Global Medical and Health Communication

Online submission: http://ejournal.unisba.ac.id/index.php/gmhc
DOI: https://doi.org/10.29313/gmhc.v7i2.3956

GMHC. 2019;7(2):108–15
pISSN 2301-9123 | eISSN 2460-5441

RESEARCH ARTICLE

The Role of Fibroblast Growth Factor Receptor 3 (FGFR3) and Androgen Receptor (AR) in a Non-invasive Urothelial Carcinoma Recurrences

Oki Meilani Dewi, Sri Suryanti, Bethy Suryawathy Hernowo
Department of Anatomical Pathology, Faculty of Medicine, Universitas Padjadjaran/
Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Abstract

Urothelial carcinoma is a bladder carcinoma that took place in the urinary tract. Non-invasive urothelial carcinoma patients have high recurrence rates (50–70%). The recurrences took so many years that may lead to the high-cost treatment and low survival rate. Fibroblast growth factor receptor 3 (FGFR3) and androgen receptor (AR) known to play a role in non-invasive urothelial carcinoma and potentially act as a prognostic marker to predict recurrences. This study aimed to discover the role of FGFR3 and AR in recurrences of non-invasive urothelial carcinoma. This research used a case-control study design. Samples took from patients diagnosed with non-invasive urothelial carcinoma registered at Dr. Hasan Sadikin General Hospital Bandung 1 January 2010–30 December 2015 period. Sixty samples consisted of 30 recurrent groups, and 30 non-recurrent groups individually fixated and embedded to paraffin block for FGFR3 and AR immunohistochemistry analysis. Analysis chi-square performed with a level of confidence 95% and statistical power 95%. p values<0.05 were considered to be statistically significant. Statistical analysis showed that FGFR3 immunoexpression was found significantly low on the recurrence group (p=0.002, OR=5.50). While AR immunoexpression was found insignificant (p=1.000, OR=1.00). FGFR3 immunoexpression from samples in the recurrent group with multiple tumors found to be significantly low (p=0.031, OR=6.067). This study showed that recurrences took place when FGFR3 lowly expressed within non-invasive urothelial carcinoma samples with multiple tumors. This finding may raise a candidate to early-predict the recurrence, thus will suggest early therapy.

Key words: AR, FGFR3, non-invasive urothelial carcinoma, recurrence

Peranan *Fibroblast Growth Factor Receptor 3* (FGFR3) dan Reseptor Androgen (RA) terhadap Kejadian Rekurensi pada Karsinoma Urotelial Buli Non-invasif

Abstrak

Karsinoma urotelial merupakan karsinoma buli yang sering terjadi pada saluran kemih. Karsinoma urotelial dibagi menjadi karsinoma urotelial non-invasif dan invasif. Pasien karsinoma urotelial non-invasif mempunyai kejadian rekurensi tinggi (50–70%) dan membutuhkan waktu lama untuk memantau kejadian rekurensi sehingga membutuhkan biaya tinggi dengan angka ketahanan hidup rendah. *Fibroblast growth factor receptor 3* (FGFR3) dan reseptor androgen (RA) berperan dalam terjadinya karsinoma urotelial non-invasif dan berpotensi sebagai penanda prognostik yang memprediksi rekurensi secara akurat. Tujuan penelitian ini mengetahui peranan FGFR3 dan RA terhadap kejadian rekurensi pada karsinoma urotelial non-invasif. Penelitian menggunakan rancangan *case-control study*. Sampel berupa blok parafin yang diagnosis sebagai karsinoma urotelial non-invasif di RSUP Dr. Hasan Sadikin Bandung periode 1 Januari 2010–30 Desember 2015. Sebanyak 60 sampel dievaluasi terdiri atas 30 sampel kelompok rekurensi dan 30 kelompok tidak rekurensi. Pemeriksaan imunohistokimia menggunakan antibodi FGFR3 dan RA. Analisis menggunakan uji *chi-square* dengan taraf kepercayaan 95% dan kuasa uji (*power test*) 95%. Nilai p<0,05 dianggap signifikan secara statistik. Pada analisis statistik, imunoekspresi FGFR3 rendah signifikan pada kelompok rekurensi (p=0,002; OR=5,50) dan imunoekspresi RA tidak signifikan (p=1,000; OR=1,00). Imunoekspresi FGFR3 rendah dengan tumor multipel signifikan pada kelompok rekurensi (p=0,031; OR=6,067). Hasil penelitian menunjukkan bahwa rekurensi terjadi ketika FGFR3 terekspresi rendah pada sampel karsinoma non-invasif dengan tumor multipel. Hal ini dapat menjadi penanda memprediksi kejadian rekurensi sehingga dapat dilakukan terapi yang lebih cepat.

Kata kunci: FGFR3, karsinoma urotelial non-invasif, RA, rekurensi

Received: 15 August 2018; Revised: 12 August 2019; Accepted: 12 August 2019; Published: 31 August 2019

Correspondence: Oki Meilani Dewi, dr. Department of Anatomical Pathology, Faculty of Medicine, Universitas Padjadjaran/ Dr. Hasan Sadikin General Hospital. Jln. Pasteur No. 38, Bandung 40161, West Java, Indonesia. Phone: (+6222) 2034953. Mobile: 081321709953. E-mail: okimeilani.dr@gmail.com

Introduction

Bladder carcinoma is the most common malignancy occurring in the urinary tract, and 3 to 4 times more likely to develop in men than women. Bladder carcinoma takes place in the urinary tract, which originated from bladder transitional epithelial cell.[1–3] In Indonesia, bladder carcinoma is the seventh most common carcinoma with an occurrence rate of 5.8 in every 100,000 people/year and mortality rate of 3.1 in every 100,000 people/year.[4] According to Dr. Hasan Sadikin General Hospital Bandung medical record, urothelial bladder carcinoma was ranked the fourteenth most common malignancy with 86 cases recorded in 2016.

Urothelial carcinoma is the most often type of bladder carcinoma with occurrence rates 80–90% of all bladder carcinoma cases.[1,2,5] Clinically, urothelial carcinoma classified into two groups based on muscle invasion degree, which are non-invasive and invasive urothelial carcinoma. The most commonly diagnosed carcinoma is the non-invasive or superficial urothelial carcinoma or non-muscle invasive bladder cancer (NMIBC), around 70–80% of patients. Non-invasive bladder urothelial carcinoma also classified into a low and high degree of non-invasive papillary urothelial carcinoma (pTa); in situ urothelial carcinoma (pTis); and infiltrating urothelial carcinoma which has invade lamina propria (pT1).[2,3,6–11]

The therapy for non-invasive bladder urothelial carcinoma is transurethral resection of the bladder tumor (TURBT) followed by intravesical chemotherapy or immunotherapy. Although patients have undergone therapy, the recurrence rate is still around 50–70% in a year and could reach 31–78% in 5 years. In 15–25% non-invasive urothelial carcinoma cases can progressively evolve to an invasive urothelial carcinoma.[10]

Recurrences defined as relapse carcinoma post-initial resection and histopathologically confirmed.[12] Clinically, predictive factors that may cause recurrences are the tumor amount, tumor size, prior recurrence state, in situ coexistent carcinoma, pathological stages, and degree of histopathological. These predictive factors are utilized to stipulate the recurrences through a scoring system and risk table calculation, performed on first and fifth-year post-therapy. Hence a molecular marker is required to anticipate recurrences on non-invasive bladder urothelial carcinoma.[10,13]

Genetic evidence shows that urothelial carcinoma can develop from two molecular pathways: FGFR3, which play a significant role in non-invasive bladder urothelial carcinoma; and TP53. FGFR itself is a high-affinity tyrosine kinase transmembrane receptor that is important for embryogenesis, cell growth, differentiation, proliferation, and angiogenesis. FGFR has 4 active isoforms, which are FGFR1, FGFR2, FGFR3, and FGFR4. FGFR3 signaling pathway particularly can activate the androgen receptor (AR) activity.[1,11,14–16]

Androgen receptor (AR) is an intracellular steroid hormone receptor found in cytoplasm or nucleus. It has a role in causing urothelial bladder carcinoma through the genomic and non-genomic pathway, for example, through FGFR3 pathway.[15] Androgen receptor found majorly expressed on urothelial carcinoma cases (44–78% of cases) while it is not expressed in benign urothelium tumor.[3,17]

In recent years, several studies have been carried out on FGFR3 and AR in urothelial bladder carcinoma, and the results reported are varied and controversial. A study of van Rhijn et al.[18] reported that the FGFR3 mutation was a predictive of recurrence in low and high degree urothelial carcinoma. Nam et al.[12] reported that in univariable analyzes AR expression was lower in recurrence. In multivariate analysis, there is a significant relationship between AR expression with low recurrence.

The objective of this study is to understand the role of FGFR3 and AR in recurrent non-invasive urothelial carcinoma, thus can early-anticipate the recurrence possibility and help to conduct proper treatment.

Methods

Samples were taken from TURBT surgery patients biopsy tissue. Patients registered at Dr. Hasan Sadikin General Hospital Bandung, and histopathologically diagnosed with non-invasive urothelial carcinoma period 1 January 2010–30 December 2015. Sixty samples were acquired, which then divided into two groups: the recurrent group (n=30) and non-recurrent group (n=30). Tissue samples were then fixated and embedded to paraffin block for FGFR3 and AR immunohistochemistry staining procedure in each group.

Mouse monoclonal antibody FGFR3 (Santa Cruz, B-9, SC-13121, USA) with 1:100 dilution,

and human AR monoclonal antibody (Santa Cruz, 441, SC-7305, USA) with 1:50 dilution used in standard immunohistochemistry (IHC) staining procedure. FGFR3 immunoexpression rated and scored by calculating the number of cells showed immunoreactivity, which was the cytoplasm-stained cells. AR immunoexpression was the nucleus-stained cells. Distribution score was explained as 0=negative; 1≤10%; 2=10–50%; 3=50–80%; and 4≥80%. Intensity score was explained as 0=negative; 1=weak; 2=medium; 3=strong.19 Histoscore (distribution x intensity) was interpreted as ≥6=high; and <6=low. IHC staining result was examined by two experts in the IHC technique using light microscope Olympus CX31.

Data obtained from this research analyzed with chi-square test for a significant difference. A significant difference interpreted from p-value with $p \leq 0.05$ statistical significant difference, while $p \geq 0.05$ showed otherwise. Odds ratio (OR) used to measure the association between exposure and outcome. In this research, it was the association between FRGR3 and AR immunoexpression; and non-invasive bladder urothelial carcinoma recurrences. The data attained from laboratory procedure recorded in distinct form and SPSS 24.0 for Windows used to analyze the data.

Samples attained after approval by the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran Bandung with assessment letter number: 73/UN6.KEP/EC/2018.

Results

Characteristics of research subjects used based on epidemiology are age, sex, and smoking risk factors. Based on recurrence prediction factors used by the European Association of Urology (EAU) consisting of tumor size, the number of tumors, pathological stage, and histopathological degree. The results of the comparative analysis of the characteristics of the recurrence and non-recurrence groups showed no differences in the characteristics of the two groups at the beginning of the study.

The results of the FGFR3 immunoexpression

Table 1 Comparison between Research Participant Characteristic on Recurrent and Non-recurrent Group

Variables	Groups		p Value
	Recurrent (n=30)	Non-recurrent (n=30)	
Age (years)			
Mean±Std	59.56±12.133	60.00±12.982	0.894
Sex			
Male	24	28	0.254
Female	6	2	
Smoking risk factor			
Yes	22	25	0.347
No	8	5	
Tumor size			
≥3 cm	18	12	0.121
<3 cm	12	18	
Number of tumor			
Single	12	20	0.038
Multiple	18	10	
Pathological stage (T)			
pTa	5	9	0.952
pT1	24	21	
pTis	1	0	
Histological degree			
Low	6	11	0.152
High	24	19	

Table 2 FGFR3 Immunoexpression Histoscore Comparison between Recurrent and Non-recurrent Group

FGFR3 Immuoexpression	Groups		OR CI (95%)	p Value
	Recurrent (n=30)	Non-recurrent (n=30)		
High	10	22	5.50 (1.813– 16.681)	0.002
Low	20	8		

Table 3 AR Immmunoexpression Histoscore Comparison between Recurrent and Non-recurrent Group

AR Immuoexpression	Groups		OR CI (95%)	p Value
	Recurrent (n=30)	Non-recurrent (n=30)		
High	3	3	1.0 (0.185–5.403)	1.000
Low	27	27		

Table 4 Comparison between FGFR3 and AR Immunoexpression Histocores on Patients with Single Tumor on Recurrent and Non-recurrent Group

Variables	Groups		OR CI (95%)	p Value
	Recurrent (n=12)	Non-recurrent (n=20)		
FGFR3 immunoexpression				
High	5	15	0.238 (0.052–1.100)	0.059
Low	7	5		
AR immunoexpression				
High	0	1	0.000	1.000
Low	12	19		

Table 5 Comparison between FGFR3 and AR Immunoexpression Histoscores on Patients with Multiple Tumor on Recurrent and Non-recurrent Group

Variables	Groups		OR CI (95%)	p Value
	Recurrent (n=18)	Non-recurrent (n=10)		
FGFR3 immunoexpression				
Low	13	3	6.067 (1.107–33.238)	0.031
High	5	7		
AR immunoexpression				
High	3	2	0.800 (0.110–5.819)	1.000
Low	15	8		

histoscore category showed p value<0.05 (p=0.002), while the AR immunoexpression histoscore category obtained p>0.05 (p=1.000). The results between FGFR3 and AR immunoexpression histoscore on patients with single tumors characteristic on recurrent

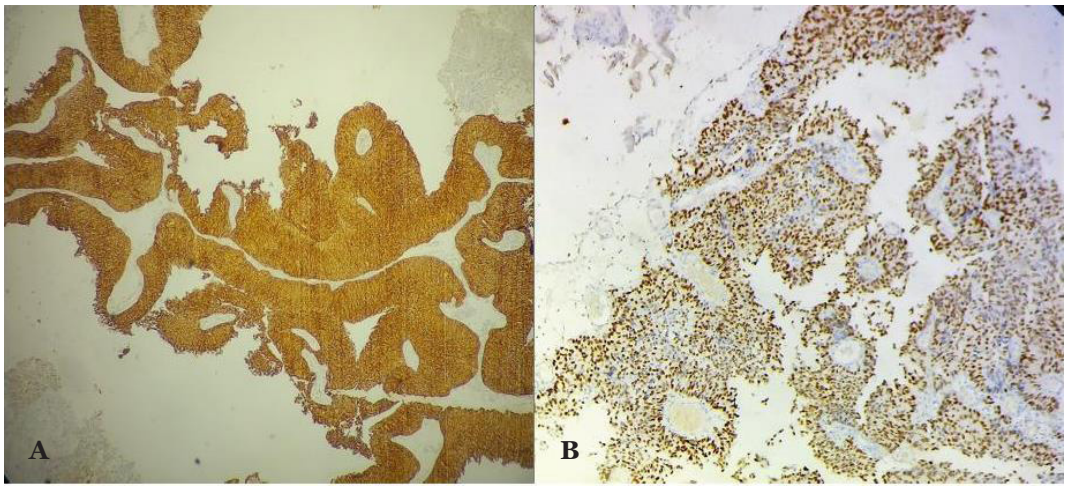

Figure (A) Immunoexpression FGFR3 and (B) Immunoexpression AR with Strong Intensity. Original Magnification, ×400

and non-recurrent groups obtained p>0.05 (p=0.059 for FGFR3 and p=1.000 for AR), which means not significant, whereas FGFR3 immunoexpression histoscore with multiple tumor characteristic obtained p values<0.05 (p=0.031) which means statistically significant, while AR immunoexpression histoscore with multiple tumor characteristic obtained p>0.05 (p=1.000) which means it is not significant.

Statistical analysis result on research groups showed that both groups were homogenous, which means both groups were feasible to be compared and perform a further statistical hypothesis test, the only number of tumor that will alter the result between both groups (Table 1).

Statistical analysis showed that there was a significant difference in FGFR3 immunoexpression proportion between the recurrent and non-recurrent group. Odds ratio value from the test showed that patients with low FGFR3 immunoexpression are 5.5 times more likely to suffer from recurrence compared to patients with high FGFR3 immunoexpression (Table 2).

Statistical analysis showed that there was no significant difference in AR immunoexpression proportion between the recurrent and non-recurrent group. Odds ratio value from the table above showed that patients with low AR immunoexpression are one time more likely to suffer from recurrence compared to patients with high AR immunoexpression (Table 3).

Statistical analysis showed that there was no statistically significant difference between FGFR3 and AR immunoexpression proportion; and single tumor characteristic on the recurrent and non-recurrent group (Table 4).

The result showed that there was a statistically significant difference in proportion between patients with low FGFR3 immunoexpression and multiple tumor characteristic on the recurrent and non-recurrent group. From the odds ratio, patients with low FGFR3 immunoexpression on multiple tumors are 6.067 times more likely to suffer from recurrence compared to patients with high FGFR3 immunoexpression. AR immunoexpression variable found to have no statistical (Table 5).

Discussion

Urothelial carcinoma is the most common bladder malignancy, with around 90% of all cases. Most bladder carcinoma incidence occurs in men in the age above 50, with smoking as the primary risk factor.[20] The finding goes parallel with this research, where 86.7% of patients are male around the age of 59.78±12.460, and 78.3% were smoking.

Non-invasive bladder urothelial carcinoma has a high recurrence rate, which is 50–60%, and likely to develop into progressive (state of) carcinoma around 15–25% in 5 years. Urothelial carcinoma originated from urothelium cancer stem cell which distributed to urothelium through migration. It behaves like a multifocal tumor, and result in recurrences. There are four reasons why

recurrences take place in urothelial carcinoma. They are incomplete resection on primary urothelial carcinoma; tumor cell reimplantation; unknown tumor cells when the primary tumor resection occur; and a new tumor formation.[21,22]

In this study, we found that patients in the recurrent group have statistically significant low FGFR3 immunoexpression (p=0.002) with OR 5.50 and CI (1.813–16.681). FGFR3 might play a significant role in non-invasive bladder urothelial carcinoma recurrence. In summary, the possibility of recurrences took place in non-invasive bladder carcinoma patients with low FGFR3 immunoexpression is 5.5 times compared to patients with high FGFR3 immunoexpression.

Results attained in this research are in line with the research conducted by van Rhijn et al.,[18] which stated that low FGFR3 expression is a strong indicator in non-invasive bladder carcinoma recurrences. The assumed recurrences caused by the remaining cancer stem cells that were still intact on the primary tumor site after primary tumor resection. On the low FGFR3 immunoexpressed tumor, cancer stem cells suspected of undergoing a slower proliferation rate. They also act as weak cell-cell interaction and poor stromal strength, altogether causing tumor cells to reimplant in the bladder epithelium easily. They migrated to inside the epithelium as well as leading to trouble-free stromal invasion. Patients with low FGFG3 immunoexpression are likely to experience recurrences in numerous sites and multiple growths.

On AR IHC staining analysis, p-value attained was 1.000 with OR 1.0 and CI (0.185–5.403), which showed that no significant difference in the proportion of AR expression between the recurrent and non-recurrent group. These results similar to results by Miyamoto et al.[19] and Mir et al.,[24] which discovered that 12.9% of samples (61 cases out of 472) were positive AR immunoexpression. Only 9.0% detected on non-invasive bladder carcinoma, and 15.1% detected on invasive bladder carcinoma. There was no difference in (AR) expression between male and female patients, and no statistically significant difference in urothelial carcinoma recurrences. There are some dissimilarities between the result from this research and other research, due to the variation in IHC expression and biological function. IHC method has a threshold in approaching (detecting) cells that express the corresponding protein. Thus there might be a chance that the IHC technique reveals false-negative results because the samples express the insufficient amount of AR to be detected, which the AR did express.[6,19,24,25]

Based on the bivariate analysis test, FGFR3 and AR simultaneously do not affect recurrence events, and only FGFR3 is related to recurrence events. It suggested that the role of AR in bladder urothelial carcinoma through non-genomic pathways with activation of FGFR3 does not occur due to low FGFR3 immunoexpression. Inactive AR causes inactivate gene transcription in the cell nucleus, which further proliferates urothelium cells. The process causes epithelial cell hyperplasia to atypia, then to dysplasia and finally to urothelial carcinoma occurrence.

According to Table 1, there was a statistically significant difference in the number/amount of tumor characteristic between the recurrent and non-recurrent group. For that reason, the chi-square test performed on FGFR3 immunoexpression category. Fisher Exact test used to analyze the AR immunoexpression category. We can compare the FGFR3 and AR immunoexpression histoscore on patients with single and multiple tumors characteristic on the recurrent and non-recurrent group. In our study, we found that there was no statistically significant difference in the proportion of FGFR3 and AR immunoexpression variable on patients with single tumor characteristic on the recurrent and non-recurrent group with p value>0.05.

Comparison between FGFR3 and AR immunoexpression histoscore on multiple tumor characteristic patients, on the recurrent and non-recurrent group, revealed that there was a statistically significant difference in proportion between the FGFR3 immunoexpression variable and multiple tumor characteristic on the recurrent and non-recurrent group (p=0.031) with OR 6.607 and CI (1.107–33.238). The opposite result obtained from AR immunoexpression variable, where there was no statistically significant difference with a p value>0.05.

Multiple tumors have an unstable genetic characteristic, and the loss of cell adhesion will cause the intraepithelial migration of tumor cells. There were two theories proposed to explain the multifocality in urothelial carcinoma. The first theory, the monoclonal theory, which elaborates that multiple tumors rise from one progenitor cell that undergoes sort of changes. They proliferate and spread to the whole urothelium through

intraluminal implantation or intraepithelial migration. Tumor cells extravasation from the primary site followed by tumor cell implantation in the different urothelium area leading to intraluminal tumor seeding. Intraepithelial spreading occurs through continuous migration and cell proliferation which distributed to the whole urothelium. Second theory, the "field cancerization" effect; the carcinogen exposure causes the simultaneous genetic alteration on various primary urothelial layer. It resulted in the new multiple tumors which have no genetic correlation.[9,23]

Conclusion

Non-invasive urothelial carcinoma patients with multiple tumor characteristic which has low FGFR3 immunoexpression (histoscore<6) are more likely to suffer from recurrence compared to patients with high FGFR3 immunoexpression. Tumor multiplicity is an essential predictive factor in recurrences on non-invasive bladder urothelial carcinoma.

Conflict of Interest

All the authors state that they have no conflict of interest in this article.

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