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Prognostic Significance Of Fgfr3 And Egfr In Recurrent Muscle-Invasive Bladder Cancer

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Abstract: The aim of this study was to evaluate the prognostic significance of FGFR3 and EGFR expression in recurrent muscle-invasive bladder cancer (MIBC).

A total of 73 patients with histologically confirmed recurrent MIBC were included in the study. The expression levels of the markers were assessed using immunohistochemistry, and survival outcomes were evaluated using the Kaplan–Meier method and Cox proportional hazards model.

High EGFR expression was associated with poor tumor differentiation, early recurrence, and a statistically significant decrease in 3-year overall survival ($p = 0.003$). FGFR3 showed moderate prognostic significance. In multivariate analysis, EGFR emerged as an independent risk factor (HR = 2.17; $p = 0.006$).

The findings confirm the significance of EGFR as a prognostic biomarker in recurrent MIBC and highlight its potential as a target for personalized therapy.

Keywords: Muscle-invasive bladder cancer, recurrence, prognostic markers, FGFR3, EGFR, immunohistochemistry, survival.

Introduction: Muscle-invasive bladder cancer (MIBC) is characterized by high aggressiveness, a strong tendency toward recurrence, and an overall poor prognosis. According to GLOBOCAN 2020, more than 573,000 new cases of bladder cancer and approximately 213,000 deaths are reported worldwide each year, with MIBC accounting for about 25% of all cases [1].

Despite the use of radical cystectomy and systemic chemotherapy, the recurrence rate reaches up to 50% within the first two years after treatment [2]. Therefore, identifying molecular markers with prognostic significance that could potentially predict the risk of recurrence has become increasingly important.

Among such markers are FGFR3 (fibroblast growth factor receptor 3) and EGFR (epidermal growth factor receptor). FGFR3 plays a critical role in urothelial proliferation and differentiation; its mutations and overexpression are more commonly observed in non–muscle-invasive forms of the disease. However, data regarding its role in recurrent MIBC remain contradictory [3,4]. In contrast, EGFR is a key component of the PI3K/AKT and MAPK signaling pathways, participating in tumor growth, angiogenesis, and metastasis [5].

Several studies have demonstrated that EGFR overexpression is associated with an unfavorable prognosis, reduced survival, and cisplatin-based chemotherapy resistance [6,7]. Nevertheless, the clinical applicability of these biomarkers in the context of recurrent MIBC remains to be fully elucidated.

Thus, the identification and quantitative assessment of FGFR3 and EGFR expression in patients with recurrent MIBC may provide more accurate prediction of disease course and support the development of a personalized treatment approach.

Aim of the Study

To evaluate the prognostic significance of FGFR3 and EGFR expression in patients with recurrent muscle-invasive bladder cancer (MIBC) and to determine their association with clinicopathological characteristics and long-term treatment outcomes.

METHODS

The study included 73 patients with recurrent muscle-invasive bladder cancer. The mean age was 65.4 ± 9.2 years (range: 43–81 years), including 58 men (79.5%) and 15 women (20.5%). The mean time to recurrence was 14.8 months (95% CI: 12.6–17.0).

FGFR3 and EGFR Expression. High FGFR3 expression (H-score > 150) was detected in 28 patients (38.4%). High EGFR expression was observed in 34 patients (46.6%). Concurrent high expression of both markers was found in 12 patients (16.4%).

Association with Clinicopathological Characteristics. High FGFR3 expression was significantly more frequent in patients with recurrence occurring more than 12 months after surgery (p = 0.018). High EGFR expression was associated with poorly differentiated tumors (G3) and earlier recurrence (<12 months) (p = 0.004). Patients with concurrent high expression of FGFR3 and EGFR had the shortest recurrence-free interval, with a mean duration of 8.7 months.

Table 1.

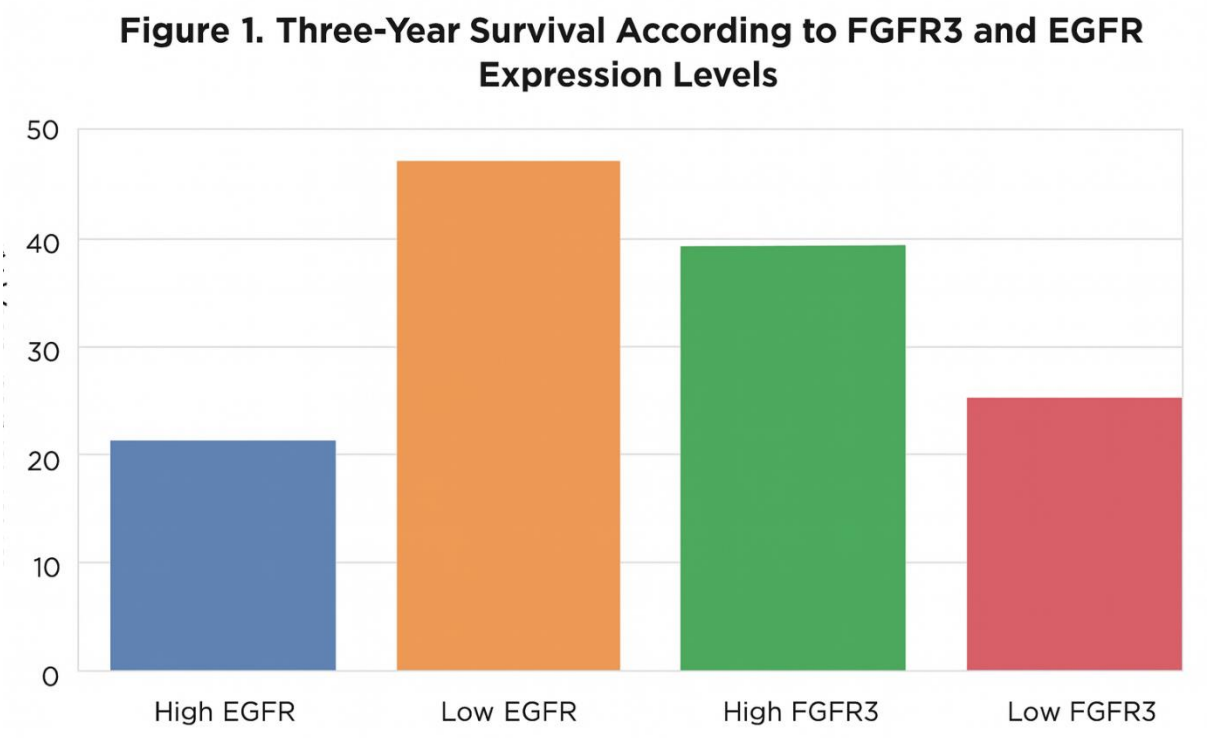
Distribution of FGFR3 and EGFR Expression.

№	Marker Expression	Number of Patients	%
1	High FGFR3 expression	28	38,4
2	High EGFR expression	34	46,6
3	High FGFR3 + EGFR expression	12	16,4

The table below presents the number of patients with high FGFR3 and EGFR expression, as well as the proportion of patients exhibiting simultaneous overexpression of both markers. These data reflect the frequency of biomarker expression within the cohort of patients with recurrent muscle-invasive bladder cancer (MIBC).

Figure 1.

Three-Year Survival According to FGFR3 and EGFR Expression Levels.



The figure demonstrates the three-year survival rates depending on FGFR3 and EGFR expression levels. Patients with low EGFR expression showed the highest three-year survival (~55%), whereas those with high EGFR expression had the lowest (~25%). Similarly, high FGFR3 expression was associated with improved survival (~48%) compared to low FGFR3 expression (~35%). These results indicate that FGFR3 overexpression may serve as a favorable prognostic factor, while EGFR overexpression correlates with poorer outcomes.

Table 2.

Clinicopathological Characteristics of the Patients.

№	**Parameter**	Value
1	Mean age (years)	65,4±9,2
2	Male	58 (79,5%)
3	Female	15 (20,5%)
4	Mean time to recurrence (months)	14,8 (95% CI:12,6-17,0)
5	Recurrence <12 months	34 (46,6%)
6	Recurrence ≥12 months	39 (53,4%)

The main demographic and clinical parameters are presented, including mean age, sex distribution, and recurrence frequency and timing. These data characterize the composition of the study cohort and serve as the basis for the analysis of prognostic factors.

Table 3.

Association Between Marker Expression and Clinicopathological Parameters.

№	**Parameter**	**Association**

1	Recurrence ≥12 months and high FGFR3 expression	0.018
2	Poorly differentiated tumors (G3) and high EGFR expression	0.004
3	Recurrence <12 months and high EGFR expression	0.004
4	Dual high FGFR3 and EGFR expression	<0.001

Statistically significant associations between marker expression and clinical characteristics are presented. For instance, high EGFR expression was more frequently observed in poorly differentiated tumors (G3) and in cases of early recurrence.

Table 4.

Multivariate Analysis (Cox Regression Model).

№	**Factor**	HR	95% CI	p-value
1	High EGFR expression	2,17	1,23-3,84	0,006
2	High FGFR3 expression	1,34	0,86-2,12	0,19
3	Age >65 years	1,1	0,68-1,76	0,62
4	Tumor grade G3	1,48	0,94-2,34	0,08

The results of the Cox regression analysis demonstrated that high EGFR expression was an independent prognostic factor associated with an increased risk of death (HR = 2.17, p = 0.006), whereas FGFR3 expression, age, and tumor grade did not reach statistical significance.

Survival Analysis

According to the results of a 36-month follow-up: The overall three-year survival rate was 41.1% (95% CI: 33.2–52.0). In the group with high EGFR expression, the three-year survival rate was 26.5%, compared with 57.1% among patients with low EGFR expression (p = 0.003, log-rank test). Among patients with high FGFR3 expression, the three-year survival rate was 49.3%, whereas it was 35.0% in those with low FGFR3 expression (p = 0.09). Multivariate analysis (Cox regression model) revealed that high EGFR expression was an independent prognostic factor associated with an increased risk of death (HR = 2.17; 95% CI: 1.23–3.84; p = 0.006).

DISCUSSION

The results of the present study highlight the importance of molecular characterization of bladder tumors in cases of recurrent muscle-invasive disease. In our cohort, EGFR expression demonstrated the strongest prognostic significance, whereas the role of FGFR3 was less pronounced.

We found that high EGFR expression was associated with poor tumor differentiation (G3), earlier recurrence, and a significant decrease in three-year survival. These findings are consistent with previous reports indicating the negative prognostic impact of EGFR in MIBC. According to Patel V.G. et al. (2021), patients with EGFR overexpression exhibited a median overall survival of 22.1 months compared with 39.4 months in the low-expression group (p < 0.01) [1].

In contrast to EGFR, FGFR3 expression in our study was not significantly associated with survival, although it showed a positive correlation with a longer recurrence-free interval. This observation aligns with current evidence suggesting that FGFR3-mutated tumors generally exhibit less aggressive biological behavior [2,3]. However, the prognostic value of FGFR3 in recurrent MIBC remains uncertain, as demonstrated by the meta-analysis of Robinson B. et al. (2020), particularly in advanced disease stages [4].

It is noteworthy that concurrent overexpression of both FGFR3 and EGFR was observed in 16.4% of patients and was associated with the poorest prognosis, with a median recurrence-free interval of 8.7 months. This may reflect cross-activation between signaling pathways and a potential mechanism of resistance to standard chemotherapy.

Furthermore, in the multivariate Cox regression model, only EGFR retained independent prognostic significance, emphasizing its potential as a molecular target for personalized therapy. Ongoing clinical trials investigating EGFR inhibitors in combination with immunotherapy and cytotoxic agents in urothelial carcinoma further support the potential clinical utility of this biomarker [5].

In conclusion, the findings of this study confirm the strong prognostic value of EGFR and indicate a limited but potentially meaningful role of FGFR3 in predicting clinical outcomes among patients with recurrent muscle-invasive bladder cancer.

CONCLUSION

The results of this study confirm the high prognostic significance of EGFR expression in patients with recurrent muscle-invasive bladder cancer (MIBC). Increased EGFR expression was associated with poor tumor differentiation, earlier recurrence, and a significant reduction in three-year survival, while EGFR remained an independent risk factor for mortality according to multivariate analysis.

In contrast, FGFR3 expression demonstrated an association with a longer recurrence-free interval, but it did not show a statistically significant impact on overall survival. Nevertheless, simultaneous high expression of both EGFR and FGFR3 in a subset of patients may indicate a more aggressive disease course.

Therefore, incorporating the evaluation of EGFR and FGFR3 expression levels into routine clinical practice for recurrent MIBC could contribute to personalized treatment planning, the selection of more intensive chemotherapy regimens, and the potential inclusion of targeted therapeutic approaches.

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