 5% positivity. Non-neoplastic urothelium, T and B lymphocytes, stroma, and muscle tissue were negative for TRK expression. Subsequent NTRK fusion analysis of tumor samples from the two patients with immunohistochemically positive TRK expression did not reveal any NTRK fusions. Therefore, these cases were considered to have TRK protein overexpression without NTRK gene fusions.

Discussion

In advanced or metastatic bladder cancer, treatment options are limited for patients who progress after cisplatin-based chemotherapy or immune checkpoint inhibitor therapy. Given the aggressive nature of the disease and its dismal prognosis, molecular profiling and personalized therapeutic approaches are becoming increasingly important (15). TRK proteins, encoded by the NTRK genes, are receptor tyrosine kinases that acquire oncogenic potential through genetic alterations, most notably gene fusions. These alterations activate intracellular signaling pathways such as the mitogen-activated protein kinase and protein kinase B pathways, thereby promoting cellular proliferation and carcinogenesis (11). Clinical trials investigating anti-TRK tyrosine kinase inhibitors (particularly larotrectinib and entrectinib) in solid tumors harboring NTRK fusions have demonstrated remarkable ORRs and durable survival benefits (16,17). NTRK fusions are relatively rare in adult tumors, with an overall prevalence of approximately 0.31% (18). In a large-scale study conducted at Memorial Sloan Kettering Cancer Center (MSKCC), NTRK fusions were detected in 87 of 33,997 patients. The highest frequencies were observed in salivary gland carcinoma (5.08%), thyroid carcinoma (2.28%), sarcomas (0.68%), colorectal cancer (0.31%), lung adenocarcinoma (0.23%), pancreatic adenocarcinoma (0.34%), cholangiocarcinoma (0.25%), breast cancer (0.13%), and melanoma (0.36%) (19). In contrast, urothelial bladder cancer has not been reported to be NTRK fusion-positive in most molecular studies. However, these studies often lack detailed information regarding the proportion of bladder cancer cases included in their cohorts (19,20). Consequently, the prevalence of TRK expression and NTRK fusions in bladder cancer remains poorly defined. In the only available report, Lai et al. (13) demonstrated immunohistochemical positivity for TRKB in commercially obtained bladder cancer specimens, with positivity rates of 76.9%, 46.7%, and 63.6% in grades I, II, and III, respectively. However, these findings were inconsistent with the broader

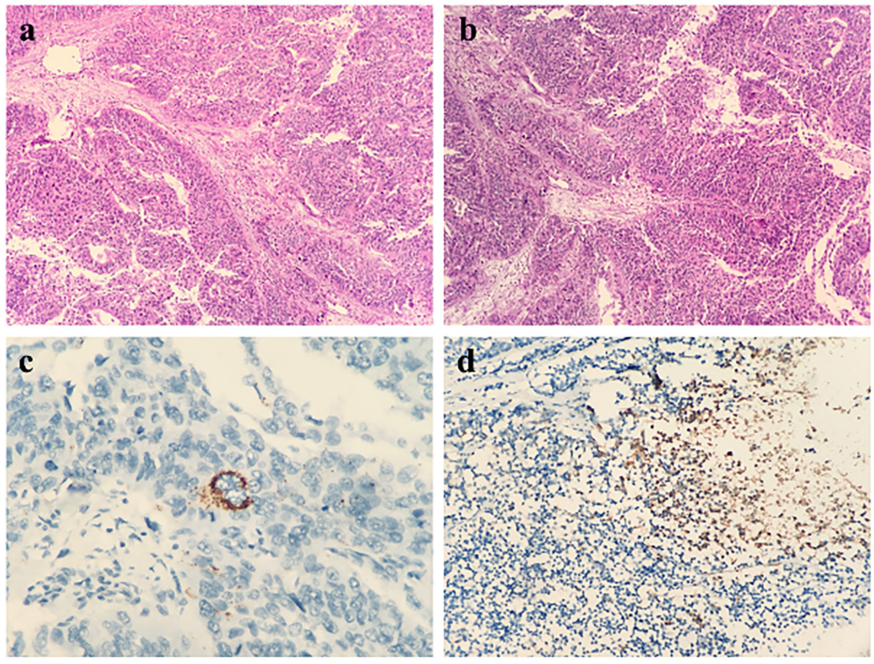

Figure 1. a-b: Representative cystectomy specimen and hematoxylin and eosin staining, c-d: Immunohistochemical staining with anti-pan tropomyosin receptor kinase antibody (c: negative and d: positive cases)

literature, and the authors themselves suggested potential artifacts related to tissue preparation or antibody cross-reactivity. Similarly, Lim et al. (14) reported TRKC expression in 54.2% of upper tract urothelial carcinoma cases, although fusion analysis was not performed to validate these results. In our study, TRK expression was detected immunohistochemically in 3.3% of cases (2/60), but no NTRK fusions were identified by molecular analysis. These findings are consistent with the results of large-scale molecular studies, further supporting the rarity of NTRK fusions in bladder cancer. For detecting NTRK fusions, next-generation sequencing (NGS) platforms that analyze DNA or RNA are generally recommended as the gold standard. Nevertheless, due to the high cost and time required for molecular testing, pan-TRK immunohistochemistry has been suggested as a practical screening tool in patients with advanced cancer (21). Several studies have evaluated the sensitivity and specificity of pan-TRK immunohistochemistry. Hechtman et al. (22) reported immunohistochemical positivity in 20 of 21 NTRK fusion-positive cases. Rudzinski et al. (23) demonstrated a sensitivity of 97% and a specificity of 98% for pan-TRK staining in pediatric mesenchymal tumors. In the MSKCC series, the sensitivity of immunohistochemistry was 96.2% for NTRK1/2 fusions but only 79.4% for NTRK3 fusions, while specificity across all tumor types was 81.1%. Specificity was particularly high (100%) in cancers not typically associated with TRK expression, such as colorectal cancer, lung cancer, pancreatobiliary tumors, and melanoma. Conversely, in tumors of neuronal origin, such as gliomas and neuroblastomas, strong background staining in normal tissue occasionally resulted in false-positive interpretations (19).

Study Limitations

Thus, pan-TRK immunohistochemistry may serve as a useful screening method, with positive cases requiring confirmatory molecular testing by NGS to verify the presence of NTRK fusions (24). Our study demonstrated that TRK expression is exceedingly rare in urothelial bladder cancer, in line with findings from other common tumor types. Limitations of our study include the relatively small sample size, retrospective design, and reliance on archived pathology specimens.

Conclusion

These findings suggest that TRK-targeted therapies are unlikely to represent a meaningful treatment strategy in unselected bladder cancer populations. Nevertheless, systematic evaluation of TRK expression and NTRK fusions remains warranted, as identifying patients harboring these rare alterations could enable the use of highly effective targeted therapies. Moreover, the negative findings in this study contribute to refining precision oncology approaches by ruling out TRK signaling as a major oncogenic driver in bladder cancer.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2019-18, date: 16.09.2019).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.F.B., Ö.D.G., S.Ş., S.A., D.T., Concept: E.A., D.T., Design: E.A., D.T., Data Collection or Processing: E.A., H.F.B., Ö.D.G., S.A., K.Y., Analysis or Interpretation: E.A., D.T., Literature Search: E.A., Writing: E.A., D.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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