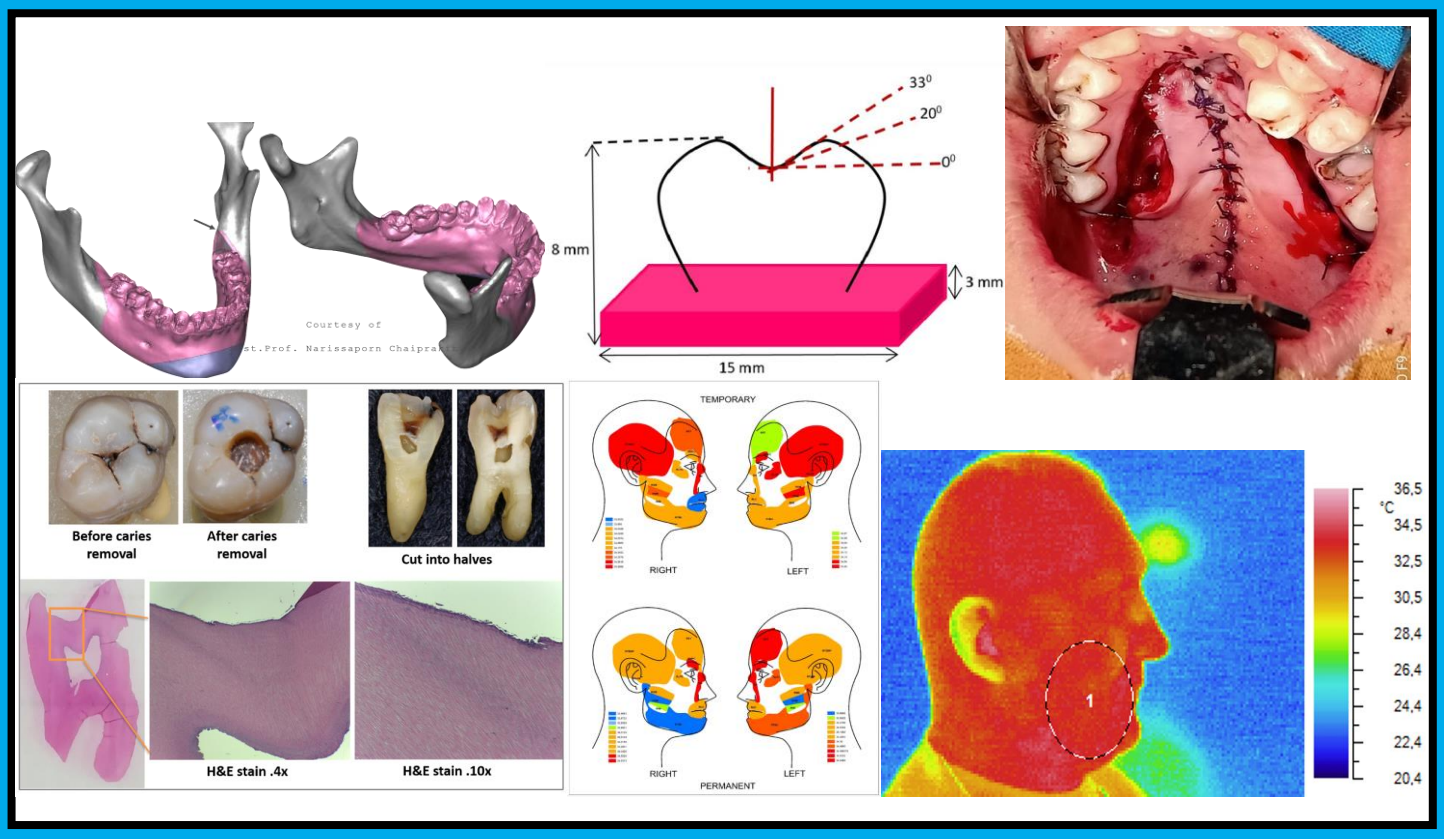
E-ISSN: 1309-100X

Journal of International Dental and Medical Research



2021 - Vol. 14 – No. 2

http://www.jidmr.com

Editorial Board of JIDMR

Advisory Board

Editorial Board

Fahinur ERTUGRUL (TURKEY)
Feral OZTURK (TURKEY)
Feridun BASAK (TURKEY)
Ferranti WONG (UNITED KINGDOM)
Feyzi Çelik (TURKEY)
Feyzullah Uçmak (TURKEY)
Figen SEYMEN (TURKEY)
Filippo BATTELLI (ITALY)
Filiz Acun KAYA (TURKEY)
Flavio Domingues Das NEVES (BRAZIL)
Folakemi OREDUGBA (NIGERIA)
Francesca De Angelis (ITALY)
Gajanan Kiran KULKARNI (CANADA)
Gamze AREN (TURKEY)
Gauri LELE (INDIA)
Gonul OLMEZ (TURKEY)
Gulsen YILMAZ (TURKEY)
Gulten UNLU (TURKEY)
Mohammad Khursheed Alam (KSA)
Mohammad SUHRON (INDONESIA)
Mohammed Mustahsen URREHMAN (UAE)
Moschos A. PAPADOPOULOS (GREECE)
Mostaphazadeh AMROLLAH (IRAN)
M.S. Rami REDDY (INDIA)
Muhammad FAHIM (INDIA)
Mukadder ATMACA (TURKEY)
Murat AKKUS (TURKEY)
Murat SOKER (TURKEY)
Mustafa KELLE (TURKEY)
Mustafa ZORTUK (TURKEY)
Muzeyyen YILDIRIM (TURKEY)
Neval Berrin ARSERIM (TURKEY)
Ufuk ALUCLU (TURKEY)
Ugur KEKLIKCI (TURKEY)
Xiong-Li YANG (CHINA)
Vatan KAVAK (TURKEY)
Yasar YILDIRIM (TURKEY)
Yasemin YAVUZ (TURKEY)
Yavuz SANISOGLU (TURKEY)
Yu LEI (USA)
Yuri LIMANSKI (UKRAINE)
Zafer C. CEHRELI (TURKEY)
Zeki AKKUS (TURKEY)
Zeynep AYTEPE (TURKEY)
Zuhal KIRZIOGLU (TURKEY)
Zurab KOMETIANI (GEORGIA)

JIDMR
JOURNAL OF INTERNATIONAL DENTAL AND MEDICAL RESEARCH

Journal of International Dental and Medical Research / ISSN: 1309-100X

TABLE OF CONTENTS / 2021; 14 (2)

DENTISTRY

JIDMR
JOURNAL OF INTERNATIONAL DENTAL AND MEDICAL RESEARCH

Journal of International Dental and Medical Research / ISSN: 1309-100X

TABLE OF CONTENTS / 2021; 14 (2)

Correlation Between VEGF and EGFR Expression in Urothelial Carcinoma of Bladder

Anny Setijo Rahaju[1,2,3,4], Arifa Mustika[5]*, Priangga Adi Wiratama[2,4], Leonita Agustina Hambalie[2], Novalia Guntarno[2], Lukman Hakim[4,6], Doddy M. Soebadi[4,6]

1. Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
2. Department of Anatomical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
3. Universitas Airlangga Hospital, Surabaya, Indonesia.
4. Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
5. Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
6. Department of Urology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

Abstract

Bladder cancer is the ninth malignancy of the genitourinary system in the world. Urothelial cell carcinoma is the commonest histological type. There are no good therapeutic options to date. Vascular endothelial growth factor (VEGF) is a growth factor that is essential to stimulate angiogenesis. Tumor growth relies on angiogenesis and determines the therapy. The epidermal growth factor receptor (EGFR) is known as a tyrosine kinase transmembrane receptor. EGFR is involved in the regulation of VEGF. Several researches have shown that EGFR stimulation induces VEGF expression. Therefore, this research was conducted to analyze the relationship between VEGF and EGFR, as the basis of therapy using anti-VEGF and anti-EGFR. An observational research was conducted on 53 formalin fixed paraffin-embedded tissue from Radical Cystectomy patients urothelial carcinoma of bladder which was at Dr. Soetomo General Academic Hospital Surabaya, Indonesia during 2010 - 2019. Immunohistochemistry was conducted using VEGF and EGFR antibodies. Significant positive correlation was seen between EGFR and VEGF expression in bladder urothelial carcinoma. VEGF and EGFR expression can use as the basis of therapy using anti-VEGF and anti-EGFR in bladder urothelial carcinoma.

Clinical article, (J Int Dent Med Res 2021; 14(2): 849-854)

Keywords: Urothelial carcinoma of Bladder, VEGF, EGFR

Received date: 14 March 2021 **Accept date:** 24 April 2021

Introduction

Urothelial cancer is one of the top ten most general types of cancer of the genitourinary system worldwide [2,3] with roughly 430,000 cases and ranks 13th in terms of yearly cancer deaths [3]. Bladder cancer also ranks 7th for the most common malignancy in men, with men having respective incidence and mortality rates four times higher than women globally [2]. In 2018, it was predicted that there would be over 80.000 recent cases of bladder cancer identified in USA, with over 15.000 deaths [4]. Cigarette smoking is known as the main risk factor for bladder cancer. In the United States, approximately 50% of bladder cancer cases are related to smoking in both sexes, other than water contaminant and exposure to chemical [2].

Tumor growth determines the therapy and prognosis of a patient. Angiogenesis, a process where new blood vessels form and distribute nutrients and oxygen to highly proliferative tumor cells, can strongly affect the growth of tumor [5]. Vascular endothelial growth factor (VEGF) is the angiogenic component that is important to stimulate angiogenesis and tumor growth factors. The significance of the VEGF expression has been recognized and researched in different types of cancer. Various researches have investigated the function of VEGF in bladder cancer development and invasion [6–8].

A tyrosine kinase transmembrane receptor, Epidermal growth factor receptor (EGFR), heavily affects carcinogenesis [9]. It is overexpressed in many tumors, such as head and neck, colon, lung, breast, kidney, bladder and prostate cancer [9]. VEGF released from

Corresponding author:
Arifa Mustika,
Division of Pharmacology and Therapy, Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine Universitas Airlangga,
Jl Moestopo 47 Surabaya, Indonesia
E-mail : arifa-m@fk.unair.ac.id

tumor cells stimulates the proliferation and sprouting of endothelial cells [10]. The significance of the VEGF expression has been investigated in various types of cancer. Several researches have investigated the role of VEGF in bladder cancer progression and invasion [6–8].

EGFR is embroiled in the control of VEGF. Several researches have shown that EGFR stimulation induces VEGF expression [11]. Biological agents alone or combined with other cytotoxic therapies targeting EGFR and VEGF pathways are proven to show clinical benefits in various cancers in humans. Inhibition of VEGF-related pathways is suspected to effect the mechanism of action agents that target EGFR. However, over activation of VEGF expression, which is independent of EGFR signaling, could result in tumor resistance towards anti-EGFR therapy [12,13]. Therefore, this study analyzes the role and the relationship between EGFR and VEGF in bladder cancer, as the basis of therapy using anti-VEGF and anti-EGFR.

Materials and methods

An analytic observational study was done on 53 paraffin-embedded tissues fixed in formalin from Radical Cystectomy (RC) patiens urothelial carcinoma of bladder which were at Dr. Soetomo General Academic Hospital's Anatomical Pathology Laboratory at Surabaya Indonesia during 2010 - 2019. Immunohistochemistry was conducted using VEGF and EGFR antibodies, measured and statistically analyzed to find the correlations between VEGF and EGFR in urothelial carcinoma of bladder.

Immunohistochemistry Staining

A 4µm cut of paraffin block, was sectioned into slides, each deparaffinized three times for 5 minutes with xylol, and rehydrated using graded alcohol for 2 minutes each. In order to reduce nonspecific staining caused by peroxidized block, hydrogen peroxide was used to incubate the slides for 10-15 minutes. Antigen retrieval was carried out using microwave treatment in sodium citrate buffer in pH 6.0 at 95°C for 45 minutes, then background sniper was applied (Biogear - Excell Block). Slides were incubated overnight with monoclonal antibodies for VEGF (C-1 - sc 7269 dilutions 1:200; Santa Cruz Biotechnology) and EGFR (0.N.268: sc-71034; dilution 1:100; Santa Cruz Biotechnology), and washed in phosphates buffer saline. It was followed by a secondary antibody (Biogear Universal HRP Excell Stain System – Biogear, BDK-HES125) for 10 minutes at room temperature and DAB chromogen for 5-15 minutes. Slides then were counterstained with Meyer's hematoxillin and dehydrated with 95% alcohol. We use human placental tissue as a positive control for EGFR while human liver tissue as a positive control for VEGF.

Evaluation of Immunohistochemistry Expression

The expression of VEGF and EGFR was evaluated by two pathologists using Olympus CX41RF light microscopes in the blinded fashion and documented using Olympus DP2-BSW. The VEGF expression was interpreted in accordance with the intensity and percentage in the cytoplasm of tumor cells. The percentage of tumor cell positively stained was determine by counting the tumor cell that had the highest immunoreactivity, as 0 (< 10%); 1 (≥10% - ≤25%); 2 (>25% - <50%) and 3 (≥ 50%). The staining intensity was scored as 1; 2; 3 for weak, moderate, and strong. Then intensity and percentage scores were summed and considered as total score 0-2 (negative), total score 3-4 (positive), and 5-6 (strongly positive) [14].

EGFR expression was evaluated on the percentage of membranous and cytoplasmic and the intensity of tumor cells staining as follows: 0 for no positive cells; 1(1–25%); 2 (26–50%); 3 (51–75%); and 4 (>75%). The staining intensity for EGFR was scored as 0 (absent), 1 (weak), 2 (moderate), and 3 (strong). Then, the calculation of the final score was done by multiplying the score of staining intensity and percentage of stained cells. The negative group had a score of 0, weak had a score of 1-4, moderate had a score of 5-8 and strong had a score of 9-12 [9].

Results

Four hundred and three patients were obtained from ten years the medical record. There is fifty-three Radical Cystectomy patients urothelial carcinoma of bladder. SPSS v 25.0 was used to calculate statistical analyses and Spearman's test was employed to analyze the correlation between VEGF and EGFR with significance level of $p<0.05$. The correlation between EGFR and VEGF expression in bladder urothelial carcinoma was significant positive correlation $r_s = 0.418$; $p=0.002$ ($p<0.05$), (Table 1, 2, Figure 1).

Variable	Score		Σ
VEGF	Negative	(Score 0-2)	10
	Positive	(Score 3-4)	18
	Strong positive	(Score 5-6)	25
	Total		**53**
EGFR	negative	(Score 0)	16
	weak	(Score 1-4)	28
	moderate	(Score 5-8)	7
	Strong	(Score 9-12)	2
	Total		**53**

Table 1. Immunohistochemistry of VEGF and EGFR.

Correlation between EGFR and VEGF	
r_s	0.418*
p	0.002
n	53

Tabel 2. Spearman Test of Correlation between EGFR and VEGF in bladder urothelial cell carcinoma. *α< 0.05, considered as significant.

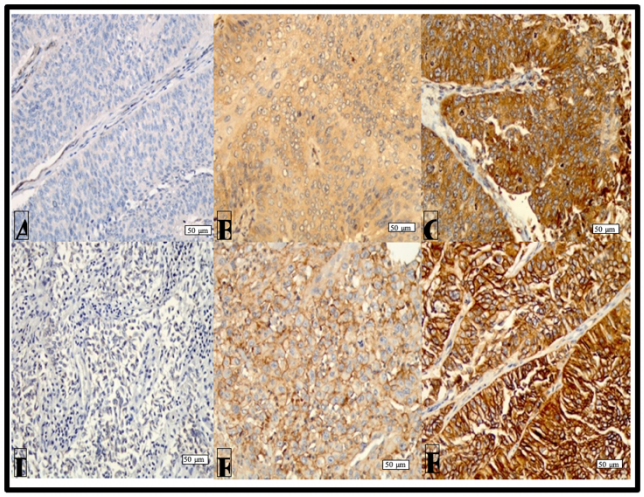


Figure 1. VEGF expression, 400 HPF (A.Weak, B.Moderate, and C.Strong); EGFR expression, 400 HPF (D. Weak, E. Moderate, and F. Strong).

Discussion

VEGF positive immunoreaction was observed as a brown color staining localized in the cytoplasm, and EGFR expressed was found at the plasma membrane and/or cytoplasm of the cell. A significant positive correlation was found between VEGF and EGFR expression in bladder urothelial carcinoma (r_s = 0.273; p=0.048).

Of all samples (53 samples), 43 samples (81.1%) were positive for VEGF, indicating that most of the samples expressed VEGF, which means that it has the opportunity to do therapy with anti-VEGF. VEGF is an angiogenic factor that is important to stimulate angiogenesis and tumor growth factors [6–8]. The growth of tumor is heavily affected by angiogenesis, which is the formation of blood vessels that distribute nutrients and oxygen to higly proliferate tumor cells [5].

VEGF, a member of a gene family, is known to be one of the main regulators of pathological and physiological angiogenesis [15,16]. Several studies found that VEGF is highly expressed in various cases of tumors in humans [16–18].Initially, the expression of VEGFR-2 was prefominantly found in endothelial cells while VEGF-A expression was detected in various tumor cell lines [16,19]. VEGF released from tumor stimulates the proliferation and sprouting of endothelial cells [10]. Although angiogenesis induction may cater the tumor with more nutrients and oxygen at first, the utmost response is insufficient.This is due to the continuously remodeled vasculature of tumor that is tortuous and leaky, which causes irregular blood flows [10]. The significance of VEGF expression has been investigated in various types of cancer.Various researches have investigated the role of VEGF in the progression and invasion of bladder cancer[6–8]

There are several factors that can regulate VEGF expression, including hypoxia, free radicals, pH imbalance, and nutrient deficiencies [20]. Tumor cells express hypoxia-inducible factors (HIF) to compensate for hypoxia, nutrient deficiency and escape tumor necrosis. This will activate the transcription of over 40 genes, such as VEGF [7]. In accordance with a previous study, there was a positive correlation between VEGF and HIF-1α immunoreactivities (P<0.001) in urothelial carcinoma [21]. VEGF and VEGF receptor transcription is directly activated by HIF-1α by binding hypoxia response element (HRE) and performs a crucial role during tumor formation and normal growth [22].

The prognostic value of VEGF-A tissue expression in urothelial bladder cancer still remains unanswered. It was discovered that high levels of VEGF-A were related to higher reccurance rates and lower survival rates [23–25], however several researches had contradicting results [6,8]. In vitro studies revealed that the inhibition of angiogenesis effectively decreases

invasion and proliferation of UBC, leading to further research on angiogenesis-targeted agents [8]. The growth of several tumor cell lines were successfully inhibited using anti-VEGF antibody treatment, which implies that blocking VEGF alone may inhibit angiogenesis thus suppress the growth of tumor [16]. Recent researches reveal that VEGF-targeted therapies have the ability to alter the interaction between tumor cells and their environment by transforming tumor cells to have a more metastatic and aggressive phenotype. This section highlights several tissues for which there are currently no clear solutions but which warrant consideration when therapeutic strategies. Methods to observe the response to anti-angiogenic therapy in vivo and several anti-angiogenic treatments for cancer are presently approved by the FDA[10].

It is apparent that the anti-tumor effects of multi-kinase inhibitors have the ability to both block signaling in tumor cells and other types of cells and also block angiogenic signaling pathways. The importance of understanding in vivo performance of anti-angiogenic drugs and also finding possible combinations of drugs is a crucial step to produce better results and improve the success of anti-angiogenic therapies. However, at this moment there are no validated biomarkers that can determine the suitablility of angiogenic therapy for different cases of cancer patients [10,26]. It is essential to conduct further research to discover new markers that are suitable to measure the efficacy of anti-angiogenic strategies [10].

Of all samples (53 samples), 37 samples (69.9%) were positive for EGFR, indicating that most of the samples expressed EGFR. This means that it has the opportunity to do therapy with anti-EGFR. As it is currently known, EGFR is a tyrosine kinase transmembrane receptor that plays an important role in carcinogenesis [1,9] It is overexpressed in many tumors, such as lung, head and neck, colon, breast, prostate, bladder and kidney cancer [9]. EGFR is a tyrosine kinase receptor that is a part of the HER/erbB family [27].

The structure of this membrane-spanning glycoprotein includes a cytoplasmic domain containing the tyrosine kinase domain, a region of hydrophobic transmembrane and an essential extracellular ligand-binding domain. Increased activitiy or disregulation of EGFR signaling pathways and EGFR overexpression are suggested mechanisms, by which malignant phenotype may confer with the presence of EGFR [13,28,29].

It is hypothesized that the increase of EGFR-mediated signaling can cause a cell to shift into a state of unregulated and continuous cell proliferation, thus increasing the mass of tumor due to the high number of malignant cells. In agreement with this, expression or overexpression of EGFR is found in various types of solid tumor [13,29].

The activation of EGFR pathways is associated to several mechanisms crucial in tumor progression, including proliferation, transformation, cell survival and metastasis, migration, adhesion, motility and differentiation [13,27]. Various solid tumors are known to express EGFR, some of the many include non-small cell lung cancer (NSCLC), pancreatic, colon, pancreatic, head and neck, ovarian, glioblastoma, breast and bladder[13,30]. EGFR expression was significantly linked with poor clinical outcome, tumor progression and high tumor stage[1]. EGFR inhibitors have clear anti-proliferative and anti-angiogenic effects [31]. Recently, it was revealed that prior chemotherapy rendered patients with muscle-invasive TCC to be resistant to EGFR family inhibitors as well. Nevertheless, family of EGFR inhibitors may work well in those groups of patients in whom no prior chemotherapy has been given, and EGFR is over expressed [28]. The EGFR score has a statistically significant association with prognostic factors like grade of tumor, size of tumor, presence of Cancer Insitu (CIS) and shape of stalk but not with age, gender, stage, muscle invasion and number of tumors. Overexpression of EGFR in TCC of bladder makes this receptor a good therapeutic target [1] It is for various reasons that underlie anti-EGFR therapy in tumors.

In solid tumors, EGFR and VEGF pathways appear to be related, specifically with respect to angiogenesis. TGF-a and EGF encourage the expression of VEGF by way of EGFR activation in cell culture models. In addition to that, these pathways also have pro-angiogenic properties [13,30,32]. Evidence has shown that tumor-associated endothelial cells express EGFR [13,33] and that aberrant EGFR expression correlates with poor prognosis [13,30]. There is a possibility that angiogenesis is modulated by the EGFR pathway which up-regulates VEGF or other key mediators in

angiogenesis [13,32]. However, the inhibition of EGFR does not block VEGF, which allows angiogenesis to occur around the tumor, thus induces tumor growth [13].

There is a close relationship between VEGF and EGFR. EFGR expression causes up-regulation of VEGF signaling. Meanwhile, VEGF up-regulation independent of EGFR signaling shows contribution to resistance to EGFR inhibition. As a result, inhibiting both VEGF and EGFR pathways may show effects in overcoming resistance to EGFR inhibition and improving the efficacy of anti-tumor [13].

Two crucial factors that affect the dissemination and growth of tumors are EGFR and VEGF. The VEGF and EGFR pathways are closely associated and share similar downstream signaling pathways [34]. In addition, VEGF expression is driven by EGF, which is a growth factor and also a key EGFR ligand [35]. EGFR and VEGF play a crucial function in the growth and progression of tumors through the exertion of direct and indirect impacts on tumor cells [34]. Biological agents administered alone or combined with standard cytotoxic therapies that target the EGFR and VEGF pathways have shown positive benefits in various types of human cancers. The inhibition VEGF-related pathways is suspected to have effect on the action mechanism of agents that target EGFR [30]. However, over activation of VEGF expression independent of EGFR signaling is suspected to cause tumor resistance to anti-EGFR therapy [12,13]. These various reasons are in accordance with the results of this research, which states that there is a relationship between EGFR and VEGF in bladder urothelial carcinoma. So that, it can be considered a combination therapy between anti-VEGF and anti-EGFR.

There is a relation between EGFR and VEGF signaling pathways. VEGF is the main mediator in angiogenesis and the over expression of VEGF may stimulate resistance to EGFR. However, inhibiting EGFR does not directly inhibit angiogenesis. Because of this, anti-VEGF agent is needed to prevent angiogenesis from occuring. So, an anti-VEGF agent should be used together with any treatement that requires anti-EGFR agent. Many agents that target EGFR or VEGF used in combination with standard chemotherapy regimens have shown positive results and has been regulatory approved for cancer therapy. The combination of EGFR and VEGF inhibitors with other therapies may contribute in overcoming tumor resistance mechanisms, thus result in better therapeutic outcomes [13].

The regulation of cancer integrity and permeability that depends on the intravastation sustaining intratumoral vessels on VEGF can be reflected in increased benefits in the combination of anti-EGFR therapies and anti-VEGF agents that are now mainly used as a treatment for late-stage cancers.

Results in this study suggest that EGFR/IL-8/ neutrophil MMP-9/VEGF pathway is a valid axis that has the ability to compromise intratumoral vasculature during anticancer therapy [36]. HER2 and EGFR are therapeutic targets that have shown promising results and are currently under investigation and futher research in bladder cancer. However, potential mechanisms of resistance and the selection of most appropriate strategies to this approach need to be futher researched as it still remains unclear [37].

The main limitation of this research is the low number of patients from only one hospital and no analysis of their current condition.

Conclusions

In summary, this study revealed an important correlation between EGFR and VEGF in bladder urothelial cancer.

Acknowledgements

We additionally thank the Director of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Declaration of Interest

The authors declare no conflicts of interest.

References

1. Barua SK, Das N, Baruah SJ, et al. Correlation of epidermal growth factor receptor score with prognostic variables in transitional cell carcinoma of urinary bladder among north-eastern Indian population. *Int Surg J*. 2018;5(9):3083. doi:10.18203/2349-2902.isj20183727
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492

3. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. *Eur Urol*. 2017;71(1):96-108. doi:10.1016/j.eururo.2016.06.010
4. Siegel RL, Miller KD, Jemal A. Cancer Statistics , 2018. *CA Cancer J Clin*. 2018;68(1):7-30. doi:10.3322/caac.21442.
5. Magalhães A, Dias S. Angiogenesis – Vessels Recruitment by Tumor Cells. 2019:141-157. doi:10.1007/978-3-030-11812-9_8
6. Kopparapu PK, Boorjian SA, Robinson BD, et al. Expression of VEGF and Its receptors VEGFR1/VEGFR2 is associated with invasiveness of bladder cancer. *Anticancer Res*. 2013;33(6):2381-2390.
7. Bronsert P, Werner M. Pathology of tumor angiogenesis. *Tumor Angiogenes A Key Target Cancer Ther*. 2019:253-274. doi:10.1007/978-3-319-33673-2_6
8. Fus ŁP, Górnicka B. Role of angiogenesis in urothelial bladder carcinoma. *Cent Eur J Urol*. 2016;69(3):258-263. doi:10.5173/ceju.2016.830
9. Li W, Wang Y, Tan S, et al. Overexpression of epidermal growth factor receptor (EGFR) and HER-2 in bladder carcinoma and its association with patients' clinical features. *Med Sci Monit*. 2018;24:7178-7185. doi:10.12659/MSM.911640
10. Weis SM, Cheresh DA. Tumor angiogenesis: Molecular pathways and therapeutic targets. *Nat Med*. 2011;17(11):1359-1370. doi:10.1038/nm.2537
11. Guéguinou M, Gambade A, Félix R, et al. Lipid rafts, KCa/ClCa/Ca2 + channel complexes and EGFR signaling: Novel targets to reduce tumor development by lipids? *Biochim Biophys Acta - Biomembr*. 2015;1848(10):2603-2620. doi:10.1016/j.bbamem.2014.10.036
12. Vallböhmer D, Zhang W, Gordon M, Yang DY, Yun J, Press OA. Molecular Determinants of Cetuximab Efficacy. 2021;23(15):3536-44. doi:10.1200/JCO.2005.09.100
13. Tabernero J. The role of VEGF and EGFR inhibition: Implications for combining Anti-VEGF and Anti-EGFR Agents. *Mol Cancer Res*. 2007;5(3):203-220. doi:10.1158/1541-7786.MCR-06-0404
14. Al-bassam SS., Kadhim H., Khashman B. Possible association of vascular endothelial growth factor with grades of breast cancer. *New Iraqi J Med*. 2013;9(3):82-84.
15. Ferrara N. History of Discovery. 2009:2008-2010. doi:10.1161/ATVBAHA.108.179663
16. Ferrara N. Pathways mediating VEGF-independent tumor angiogenesis. *Cytokine Growth Factor Rev*. 2010;21(1):21-26. doi:10.1016/j.cytogfr.2009.11.003
17. Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. 2008;8(august). doi:10.1038/nrc2403
18. Oncology M, Francisco SS. Vascular Endothelial Growth Factor : Basic Science and. 2004;25(4):581-611. doi:10.1210/er.2003-0027
19. Ferrara N. VEGF and the quest for tumour angiogenesis factors. 2002;2(October).
20. Wang F, Xu P, Xie KC, Chen XIAF, Li CY, Huang Q. Effects of tumor microenviromental factors on VEGF expression. 2013:539-544. doi:10.3892/br.2013.115
21. Gu ME. Evaluation of relationship between HIF-1 a immunoreactivity and stage , grade , angiogenic profile and proliferative index in bladder urothelial carcinomas. 2010:103-107. doi:10.1007/s11255-009-9590-5
22. Yang Y, Sun M, Wang L, Jiao B. Cellular Biochemistry. 2013;974(September 2012):967-974. doi:10.1002/jcb.24438
23. Sun YW, Xuan Q, Shu QA, et al. Correlation of tumor relapse and elevated expression of survivin and vascular endothelial growth factor in superficial bladder transitional cell carcinoma. 2013;12(2):1045-1053.
24. Fauconnet S, Lascombe I. Expression analysis of VEGF-A and VEGF-B : Relationship with clinicopathological parameters in bladder cancer. 2009;(June). doi:10.3892/or
25. Yang CC, Chu KC, Yeh WM. The expression of vascular endothelial growth factor in transitional cell carcinoma of urinary bladder is correlated with cancer progression. *Urol Oncol Semin Orig Investig*. 2004;22(1):1-6. doi:10.1016/S1078-1439(03)00015-2
26. Jain RK, Duda DG, Willett CG, et al. therapy. 2011;6(6):327-338. doi:10.1038/nrclinonc.2009.63.Biomarkers
27. Yarden Y, Sliwkowski MX. UNTANGLING THE ErbB SIGNALLING NETWORK. 2001;2(February).
28. Mooso BA, Vinall RL, Mudryj M, Yap SA, White RW, Ghosh PM. HHS Public Access. 2016;193(1):19-29. doi:10.1016/j.juro.2014.07.121.The
29. Laskin JJ, Sandler AB. Epidermal Growth Factor Receptor Inhibitors in Lung Cancer Therapy. 2004.
30. Ellis LM. Epidermal growth factor receptor in tumor angiogenesis. 2004;18:1007-1021. doi:10.1016/j.hoc.2004.06.002
31. Kassouf W, Dinney CPN, Brown G, et al. Uncoupling between Epidermal Growth Factor Receptor and Downstream Signals Defines Resistance to the Antiproliferative Effect of Gefitinib in Bladder Cancer Cells. 2005;2(22):10524-10536. doi:10.1158/0008-5472.CAN-05-1536
32. Perrotte P, Matsumoto T, Inoue K, et al. Advances in Brief Anti-epidermal Growth Factor Receptor Antibody C225 Inhibits Angiogenesis in Human Transitional Cell Carcinoma Growing Orthotopically in Nude Mice 1. 1999;5(February):257-264.
33. Kim S, Uehara H, Karashima T, Shepherd DL, Killion JJ, Fidler IJ. Blockade of Epidermal Growth Factor Receptor Signaling in Tumor Cells and Tumor-associated Endothelial Cells for Therapy of Androgen-independent Human Prostate Cancer Growing in the Bone of Nude Mice 1. 2003;9(March):1200-1210.
34. Herbst RS, Johnson DH, Mininberg E, et al. Phase I / II Trial Evaluating the Anti-Vascular Endothelial Growth Factor Monoclonal Antibody Bevacizumab in Combination With the HER-1 / Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Erlotinib for Patients With Recurrent Non – Small-Cell Lun. 2021;23(11). doi:10.1200/JCO.2005.02.477
35. Niu G, Wright KL, Huang M, et al. Constitutive Stat3 activity up-regulates VEGF expression and tumor angiogenesis. 2008;(December 2001):2000-2008. doi:10.1038/sj/onc/1205260
36. Minder P, Zajac E, Quigley JP, Deryugina EI. EGFR Regulates the Development and Microarchitecture of Intratumoral Angiogenic Vasculature Capable of Sustaining Cancer Cell Intravasation. *Neoplasia (United States)*. 2015;17(8):634-649. doi:10.1016/j.neo.2015.08.002
37. Mora Vidal R, Regufe da Mota S, Hayden A, et al. Epidermal Growth Factor Receptor Family Inhibition Identifies P38 Mitogen-activated Protein Kinase as a Potential Therapeutic Target in Bladder Cancer. *Urology*. 2018;112:225.e1-225.e7. doi:10.1016/j.urology.2017.10.041.

Source details

Journal of International Dental and Medical Research

Scopus coverage years: from 2009 to Present

Publisher: Ektodermal Displazi Grubu

ISSN: 1309-100X

Subject area: Dentistry: General Dentistry

Source type: Journal

View all documents > | Set document alert | Save to source list | Source Homepage

CiteScore 2021
1.1

SJR 2021
0.212

SNIP 2021
0.460

CiteScore | CiteScore rank & trend | Scopus content coverage

¡ Improved CiteScore methodology

CiteScore 2021 counts the citations received in 2018-2021 to articles, reviews, conference papers, book chapters and data papers published in 2018-2021, and divides this by the number of publications published in 2018-2021. Learn more >

CiteScore 2021

$$1.1 = \frac{1{,}171 \text{ Citations } 2018 - 2021}{1{,}039 \text{ Documents } 2018 - 2021}$$

Calculated on 05 May, 2022

CiteScoreTracker 2022

$$0.9 = \frac{754 \text{ Citations to date}}{839 \text{ Documents to date}}$$

Last updated on 05 May, 2022 • Updated monthly

CiteScore rank 2021

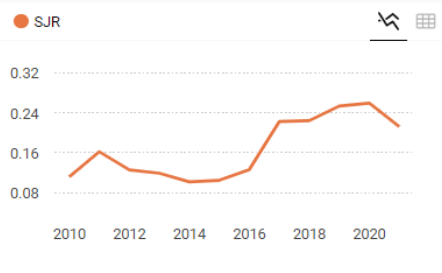
Category	Rank	Percentile
Dentistry └ General Dentistry	#79/109	27th

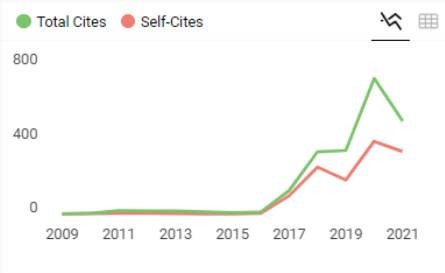
View CiteScore methodology > | CiteScore FAQ > | Add CiteScore to your site

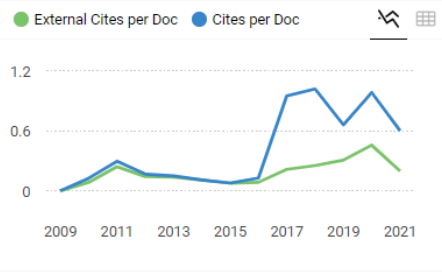
Journal of International Dental and Medical Research

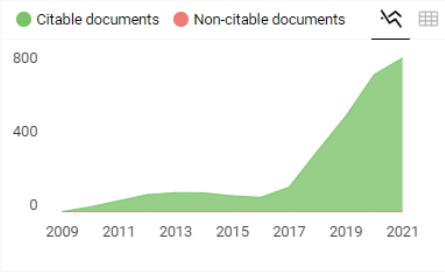
COUNTRY	SUBJECT AREA AND CATEGORY	PUBLISHER	H-INDEX
Turkey Universities and research institutions in Turkey	Dentistry Dentistry (miscellaneous)	Ektodermal Displazi Grubu	14

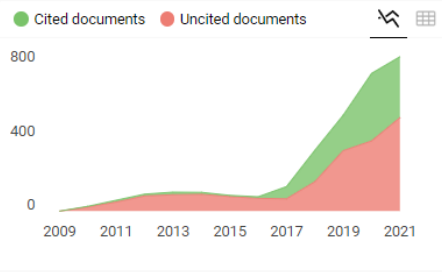
PUBLICATION TYPE	ISSN	COVERAGE
Journals	1309100X	2009-2021











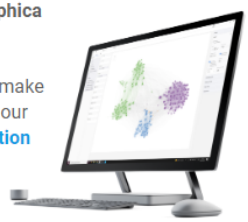
← Show this widget in your own website

Just copy the code below and paste within your html code:

<a href="https://www.scima(

SCImago Graphica

Explore, visually communicate and make sense of data with our **new data visualization tool.**



KOMITE ETIK PENELITIAN KESEHATAN
RSUD Dr. SOETOMO SURABAYA

KETERANGAN KELAIKAN ETIK
(" ETHICAL CLEARANCE ")

1851/KEPK/II/2020

KOMITE ETIK RSUD Dr. SOETOMO SURABAYA TELAH MEMPELAJARI SECARA SEKSAMA RANCANGAN PENELITIAN YANG DIUSULKAN, MAKA DENGAN INI MENYATAKAN BAHWA PENELITIAN DENGAN JUDUL :

" Korelasi antara Ekspresi VEGF dan MMP-9 dengan Stadium T Karsinoma Urothelial Buli "

PENELITI UTAMA : Anny Setijo Rahaju, dr., Sp.PA (K)
PENELITI LAIN : 1. Nila Kurniasari, dr., Sp.PA (K)
2. Novalia Chumaladewi Guntarno, dr
UNIT / LEMBAGA / TEMPAT PENELITIAN : RSUD Dr. Soetomo

DINYATAKAN LAIK ETIK

Berlaku dari : 27/02/2020 s.d 27/02/2021
Surabaya, 27 February 2020
KETUA

RSUD Dr. Soetomo Komite Etik Penelitian Kesehatan

(Dr. Eliezus Hanindito, dr., Sp.An, KIC,KAP)
NIP. 19511007 197903 1 002

) Sertifikat ini dinyatakan sah apabila telah mendapatkan stempel asli dari Komite Etik Penelitian Kesehatan