Original Article

Significance of the FGFR3 mutation in Chinese patients with bladder cancer

Lanxiang Hao[1#], Jiang Fang[2,3#], Ran Xu[4], Shuo Liu[4], Guangcheng Luo[3,4], Xinjun Wang[3,4]

[1]Department of Pathology, Zhongshan Hospital Xiamen University, School of Medicine, Xiamen University, Xiamen, China; [2]Department of Thyroid and Breast Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong, China; [3]The School of Clinical Medicine, Fujian Medical University, Fuzhou, China; [4]Department of Urology, Zhongshan Hospital Xiamen University, School of Medicine, Xiamen University, Xiamen, China

Contributions: (I) Conception and design: G Luo, X Wang, J Fang; (II) Administrative support: G Luo, X Wang; (III) Provision of study materials or patients: G Luo, X Wang, L Hao, J Fang; (IV) Collection and assembly of data: L Hao, J Fang; (V) Data analysis and interpretation: L Hao, J Fang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work and should be considered as co-first authors.

Correspondence to: Xinjun Wang, MD, PhD; Guangcheng Luo, MD, PhD. The School of Clinical Medicine, Fujian Medical University, Fuzhou, China; Department of Urology, Zhongshan Hospital Xiamen University, School of Medicine, Xiamen University, 201 South Hubin Road, Xiamen 361004, China. Email: wxj@xmu.edu.cn; lgch@xmu.edu.cn.

Background: Bladder cancer (*BC*) is the 10th most common malignancy worldwide. The high recurrence rates of *BC* lead to significant treatment challenges. With the development of molecular biology techniques, research has shown that gene abnormalities are closely related to the occurrence and development of *BC*. This study analyzed the detection results of gene mutations in the tissue samples of *BC* patients and explored the relationship between fibroblast growth factor receptor 3 (*FGFR3*) and the prognosis and recurrence of *BC*.

Methods: This study examined 82 Chinese patients with BC. Of these patients, 34 underwent radical cystectomy (*RC*), and 48 underwent transurethral resection with intravesical instillation. In addition, multi-gene panel targeted next-generation sequencing (*NGS*) of the samples was performed.

Results: The mutational spectra revealed that *C* > *T* was the most common base substitution. Single nucleotide polymorphism (*SNP*) and deletion (*DEL*) were the common variant types in our cohort. The top 10 mutant genes were *ROS1* (37%), *PIK3CA* (35%), *FGFR3* (34%), *BRAF* (34%), *ERBB2* (32%), *ALK* (27%), *RET* (27%), *NTRK1* (24%), *MET* (23%), and *EGFR* (18%). *FGFR3* mutations were detected more frequently in non-muscle-invasive bladder cancer (stages 0a, I) patients than in muscle-invasive bladder cancer (stage II, III, and IV) patients. The top 3 altered types of *FGFR3* were p.Ser249Cys, p.Tyr375Cys, and p.Arg248Cys.

Conclusions: This study examined the mutated types and frequency of *FGFR3* and the prognosis of Chinese *BC* patients with *FGFR* mutations. We hope that our findings will enable clinical individualization strategies for *BC* patients to be optimized.

Keywords: Bladder cancer (*BC*); fibroblast growth factor receptor 3 (*FGFR3*); next-generation sequencing (*NGS*); mutation types

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Introduction

Bladder cancer (*BC*) is the tenth most common malignancy in the world, with 570,000 new cases and 210,000 reported globally in 2020, placing a massive burden on the healthcare system (1). In terms of the pathological type, >90% of *BCs* are urothelial cell carcinomas, and about 5% are squamous cell carcinomas, while adenocarcinomas are rare (2). In the clinic, about 75% of newly diagnosed patients have non-muscle invasive *BC*. The common treatments for non-muscle invasive BC include transurethral resection, followed by intravesical chemotherapy or Bacillus Calmette Guerin immunotherapy. After treatment, the long-term survival rate of patients is reasonable, but the recurrence rate is high, and 10–15% of patients show disease progression. Muscle invasive *BC*, which is highly malignant, prone to lymph node metastasis, and has a low 5-year survival rate, accounts for about 25% of *BC* cases (3-5). The main treatment for muscle invasive *BC* rely on radical cystectomy and lymph node dissection, different urinary diversion performed according to the situation. In addition, local radiotherapy or systemic adjuvant chemotherapy can be used if local progression or distant metastasis occurs. In recent years, the efficacy of surgical treatment, immunotherapy, and combined chemoradiotherapy in the treatment of *BC* has progressed (6-8). However, the prognosis of invasive and metastatic *BC* patients has not been significantly improved due to limited understanding of the biological mechanisms of disease recurrence and progression. Thus, an in-depth exploration of the genes related to malignant tumor progression would help to better predict the progression of *BC* patients and provide new ideas and directions for diagnosis and treatment (9). Some FGFR inhibitors are becoming new treatment options for metastatic urothelial cancer (10).

FGFR3 is a tyrosine-protein kinase family and transmembrane tyrosine kinase receptor with autophosphorylation activity. After binding to fibroblast growth factor, it can activate various downstream signaling pathways, which mainly include the *PI3K/AKT* and *Ras/Raf/MAPK* signaling pathways (11-13). Some centers in Europe have studied the mutation frequency and mutation site of *FGFR3* gene in bladder cancer (14,15). Several studies have shown that the *FGFR3* mutation is significantly associated with low-grade and low-stage *BC* and is associated with low-grade and low-stage papillary *BC* (16). van Rhijn *et al.* found an association between mutations and low-grade *BC* (17). Hernández *et al.* found that the *A393E* mutation has a high frequency in bladder tumors with low malignant potential (15). Rizzo *et al.*'s study found that 150 of the 358 patients with upper urinary tract urothelial cancer (UTUC) had FGFR3 mutations, and patients with FGFR3 mutations had a longer overall survival than wild-type patients who received radical surgery (18). In addition, FGFR3 mutations were more frequent in low-grade UTUCs with early-stage disease (18).

This study analyzed the detection results of gene mutations in the tissue samples of *BC* patients and explored the relationship between *FGFR3* and the prognosis and recurrence of *BC*. We present this article in accordance with the MDAR reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-247/rc).

Highlight box

Key findings

- We obtained the mutation frequency and type of *FGFR3* gene in the Chinese bladder cancer population through next-generation sequencing, which is beneficial to the treatment of bladder cancer.

What is known and what is new?

- The frequency of *FGFR3* mutations is high in *BC*. Transurethral resection with intravesical chemotherapy are typical treatments for *BC*.
- This was the first study to focus on the outcomes of *FGFR3* mutations and transurethral resection with intravesical therapy.

What is the implication, and what should change now?

- *BC* patients who undergo transurethral resection with intravesical therapy are more likely to benefit from combined anti-FGFR3 therapy. Further large-scale studies need to be conducted to explore the use of this combination strategy in the treatment of *BC*.

Methods

This study is a retrospective study of bladder cancer patients treated at Zhongshan Hospital Xiamen University between January 2017 and December 2019. These patients have all received multi-gene panel targeted next-generation sequencing. We used the results of gene mutations in tissue samples of BC patients to explore the relationship between FGFR3 and BC prognosis and recurrence.

Clinical samples

A total of 82 Chinese patients from the Zhongshan Hospital Xiamen University were enrolled in this study. These patients contain both non-muscle-invasive bladder cancer patients and muscle-invasive bladder cancer patients, and include all clinical stages (*Table 1*). Of these patients, 34

Table 1 Basic clinical characteristics of the BC patients

Characteristic	No. of patients
All patients	82
Gender, n (%)	
Female	13 (15.85)
Male	69 (84.15)
Age, year, median [range]	69 [36–88]
Stage, n (%)	
0a	41 (50.00)
I	4 (4.88)
II	12 (14.63)
III	20 (24.39)
IV	5 (6.10)
Smoking, n (%)	
Non-smoker	49 (59.76)
Smoker/ex-smoker	33 (40.24)
Treatment, n (%)	
Radical cystectomy	34 (41.46)
Transurethral resection with intravesical therapy	48 (58.54)

BC, bladder cancer.

underwent radical cystectomy (*RC*), and 48 underwent transurethral resection with intravesical therapy. The tumor samples were obtained from the *BC* surgery, and the tissue was paraffin-embedded after the surgery. All the samples were checked for quality control and met the requirements for gene sequencing. This study was approved by the Ethics Committee of Zhongshan Hospital Xiamen University (No. 2022-181). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all the study participants.

NGS and annotation

Genomic DNA was extracted from the formalin-fixed, paraffin-embedded tissue sections. Sonication was then performed to obtain 200-bp DNA fragments. The Roche SeqCap EZ Exome V3 (Roche NimbleGen Inc., Basel, Switzerland) and TruePrep DNA Library Prep Kit (version 2) were used for Illumina (#TD501, Vazyme, Nanjing, China) sequencing to capture the target DNA fragments. Multi-gene panel targeted next-generation sequencing (*NGS*) (Tongshu BioTech, Shanghai, China) was performed using the Illumina HiSeq machine to generate paired-end sequence data. Subsequently, the received sequencing results were compared using *BWA* software. Corrections were compared using the Genome Analysis Toolkit, and *CNVKIT* was used to detect copy number variations in the sequencing data. Finally, somatic mutations were converted into MAF format and visualized using R maftools (https://bioconductor.org/packages/release/bioc/vignettes/maftools/inst/doc/maftools.html).

Statistical analysis

The results are presented as the mean ± standard deviation, and the Mann-Whitney U test, Wilcoxon signed-rank test, and a Spearman correlation analysis were used in this study. Relapse-free survival (*RFS*) was determined using the Kaplan-Meier method. A 2-tailed P value of <0.05 was considered statistically significant in this study. Multivariate analysis was done using Cox regression analysis after adjusting for other prognostic factors (P value <0.05 was considered significant). All the statistical analyses were conducted using IBM SPSS Statistics V.25.0, R V.3.5.1, and GraphPad Prism Software V.8.0.

Results

Patient characteristics

A total of 82 BC patients who met the inclusion criteria were enrolled in this study. The available characteristics of the patients are set out in *Table 1* and Table S1. All the participants were aged between 36 and 88 years (median age: 69 years), and 13 (15.85%) of the patients were female and 69 (84.15%) were male. Among the 82 patients, 41 (50.00%), 4 (4.88%), 12 (14.63%), 20 (24.39%), and 5 (6.10%) patients had clinical stages 0a, I, II, III, and IV, respectively. Among the patients, 33 (40.24%) were smokers/ex-smokers and 49 (59.76%) were non-smokers. Surgery was performed in all patients.

The mutational profile of the BC patients

Multi-gene panel targeted *NGS* was performed on samples from the 82 *BC* patients to detect somatic mutations (available online: https://cdn.amegroups.cn/static/public/10.21037tau-23-247-1.xlsx). The average

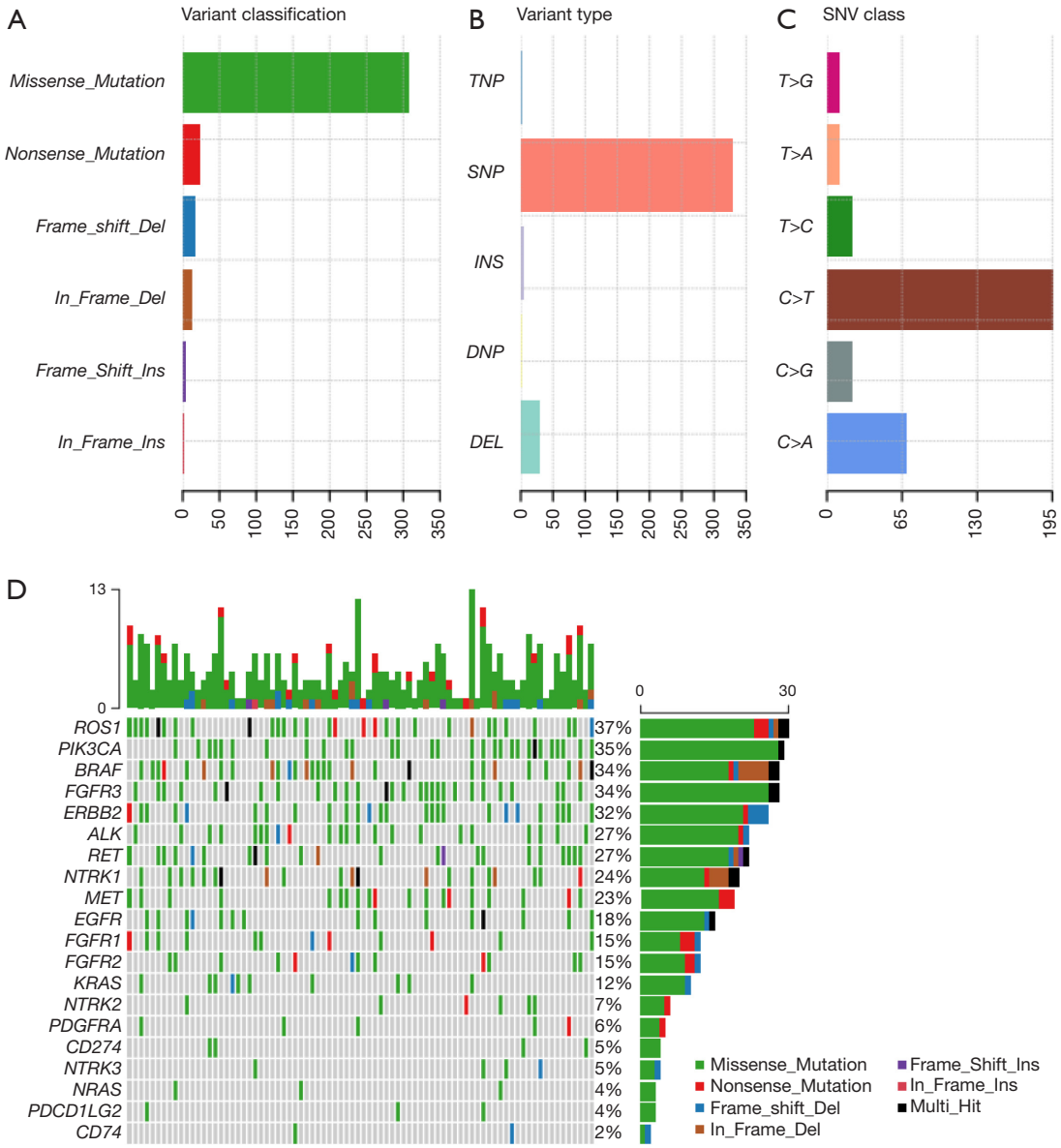

Figure 1 Mutation spectrum of the BC patients. (A) Variant classification summary; (B) number of variants; (C) SNV class; (D) mutation spectrum of the BC samples. SNV, single nucleotide variant; BC, bladder cancer; TNP, triple nucleotide polymorphism; SNP, single nucleotide polymorphism; INS, insertion; DNP, double nucleotide polymorphism; DEL, deletion.

coverage depth for the samples was ×2,000. We then analyzed a total of 82 mutation profiles using *NGS* detection. The mutational spectra revealed that *C* > *T* was the most common base substitution, and *SNP* and *DEL* were the common variant types in our cohort (*Figure 1A*,*1B*). The variant classification revealed that that the missense mutation was the most common type of mutation, followed by the nonsense nutation, frame-shift deletion, in-frame deletion, frame-shift insertion, and in-frame insertion (*Figure 1C*). As *Figure 1D* shows, the top 10 mutant genes were *ROS1* (37%), *PIK3CA* (35%), *FGFR3* (34%), *BRAF* (34%), *ERBB2* (32%), *ALK* (27%), *RET* (27%), *NTRK1* (24%), *MET* (23%), and *EGFR* (18%).

Correlations between the FGFR3 mutations and patients' clinical characteristic

The mutation frequency of *FGFR3* in male patients (22/69,

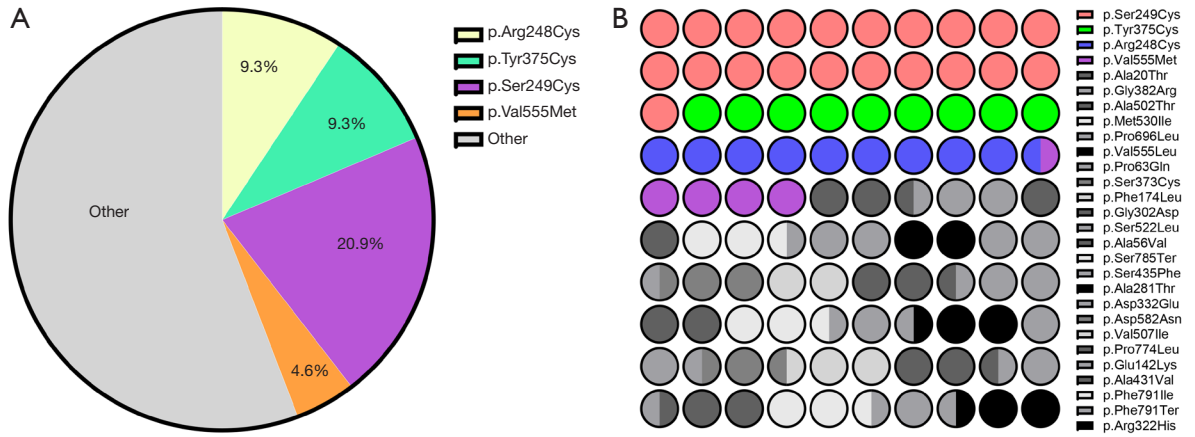

Figure 2 FGFR3 mutations in BC patients. (A) The pie charts display the distribution of frequencies and positions of the FGFR3 mutations in BC patients. (B) FGFR3 mutation status of BC patients. FGFR3, fibroblast growth factor receptor 3; BC, bladder cancer.

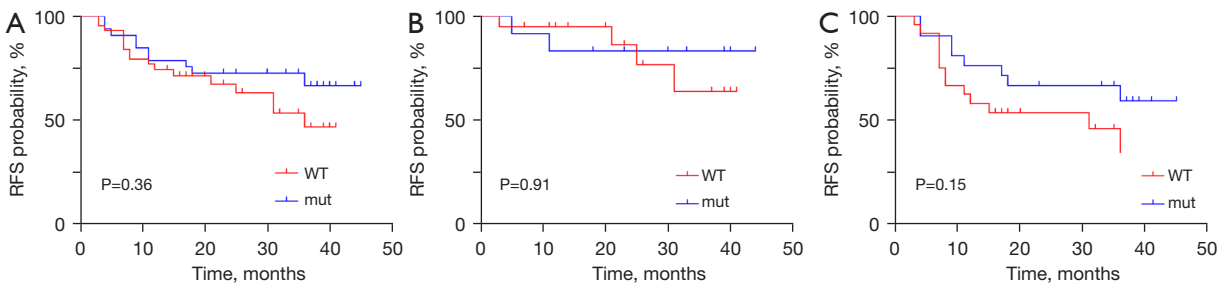

Figure 3 Kaplan-Meier survival curves for the BC patients. (A) RFS of the BC patients (FGFR3 mutations *vs.* non-mutations); (B) RFS of the BC patients with radical cystectomy (FGFR3 mutations *vs.* non-mutations); (C) RFS of the BC patients with transurethral resection with intravesical therapy (FGFR3 mutations *vs.* non-mutations). RFS, relapse-free survival; BC, bladder cancer; FGFR3, fibroblast growth factor receptor 3; WT, wild type.

31.88%) was similar to that in female patients (5/13, 38.46%). Patients under the median age (12/40, 30.0%), and elderly patients (≥ median age) (15/42, 35.71%) had similar mutation frequencies. In terms of the clinical stage, *FGFR3* mutations were detected more frequently in stage 0a and I (non-muscle-invasive bladder cancer) patients (35.56%, 16/45) than stage II, III, and IV (muscle-invasive bladder cancer) patients (29.73%, 11/37). The proportions were similar in patients with a history of smoking and non-smokers (15/49 smokers, 30.61%; non-smokers 12/33, 36.36%). The top 3 altered types were p.Ser249Cys, p.Tyr375Cys, and p.Arg248Cys (*Figure 2A,2B*).

Correlations between the FGFR3 mutations and patient outcomes

Of the 82 patients, 78 (95.12%; 78/82) had recurrence-free survival data, of whom 34 (41.46%; 34/82) underwent *RC* and 48 (58.54%; 48/82) underwent transurethral resection with intravesical therapy. We also analyzed the association between *FGFR3* mutations and post-treatment RFS. After treatment, no significant difference was observed in the RFS of the *FGFR3* mutation patients and the non-mutation patients [P=0.36; hazard ratio (HR) =1.59, 95% confidence interval (CI): 0.74 to 3.38] (*Figure 3A*). Similarly, there was no RFS difference between the *FGFR3* mutation patients and non-mutation patients in the *RC* cohort (P=0.91; HR =1.44, 95% CI: 0.28 to 7.31) (*Figure 3B*). Intriguingly, transurethral resection with intravesical therapy appeared to be more effective in patients with *FGFR3* mutations (P=0.15; HR =1.87, 95% CI: 0.79 to 4.42) (*Figure 3C*). In the multivariable analysis, the RFS is worse with age (P=0.016), other factors were no statistical difference (Table S2).

Discussion

BC is one of the most common malignant tumors of the urinary system. According to global tumor epidemiological statistics, there are about 573,278 new cases worldwide every year (1). The occurrence of *BC* seriously affects the survival of patients. The typical clinical treatment methods mainly include surgery, chemotherapy, radiation therapy, and biological therapy (6). There are many clinical treatment methods for *BC*; however, various side effects, such as bladder irritation, occur. In addition, *BC* has a high recurrence rate, and once it recurs, it is often accompanied by metastasis, and tumor invasiveness and malignancy are also high (19). Thus, research on the prevention and treatment of *BC* urgently needs to be conducted.

Cappellen *et al.* were the first to report the *FGFR3* mutation in *BC* (20). Of the 26 *BC* patients examined by Cappellen *et al.*, 9 had the *FGFR3* mutation, and the mutation sites were *R248C*, *S249C*, *G372C*, and *K652E*. All of these mutations are consistent with germline mutations. Additional mutation sites in *BC* have also been found in skeletal dysplasia (21). However, the frequency and distribution of *FGFR3* mutations differ. *Codons 248*, *249*, and *375* are the most common mutations in *BC*. Among these mutations, *codon 249* mutations account for 70% (14). The mutation frequency of the *FGFR3* in *BC* is about 17.86%, and the *FGFR3* mutation is associated with low-grade and low-stage *BC* and the generation of cysteine residues in the first part of the extracellular domain of the transmembrane region, such as *S249C*, *Y375C*, *R248C*, and *G372C* (22). This study found that *FGFR3* was more frequent in stage 0a and I patients than stage II, III, and IV patients. The top 3 altered types of *FGFR3* were *p.Ser249Cys*, *p.Tyr375Cys*, and *p.Arg248Cys*.

Several studies have shown that *FGFR3* expression is abnormal in *BC* patients. Matsumoto *et al.* reported that 49% of *BCs* expressed *FGFR3* protein at moderate to high levels, but found no correlation between stage and grade (23). In another study, *FGFR3* overexpression was associated with low-stage and low-grade tumors (24). Compared to the normal ureter and bladder control group, the *FGFR3* protein was overexpressed in the tumor group. Increased *FGFR3* protein expression was associated with *FGFR3*-mutated *BCs*, and non-invasive *BCs* had higher mutation frequencies than invasive *BCs* (16). A higher proportion of *FGFR3* protein overexpression was found in invasive tumors without mutations, it may be that the tumor *FGFR3* signaling pathway without mutation promotes phenotypic transformation (12).

With the continuous progress of molecular biology research, tumor-targeted therapy has reached a new stage of development. Targeted therapy aims to interfere with tumor-specific signaling pathways, and the targets currently being researched include human epidermal growth factor receptor 2 (*HER2*), fibroblast *EGFR*, and immune checkpoints (9). Some targeted therapies have entered clinical trials; for example, clinical trials are being conducted on the use of the *EGFR* inhibitor gefitinib combined with chemotherapy as a first-line treatment for metastatic *BC* patients, and on the use of trastuzumab combined with chemotherapy as a treatment for *HER2*-positive metastatic *BC* patients (25). Currently, many *EGF/EGFR* signaling pathway inhibitors are being used in the clinic to treat lung cancer, breast cancer, and other related tumors, which have achieved sound curative effects (26). However, the activation of the *FGF/FGFR* signaling pathway was observed in many cases of later recurrence (27). The recurrence or metastasis of tumors is closely related to the stemness of the tumor (28), which proves that the *FGF/FGFR* signaling pathway has a function independent of the *EGF/EGFR* signaling pathway in tumors and that the function is related to the stemness of the tumor.

FGFR belongs to receptor tyrosine kinase (*RTK*), and its direct downstream channels include *MAPK*, *PI3K/AKT*, *ERK*, and cross-talk with *WNT* and other signaling pathways (29). Abnormalities in these pathways can cause tumor occurrence and deterioration, including epithelial-mesenchymal transition, increased tumor cell stemness, and related metabolic changes (29). As the *MAPK* pathway downstream of *RTK* is closely related to tumor proliferation and survival, many drugs targeting *RTK* are currently being used for the clinical treatment of tumors. The inhibition of *RTK* can effectively kill tumors that depend on the *MAPK* pathway (30).

Based on these findings, researchers have begun to focus on the *FGF/FGFR* signaling pathway, and its inhibitors have also entered the clinical testing stage. This research may lead to new treatment options for tumors. *FGFR3* is a class of targeted drugs that is being studied and has excellent prospects. Preliminary clinical studies have shown that the short-hairpin RNA-mediated knockout of *FGFR3* in *FGFR3b* mutant cell lines inhibits proliferation, supports independent growth, and reduces colony formation (31). Tumor cells rely solely on *FGFR3* mutants for growth to maintain the neoplastic phenotype, which may be a drug-targeted therapy with minimal systemic toxicity (32).

FGFR-targeted inhibitors have also entered an era of rapid development. Some *FGFR*-targeted inhibitors (such as erdafitinib) have been approved by *FDA* for clinical use, and many *FGFR*-targeted inhibitors are in preclinical or clinical trials (33). *FGFR* targeting is expected to improve the prognosis of tumor patients. Recently, at the American Society of Clinical Oncology (ASCO) 2023 Congress, data from the THOR-2 cohort 3 were reported, showing that erdafitinib was effective in the treatment of adult patients with intermediate-risk non-muscle-invasive bladder cancer carrying FGFR mutations. Some pathogenic mechanisms of *FGFR* have been confirmed in preclinical models. However, they still need to be verified in clinical trials, and there are more pathogenic mechanisms of *FGFR* to be discovered.

Nevertheless, this study also has some limitations. Even though we used 82 samples for analysis, the number of BC samples still needs to be increased, which can lead to potential errors/biases. In addition, multiple centers and more extensive sample size data are still required to support it. A clinical study of patients with metastatic urothelial carcinoma treated with the FGFR inhibitor erdafitinib showed higher response rates in patients who had previously received cancer immunotherapy. Bladder cancer patients with FGFR3 mutations were significantly associated with a lower tumor mutation burden (TMB). Future combination therapy strategies may show more responsiveness in the TMB-high tumor patient population (34). The data in this study are unsuitable for analyzing TMB, and the relationship between TMB and FGFR3 mutations still needs to be explored, which is also a limitation of this study.

Conclusions

This study conducted *NGS* and found that *ROS1*, *PIK3CA*, *FGFR3*, *BRAF*, *ERBB2*, and other genes were frequently mutated in *BC* patients. *FGFR3* has a higher mutation frequency in non-muscle-invasive bladder cancer patients. The primary mutation types of *FGFR3* were *p.Ser249Cys*, *p.Tyr375Cys*, and *p.Arg248Cy*. It appears that patients with *FGFR3* mutation are more likely to benefit from anti-FGFR3 therapy. In addition, we hope that our findings will enable clinical individualization strategies for *BC* patients to be optimized.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-247/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-247/dss

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-247/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-247/coif). All authors report the technical support from Shanghai Tongshu Biotechnology Co., Ltd. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Zhongshan Hospital Xiamen University (No. 2022-181). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all the study participants.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Lopez-Beltran A, Requena MJ, Cheng L, et al. Pathological variants of invasive bladder cancer according to their suggested clinical significance. BJU Int 2008;101:275-81.
3. Burger M, van der Aa MN, van Oers JM, et al. Prediction of progression of non-muscle-invasive bladder cancer by WHO 1973 and 2004 grading and by FGFR3 mutation status: a prospective study. Eur Urol 2008;54:835-43.
4. Lamm D, Persad R, Brausi M, et al. Defining progression in nonmuscle invasive bladder cancer: it is time for a new, standard definition. J Urol 2014;191:20-7.
5. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466-5; discussion 475-7.
6. Lenis AT, Lec PM, Chamie K, et al. Bladder Cancer: A Review. JAMA 2020;324:1980-91.
7. Rizzo A, Mollica V, Massari F. Expression of Programmed Cell Death Ligand 1 as a Predictive Biomarker in Metastatic Urothelial Carcinoma Patients Treated with First-line Immune Checkpoint Inhibitors Versus Chemotherapy: A Systematic Review and Meta-analysis. Eur Urol Focus 2022;8:152-9.
8. Viscardi G, Tralongo AC, Massari F, et al. Comparative assessment of early mortality risk upon immune checkpoint inhibitors alone or in combination with other agents across solid malignancies: a systematic review and meta-analysis. Eur J Cancer 2022;177:175-85.
9. Tran L, Xiao JF, Agarwal N, et al. Advances in bladder cancer biology and therapy. Nat Rev Cancer 2021;21:104-21.
10. Mollica V, Rizzo A, Montironi R, et al. Current Strategies and Novel Therapeutic Approaches for Metastatic Urothelial Carcinoma. Cancers (Basel) 2020;12:1449.
11. López-Knowles E, Hernández S, Malats N, et al. PIK3CA mutations are an early genetic alteration associated with FGFR3 mutations in superficial papillary bladder tumors. Cancer Res 2006;66:7401-4.
12. Tomlinson DC, Baldo O, Harnden P, et al. FGFR3 protein expression and its relationship to mutation status and prognostic variables in bladder cancer. J Pathol 2007;213:91-8.
13. Kompier LC, Lurkin I, van der Aa MN, et al. FGFR3, HRAS, KRAS, NRAS and PIK3CA mutations in bladder cancer and their potential as biomarkers for surveillance and therapy. PLoS One 2010;5:e13821.
14. van Rhijn BW, Vis AN, van der Kwast TH, et al. Molecular grading of urothelial cell carcinoma with fibroblast growth factor receptor 3 and MIB-1 is superior to pathologic grade for the prediction of clinical outcome. J Clin Oncol 2003;21:1912-21.
15. Hernández S, López-Knowles E, Lloreta J, et al. Prospective study of FGFR3 mutations as a prognostic factor in nonmuscle invasive urothelial bladder carcinomas. J Clin Oncol 2006;24:3664-71.
16. Pandith AA, Shah ZA, Siddiqi MA. Oncogenic role of fibroblast growth factor receptor 3 in tumorigenesis of urinary bladder cancer. Urol Oncol 2013;31:398-406.
17. van Rhijn BW, van der Kwast TH, Liu L, et al. The FGFR3 mutation is related to favorable pT1 bladder cancer. J Urol 2012;187:310-4.
18. Rizzo A, Mollica V, Santoni M, et al. Clinicopathological Features of FGFR3 - Mutated Upper Tract Urothelial Carcinoma: A Genomic Database Analysis. Clin Genitourin Cancer 2022;20:482-7.
19. DeGeorge KC, Holt HR, Hodges SC. Bladder Cancer: Diagnosis and Treatment. Am Fam Physician 2017;96:507-14.
20. Cappellen D, De Oliveira C, Ricol D, et al. Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas. Nat Genet 1999;23:18-20.
21. Wang CY, Tang YA, Lee IW, et al. Development and validation of an expanded targeted sequencing panel for non-invasive prenatal diagnosis of sporadic skeletal dysplasia. BMC Med Genomics 2021;14:212.
22. Qing J, Du X, Chen Y, et al. Antibody-based targeting of FGFR3 in bladder carcinoma and t(4;14)-positive multiple myeloma in mice. J Clin Invest 2009;119:1216-29.
23. Matsumoto M, Ohtsuki Y, Ochii K, et al. Fibroblast growth factor receptor 3 protein expression in urothelial carcinoma of the urinary bladder, exhibiting no association with low-grade and/or non-invasive lesions. Oncol Rep 2004;12:967-71.
24. Martínez-Torrecuadrada J, Cifuentes G, López-Serra P, et al. Targeting the extracellular domain of fibroblast growth factor receptor 3 with human single-chain Fv antibodies inhibits bladder carcinoma cell line proliferation. Clin Cancer Res 2005;11:6280-90.

25. Thibault C, Loriot Y. Emerging Targeted Therapy for Bladder Cancer. Hematol Oncol Clin North Am 2021;35:585-96.
26. Sigismund S, Avanzato D, Lanzetti L. Emerging functions of the EGFR in cancer. Mol Oncol 2018;12:3-20.
27. Touat M, Ileana E, Postel-Vinay S, et al. Targeting FGFR Signaling in Cancer. Clin Cancer Res 2015;21:2684-94.
28. Ishiwata T. Cancer stem cells and epithelial-mesenchymal transition: Novel therapeutic targets for cancer. Pathol Int 2016;66:601-8.
29. Dienstmann R, Rodon J, Prat A, et al. Genomic aberrations in the FGFR pathway: opportunities for targeted therapies in solid tumors. Ann Oncol 2014;25:552-63.
30. Audenet F, Attalla K, Sfakianos JP. The evolution of bladder cancer genomics: What have we learned and how can we use it? Urol Oncol 2018;36:313-20.
31. Tomlinson DC, Hurst CD, Knowles MA. Knockdown by shRNA identifies S249C mutant FGFR3 as a potential therapeutic target in bladder cancer. Oncogene 2007;26:5889-99.
32. Scholtes MP, Alberts AR, Iflé IG, et al. Biomarker-Oriented Therapy in Bladder and Renal Cancer. Int J Mol Sci 2021;22:2832.
33. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. N Engl J Med 2019;381:338-48.
34. Murugesan K, Necchi A, Burn TC, et al. Pan-tumor landscape of fibroblast growth factor receptor 1-4 genomic alterations. ESMO Open 2022;7:100641.

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