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THE POTENTIAL OF EPIDERMAL GROWTH FACTOR RECEPTOR MOLECULES AS PREDICTORS OF CLINICAL STAGE AND PROGNOSIS OF SQUAMOUS CELL CARCINOMA IN MEDAN CITY

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ABSTRACT

Squamous cell carcinoma (SCC) is a non-melanoma skin malignant tumor originating from the suprabasal keratinocytes of the epidermis. Exposure to ultraviolet radiation is known to be one of the main triggers so that the place of predilection for this malignancy is an area that is often exposed to sunlight, especially the head and neck. Assessing the potential of the Epidermal Growth Factor Receptor (EGFR) molecule in predicting theclinical stage and prognosis of squamous cell carcinoma of the skin. This study used 40 samples of keratinized and non-keratinized SquamousCell Carcinoma patients who were then given EGFR staining by immunohistochemistry. The result of staining on EGFR by immunohistochemistry is brown, whereas if it appears blue, the result is negative. The relationship of EGFR expression from 40 slides of SCC collected with EGFR immunohistochemical staining found 6 malignant tumors (15%) negative EGFR, then 14 malignant tumors (35%) showed weak grade (positive 1), 6 malignant tumors (15%) showed moderate expression level (positive 2) and 14 malignant tumors (35%) showed strong expression (positive 3). The test results showed a significant relationship between the level of EGFR with the clinical stage of squamous cell carcinoma as indicated by the value of $p = 0.030$ (< 0.05). The analysis was analyzed using the two-tailed Bivariate Correlation test. Expression of EGFR molecules on immunohistochemical staining of SCC of the skin canbe used to determine the clinical stage of SCC of the skin.

Keyword :Epidermal Growth Factor Receptor, EGFR, skin cancer, squamous cell carcinoma, SCC, Immunohistochemistry

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1. INTRODUCTION

Skin cancer is the third most common cancer after uterine cancer and breast cancer inIndonesia.[1] There are several types of skin cancer, one of which is Squamous Cell Carcinoma (SCC) of the skin. Squamous Cell Carcinoma is a non-melanoma skin cancer originating from the suprabasal keratinocytes of the epidermis. Excessive exposure to ultravioletradiation is known to be one of the main triggersfor SCC, the site of predilection for this malignancy is most often areas exposed to sunlight, especially the head and neck.[2] In the development of its incidence, skin SCC ranks second most after the type of skin cancer Basal Cell Carcinoma (BSC).[3] Predisposing factors that influence the occurrence of SCC include carcinogens and ultraviolet (UV) radiation.

Indonesia is geographically located on the equator of the sun where the potenti for UV radiation to the skin is greater. Ultraviolet A and B are harmful to the skin, but ultraviolet B (UVB)with a wavelength (200-320 nm) is morecarcinogenic. UVB radiation causes covalent bonds to form between pyrimidines and the formation of mutagens.[2] Excessive exposure of the skin to UV rays is a risk for skin tumors that progress to skin cancer, especially SCC in normal epithelial tissue due to damage Deoxy Nucleic Acid (DNA) and mutations TP53 in the cell cycle process.[4] Benign and

malignant so thatskin cancer is not diagnosed with certainty. Analysis of gene expression is needed to monitorthe global gene expression profile of skin cancertissues.[5] By using the theory of the origin of genes in humans, candidate tumor markers canbe identified to be used as a means of diagnosing and prognosticating skin cancer, oneof which is EGFR.

Epidermal Growth Factor Receptor (EGFR) is a 170 kDa transmembrane tyrosine kinase receptor which is a member of the cell surface receptor. The EGFR gene is located on chromosome 7p12. Normal skin epithelial tissuehas expression EGFR at a certain level and indicates that the signal expressed by EGFR isrequired for proliferation.[6,7]

Several previous studies suggest that there is an increase in expression EGFR in head and neck malignancies. Fajriyah et al, conducted a study on lung cancer tissue samples, using immunohistochemical examination found EGFR mutations 61.1% in women, 44% in men, with a history of not smoking 60.7%, smokers 37.3%, in Asian race, the highest was found in Vietnam 64.2%and India only 22.2%.[8] Research by Lenny S et al in2016, used 196 samples as material for examining EGFR mutations using the Formalin-Fixed Paraffin- Embedded (FFPE) method. As a result, the number of cases detected by EGFR mutations was 71/196 (36%), wild type was 106/196 (54%), and invalid was19/196 (10%). In 71 cases where EGFR mutations were detected, single and combination mutationswere found.[8]

Epidermal Growth Factor Receptor which is elevated in some carcinomas is a transmembrane glycoprotein resulting from activation of the proto- oncogene c-Erb-B2. Under normal conditions, this protein is expressed in small amounts in human tissues, but overexpression of EGFR in many types of carcinoma in humans can be caused by activationof the proto-oncogene c-Erb-B2.[9]

Epidermal Growth Factor Receptor has a role in cells as an enhancer of cell proliferation, angiogenesis, and inhibits apoptosis so that it is needed in normal conditions of the cell cycle. EGFR-ligand binding will activate various signal transduction pathways in cell regulation resulting in the process of differentiation, apoptosis, proliferation, and angiogenesis. The pathways that are activated by EGFR are the RasRaf-MEK-ERK pathway that affects cell proliferation and differentiation and the phosphatidylinositol 3-kinase-Akt/PKB pathway that affects angiogenesis and inhibits apoptosis. Overexpression of EGFR indicates a malignant transformation and is associated with tumor differentiation.

Recently, medical science has looked at the use of antibody markers in immunological examinations, especially in very wide and varied skin pathologies. So the authors were interested in seeing whether the conventional microscopic assessment of cutaneous epithelial malignancies could be comparable to immunohistochemicaltesting EGFR. If the expression is EGFR found in tissue samples from skin cancer patients, EGFR can be used as a histopathological diagnosis, clinical staging, prognosis, and also the development of the latest anti-EGFR therapy as a targeted therapy that has a direct effect on malignant cells. The findings of this study could support the work of clinicians and provide the best service to patients.

Hopefully, with this study, the accuracy of thediagnosis of malignancy of epithelial cancer will become more apparent and have an impact on. Assessment of expression was *EGFR* determined based on analysis of the percentage of positive tumor cells, which were then given a score of 0: not twisted, positive 1: twisted in 1-25% of tumor cells, positive 2: twisted in 26-25% of tumor cells, positive 3: twisted in 51-75% tumor cells, positive 4: twisted in 76-100% tumor cells. Furthermore, scores of 0 are called negative, and scores 1, 2, 3, and 4 are called positive.

Immunohistochemical values were *EGFR* Statistical analysis performed by statistical analysis of Bivariate Correlation Test (two-tailed).

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2. METHOD

The method used in this study is a cross sectional study with a sample of parafifin blocks of patients with a diagnosis of keratin and nonkeratin Squamous Cell Catcinoma obtained from the Faculty Of Anatomical Pathologu Laboratory. Medical University Of Muhammadiyah North Sumatera has many as 40 samples. Furthemore, the sample was given immunohistochemical EGFR staining. Evaluation of resulth in the form of histology of skin organs from the reslth in the form of H&E and hisyopahological staining and expression of EGFR proteins with immunohistochemistry. H$E preparation are observed descriptively qualitatively to find out about the severity of skin cancer. EGFR immunohistochemical preparations are analyzed semi-quantitatively.

Assesment of expression was EGRF determined based in analysis of the pecentage of positive tumor cells, wicch were then given a score of 0: not twisted, possitive 1:twisted in 1-25% of tumor cells, possitive 2: twisted in 26-25% of tumor cells, possitive 3: twisted in 51-75% tumor cells, positive 4 :twisted in 76-100% tumor cells. Furthermore, scores of 0 are calls negative and scores 1,2,3, and 4 are called positive.

Immunohistochemical values were EGFR Statistical analysos performed by statistical analysis of Bivariate Correlation test (two-tailed).

3. RESULTS

Details of the samples used based on their microscopis diagnosis can be seen in table 1.

Table 1 : Pecentage Of Histopathological diagnoses

	Histopathological Diagnosis	Total	Percentage (%)
Skin tumor	Keratinized squamous cell carcinoma	32	80
	Non-keratinized squamous cell carcinoma	8	20
	Total	40	100

On histopathological examination with hematoxylin-eosin staining obtained a diagnosis of squamous cell carcinoma insistent as many as 32 cases (80%) and non-keratin squamous cell carcinomaas many as 8 cases (20%). EFGR immunohistochemical staining is performed to be able to assess the appearance of eachsample on malignant skin tumors. An assessment of 6 malignant tumors (15%) showed no EGFR (negative) protein expression, 14 malignant tumors (35%) showed weak expressions (positive 1), 6 malignant tumors (15%) showed moderate expression and 14 malignant tumors (35%) showed strong expressions (Tables 4.2 and 4.3).

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Table 2: Immunohistochemical appearance of EGFR in histopathology of skin tumors

		Skin tumor				Total	Percentages(%)
		Keratinized squamous cell carcinoma		Non-keratinized squamous cell carcinoma			
		n	%	n	%		
Immunohistochemistry EGFR	Positive	26	81	8	100	34	85
	Negative	6	19	0	0	6	15
	Total	32	100	8	100	40	100

Table 3: Immunohistochemistry display of EGFR (+) on histopathology of skin tumors

		Skin tumor				Total	Percentages(%)
		Keratinized squamous cell carcinoma		Non-keratinized squamous cell carcinoma			
		n	%	n	%		
Immunohistochemistry EGFR	Strong positives	11	42	2	25	13	38
	Moderate positives	6	23	2	25	8	26
	Weak positives	9	35	4	50	13	38
	Total	26	100	8	100	34	100

Table 4: Bivariate Correlation Test (two-tailed)

		Outward score EGFR	Clinical Stadium
Outward score EGFR	Pearson Correlation	1	,344*
	Sig. (2-tailed)		,030
	N	40	40
Clinical stage	Pearson Correlation	,344*	1
	Sig. (2-tailed)	,030	
	N	40	40

Bivariate correlation test (two-tailed) between *EGFR* immunohistochemical ratings obtained a value of p = 0.030 (<0.05) which means there is a significant correlation. Results can be seen in table 4.

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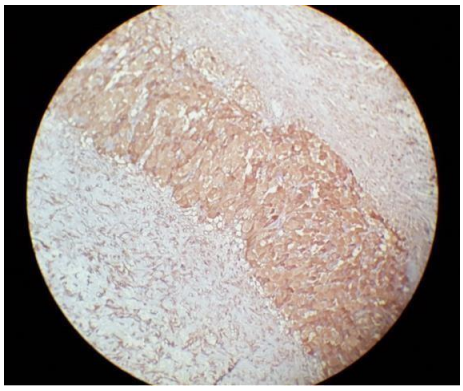

Figure 1. Squamous cell carcinomawith a strong positive appearance

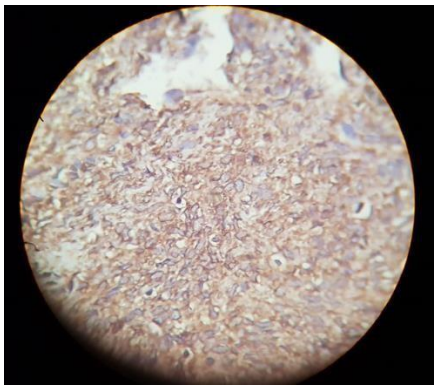

Figura 2. Squamous cell carcinoma with a moderate positive

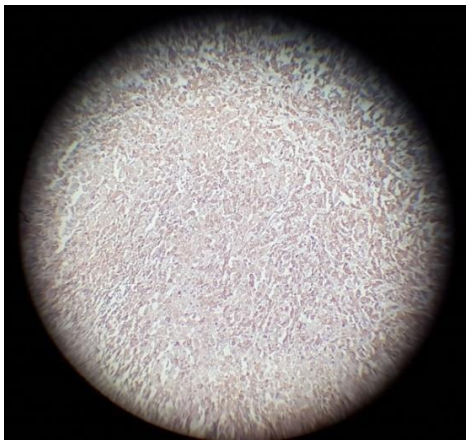

Figure 2. Squamous cell carcinoma witha moderate positive appearancE

DISCUSSIONS

EGFR immunochemical examinationcan be used as a marker of increased expressionof these proteins in tissues. This study obtained data on the appearance (expression) of EGFR immunohistochemical which is one of the tumor suppressor genes known as the master guardian of the genome and acts as the main element thatmaintains genetic stability. To maintain controlledcell division, a tumor suppressor gene is needed.Where the tumor suppressor gene does not function properly, cell proliferation cannot be controlled and causes cancer.

The detection of the gene shows thatthere has been a mutation due to damage to the tumor suppressor gene, EGFR. The stronger theEGFR expression indicates the aggressiveness ofthe tumor is increasing. Increased EGFRexpression is related to the development of the EGFR gene itself, starting from the early stages ofthe tumor to the advanced stage which indicates that the higher

the tumor stage, the deviation of EGFR-forming genes will increase and will show an increase in the expression of EGFR, especially at the KSS level.

4. CONCLUSION

There is a link between increasedexpression of Epidermal Growth Factor Receptor(EGFR) and clinical stage skin squamous cellcarcinoma.

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REFERENCES

Djuanda A. Ilmu penyakit kulit dan kelamin. Jakarta: Balai Penerbit FKUI. h.229-41; 2007.

Widiawaty, A. Metode Pemeriksaan pada Sistem TNM untuk Karsinoma Sel SkuamosaKulit. JIK. 2016; Jilid 10, Nomor 1:5-16

Hendaria MP. Kanker Kulit. Denpasar: Departemen Ilmu Bedah FakultasKedokteran Universitas Udayana; 2015.

Kumar V, Cotran R S, Robbins S L. Robbins Basic Pathology. 9th ed. Canada: Elsevier; 2013

Colleen D, Cheryl A, Sherman B, Ellen S, Pizer F J, Montz D. Large-Scale Serial Analysis of Gene Expression Reveals GenesDifferentially Expressed in Ovarian Cancer,Cancer Research. 2000; 60:6281–6287.

Liang M, Carmen J, Michael D, Heather H, Brock C, Robert I, et al,. Biomarkers of HPV in Head and Neck Squamous Cell Carcinoma. Cancer Res. 2012; 72:5004-13.

Braut T, Krstulja M, Manestar D, HadzisejdicI, Jonjic N, Grahovac B, et al,. Epidermal growth factor receptor protein expression and gene amplification in normal, hyperplastic, and cancerous glottic tissue: immunohistochemical and fluorescent in situ hybridization study on tissue microarrays.Croat Med J. 2009; 50:370-9.

Fajriyah, ADENOCARCINOMA DENGAN MUTASI EGFR. Jurnal Kedokteran Syiah Kuala. 2018; 18 1): 66-68, April 2018.

Vaezi A dan Grandis J R. Bailey's Head and Neck Surgery Otolaryngology fifth edition dalam Head and Neck Tumor Biology.Lippincott Williams&. WJ.lkins, a Wolters Kluwer business. 2014:1645-70.

Chobanian N, Dietrich CS. Surgical Clinics ofNorth America; 2008.

Laurentia A, Djawad K, Vitayani S, Suswardana. Karsinoma Sel Skuamosa yangBerkembang dari Ulkus Marjolin Akibat Luka Gigit. Makassar: Bagian Ilmu Kesehatan Kulit dan Kelamin RS Wahidin Sudirohusodo; 2009.

Lubis H M L, Hariaji I. Potensi Ekstrak buah legundi (vitrex trifolia) sebagai penghambat pembelahan dan pertumbuhan sel tumor kulitpada tikus putih yang diinduksi benzoalphopyrene. Medan: Penelitian Dosen Pemula Dikti; 2016.

Musyarifah Z. Profil Klinikopatologi Karsinoma Sel Skuamosa Kepala dan Leherdi Padang. Jurnal Kesehatan Andalas. 2020;9(2).

Sari, L. Mutasi EGFR pada Non-Small Cell Lung Cancer di Rumah Sakit Kanker "Dharmais" Indonesian Journal of Cancer.2016; Vol. 10, No. 4 October – December.