Analysis Titer of Epidermal Growth Factor Receptor on Nasopharyngeal Cancer Patients Based on Stadium and Histopathological Profile in Dr. Zainoel Abidin General Hospital Banda Aceh

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Analysis Titer of Epidermal Growth Factor Receptor on Nasopharyngeal Cancer Patients Based on Stadium and Histopathological Profile in Dr. Zainoel Abidin General Hospital Banda Aceh

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Abstract

Introduction: Nasopharyngeal carcinoma ranks first in incidence at the head and the neck departement. Epidermal Growth Factor Receptor (EGFR) is a transmembrane tyrosine kinase receptor from the ErbB family. Excess EGFR titer is an indication of a malignant transformation and cell differentiation that can ultimately determine the effectiveness of using anti EGFR drugs nasopharyngeal carcinoma patients.

Objective: To determine the EGFR titer of nasopharyngeal cancer tissue based on the stage and histopathological profile in Dr. Zainoel Abidin Banda Aceh.

Methods: Patients with suspected nasopharyngeal carcinoma were subjected to a nasopharyngeal biopsy examination, some samples were sent to the Anatomical Pathology Laboratory of the General Hospital Dr. Zainoel Abidin Banda Aceh for histopathological examination and some were sent to the Research Laboratory of the Faculty of Dentistry, Syiah Kuala University for examination of EGFR titers. This study was conducted from January 2020 to October 2020.

Results: There were 17 samples of nasopharyngeal carcinoma. Based on the results of the Paired T test analysis, it can be seen that there is a difference in the quantity of EGFR titers of each study subject with the variable stage and histopathological profile. Specifically, the Paired T test analysis between EGFR titers and Stadium (P<0.05; 0.00); and analysis of EGFR titer with histopathological profile (P<0.05; 0.00). In general, the Friedmann test analysis showed that there were significant differences in the incidence of nasopharyngeal carcinoma in patients with regard to age, histopathological profile and stage (P<0.05).

Conclusion: EGFR titer quantity has a positive relationship with nasopharyngeal carcinoma stage and there is no relationship between EGFR titer and histopathological profile of nasopharyngeal carcinoma

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1. INTRODUCTION

Nasopharyngeal carcinoma is a malignant tumor originating from the nasopharyngeal epithelium with the most common from Rosenmuller fossa [1]. Nasopharyngeal carcinoma is more common in Mongoloid races. The incidence rate is relatively high in South China at 20 to 40 per 100,000 per year [2]. The incidence of nasopharyngeal carcinoma in Indonesia reaches 4.7 per 100,000 population per year [3]. The World Health Organization (WHO) developed classification of nasopharyngeal carcinoma into keratinizing squamous cell carcinoma (Type 1), nonkeratinizing squamous cell carcinoma (Type 2) and undifferentiated squamous cell carcinoma (Type 3) [4]. Epidermal Growth Factor Receptor (EGFR) is a glycoprotein transmembrane made by "protooncogen c-erb-B2". Epidermal Growth Factor Receptors are increased in some carcinomas. This protein is expressed in small amounts in human tissue, but activation of the protooncogen "c-erb-B2" causes overexpression in many types of cancer in humans [1]. EGFR activation signals an increase in cell proliferation, angiogenesis and decrease in the apoptosis process. Increased expression of EGFR is also associated with the severity of the tumor stage such as tumor size, lymph node involvement and distant metastases, thus associated with prognosis [5]. In the last two decades, EGFR is the first receptor as a target therapy in cancer therapy with several forms of anti-EGFR drugs that are can be used clinically [6]. This study was conducted to determine the expression of EGFR protein titer in patients with nasopharyngeal carcinoma based on the stage and histopathological profile.

2. MATERIALS AND METHODS

This research is an observational analytic study based on molecular biology. The sampling site was carried out in the ENT-KL clinic at Dr. Zainoel Abidin General Hospital Banda Aceh. The histopathological examination was carried out at the Anatomical Pathology Laboratory of the Dr. Zainoel Abidin General Hospital Banda Aceh. The EGFR examination was carried out at the Research Laboratory of the Faculty of Dentistry, Syiah Kuala University. This research was conducted in January 2020 to October 2020. The samples are all patients diagnosed with new cases of nasopharyngeal carcinoma based on the results of histopathological examination were in accordance with WHO criteria and met the inclusion criteria. Based on the sample formula for estimating one proportion, a total sample size of 17 samples was obtained for examination of the EGFR titer analysis. Inclusion criteria are all patients who went to the ENT-KL clinic in Dr. Zainoel Abidin General Hospital Banda Aceh and diagnosed with new cases of nasopharyngeal carcinoma. Age range 18 to 70 years. Nasopharyngeal carcinoma patients who are not diagnosed with other malignancies. Statistical analysis using IBM SPSS software, EGFR titer data associated with staging and histopathological profiles were analyzed by Paired sample t-test, while the relationship was analyzed by Paired t-test correlation and Spearmann Rho. Data on the significance relationship between EGFR and all analysis variables were tested by the Friedman test with a limit of significance P<0.05 and a limit of correlation strength (r=1).

3. RESULTS

Baseline data recorded in this study included age, histopathological profile, and stage.

Table 1. The results obtained from the age range

Age (year)	Amount	%
30-40	4	23,5
41-50	4	23,5
51-60	5	29,5
61-70	4	23,5
Total	**17**	**100,00**

From the table above, the results obtained from the age range of 30-40 years are 4 (23.5%) patients, 4 (23.5%) patients, 41-60 years (4 (29.5% 35 patients, and 61-70 years as many as 4 (23.5%) patients. In this study, the youngest age was 30 years and the oldest was 68 years old. The mean age was 49 years. Most sufferers are found in the age range 51-60 as many as 5 sufferers.

Table 2. The results obtained from the gender

Gender	Amount	%
Male	9	52
Female	8	48
Total	**17**	**100**

From the table above, it is found that 9 (52%) men (52%) sufferers and 8 (48%) women sufferers. From the table above, there are more male sufferers than female sufferers

Table 3. The results of the histopathological profile

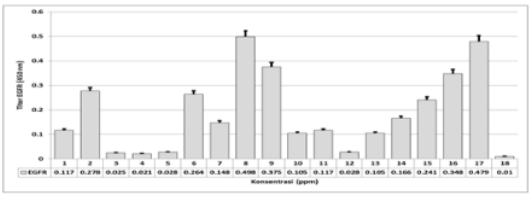
Histopathological profile	Amount	%
WHO Type1	1	6
WHO Type 2	13	76
WHO Type 3	3	18
Total	**17**	**100**

From the table above, the results of the histopathological profile of type 1 WHO were 1 (6%) patients, type 2 WHO was 13 (76%) patients, and type 3 WHO was 3 (18%) patients

Table 4. The results of the stage

Stage	Amount	%
0	0	0
I	0	0
II	0	0
III	3	18
IVa	13	76
IVb	1	6
Total	**17**	**100**

From the table above, it is found that 45 e are no patients with stages 0 to II. Patients with stage III were 3 (18%) patients, Stage IVa were 13 (76%) patients and Stage IVb were 1 (6%) patients.



Graphic 1. EGFR titer quantification of nasopharyngeal carcinoma

Graphic 1 shows that the EGFR titer quantification is seen to be the highest (0.498 ppm) in sample number 8, and the lowest seen in sample number 4 (0.025ppm).

Table 5 General data of EGFR based on age, gender, sex, stage and histopathological profile

Sample number	Gender	Age	WHO type	Stage	EGFR titer Kons (ppm)	Friedman test
1	Female	66	3	IVb	0.117	
2	Female	64	2	IVa	0.278	
3	Male	67	2	III	0.025	
4	Female	68	2	III	0.021	
5	Female	46	2	III	0.028	
6	Male	55	2	IVa	0.264	
7	Female	53	2	IVa	0.148	
8	Female	34	1	IVa	0.498	
9	Male	53	2	IVa	0.375	
10	Male	43	2	IVa	0.105	
11	Female	38	2	IVa	0.117	P<0.05 (0.00)
12	Male	41	3	IVa	0.028	
13	Male	56	3	IVa	0.105	
14	Male	54	2	IVa	0.166	
15	Female	38	2	IVa	0.241	
16	Male	30	2	IVa	0.348	
17	Male	45	2	IVa	0.479	

Table 5 shows that the EGFR titers based on stage and histopathological profile. The highest EGFR titer was seen in stage IVa and the histopathological profile of keratinizing squamose cell carcinoma.

Based on the results of the Paired T test analysis, it shows that there are differences in the quantity of EGFR titers of each study subject with variables of age, histopathological profile and cancer stage. Specifically, the Paired T test analysis between EGFR protein titer and age (P<0.05; 0.00); EGFR titer analysis with staging (P<0.05; 0.00); and analysis of EGFR titer with histopathological profile (P<0.05; 0.00). In general, the Friedmann test analysis showed that there were significant differences in nasopharyngeal carcinoma with respect to age, histopathological profile and stage (P<0.05). Based on the correlation analysis Paired T test shows that the EGFR titer has a significant relationship with the stage, meaning that the higher the stage, the higher the EGFR titer (positive correlation), while the relation between EGFR titers and age has a negative correlation. The expression of EGFR protein titer had no relationship with the histopathological profile. In addition, based on the non-parametric correlation test (Spearman'rho), it showed that the EGFR protein titer was a significant determinant (P<0.05: 0.037).

4. DISCUSSION

The general objective of this study was to evaluate the EGFR titer of nasopharyngeal carcinoma tissue based on staging and histopathological profile. The data obtained specifically analyzed the relationship between EGFR titer expression with the stage of nasopharyngeal carcinoma and the histopathological profile of nasopharyngeal carcinoma. The selection of EGFR protein titer in this study is related to the nature of the protein which acts as a receptor that responds to the growth of cancer cells. EGFR is usually overexpressed in nasopharyngeal carcinoma and is associated with its pathogenesis [7].

Increased EGFR titer is very common in nasopharyngeal carcinoma. It is estimated to be 85%. In addition, overexpression of EGFR titers in nasopharyngeal carcinoma is associated with tumor metastasis, progression, and poor survival in patients with nasopharyngeal carcinoma [8]. Increased expression of EGFR is also associated with the severity of the tumor stage such as tumor size, lymph node involvement and distant metastases, so it is associated with prognosis [9]. Prabowo et al compared the expression of stage III and IV EGFR, found that all stage III nasopharyngeal carcinomas showed negative EGFR while at stage IV all were obtained with positive EGFR [10]. Sukri Rahman et al also had excess EGFR results in advanced nasopharyngeal carcinoma.[11].

Prabowo et al also mentioned that EGFR is highly expressed in advanced nasopharyngeal carcinoma [12]. These results are in line with this study, it was found that the expression of high EGFR titers occurred at stages IVa and IVb. The meaning the development of this tumor is strongly influenced by the EGFR titer. It shows a statistically significant relationship. So it can be assumed that EGFR plays an important role in the development and development of nasopharyngeal carcinoma because EGFR is one of the tyrosine kinase receptors that plays the most role through the binding mechanism between EGF and TGF-α ligands with the EGFR extracellular domain, thereby activating receptors and signaling proteins that trigger activation. or modulation of various cellular processes [13].

In general, the data of this study indicate the age is under 55 years have a tendency to express EGFR titer higher than those over 55 years of age. This data is in line with Bray's research report which states that interesting epidemiological observations at the initial peak in the age curve of incidence observed in geographically different populations indicate different causal entities and the likelihood of fatigue of susceptible individuals from the population at a given age. Results of systematic evaluation of the age profile of the incidence of nasopharyngeal carcinoma worldwide on population partitioning by risk level using data from 23 high-quality population-based cancer registries found a consistent pattern of bimodality. Continued increase in risk of nasopharyngeal carcinoma at age until the first peak in late adolescence / early adulthood (ages 15-24 years) [14]. Age at diagnosis has been found to be a prognostic factor in outcome in various cancers. However, the effect of age at diagnosis on the development of nasopharyngeal carcinoma has not been explored.

Xie's study data reported that correlation analysis showed that age >61 years was significantly correlated with tumor progression and therapeutic measures in cohort testing and validation (P<0.05). Furthermore he observed that older age (>61 years) was a strong predictor (P<0.05) of cancer-specific survival [15]. This study's data correlated with age-specific nasopharyngeal cancer incidence, but when associated with titer expression. EGFR, precisely at the age above 55 years of age had a decrease in EGFR expression (negative relationship), but had a significance (P<0.05) for the development of nasopharyngeal cancer based on the EGFR titer which decreased with age. These two findings provide mutual insight into the level of influence of EGFR titer on the development of nasopharyngeal carcinoma in the elderly. From these findings, it can be seen that in the development of nasopharyngeal carcinoma over 55 years of age the EGFR protein is no longer involved in a dominant manner. protooncogen protein, protein G, and other protein kinases are reported to have balanced stability in the pathogenesis of cancer in the elderly [16]. Based on the results of this study, the EGFR titer has a low sensitivity in old age, so that the possibility of eliminating cancer in the elderly with the help of other treatments besides anti-egfr is preferred [17].

Based on the data obtained from this study, it can be seen that there is a difference in the EGFR titer between the early stage and the advanced stage of nasopharingeal carcinoma. In stage III, it is only seen that sometimes the average EGFR titer is 0.025 ppm, while in the advanced stages (IVa and IVb) it looks much higher. The development of EGFR titers at this advanced stage is associated with metastasis of nasopharyngeal carcinoma as well as suppression of the immune system and inhibition of apoptosis of cancer cells. The increase in the EGFR titer which increases with increasing stage shows a significant incidence of cancer cell defense [18]. Chua reported that the expression of EGFR titers was common in cases nasopharyngeal carcinoma at an advanced stage. Correlative analysis shows that EGFR level is a strong independent prognostic factor that determines disease-specific survival in stage III-IV nasopharyngeal carcinoma. The findings of Chua et al. Suggest that the expression status of EGFR titers can identify a subgroup of patients with advanced disease, so that anti-EGFR targeted therapy and treatment strategies can be determined. Furthermore, Utomo confirmed that the expression EGFR is related to development of the stage of nasopharyngeal cancer [19].

Alni et al. Stated that the distribution of nasopharyngeal malignancy according to histopathological type according to the classification based on WHO criteria found that the type of undifferentiated carcinoma (WHO type III) had the highest number, namely 136 (68.3%) cases. Then followed by the non-keratinizing type squamous cell carcinoma (WHO type II) as many as 60 (30.2%) cases and type keratinizing squamous cell carcinoma (WHO type I) had the lowest rate, namely 3 (1.5%) cases in hospitals in Pekanbaru City [20]. In this study, it was found that the most type was non keratinizing squamous cell carcinoma (WHO type II). The similarity is that the distribution of nasopharyngeal malignancy according to histopathological type is in accordance with the classification based on WHO criteria. In this study, it was found that WHO type 1 had the lowest number, which was only 1 (6%) sample from 17 samples studied. Sukri Rahman et al in their research stated that there was no difference in EGFR expression between non keratinizing squamous cell carcinoma (WHO type II) and type undifferentiated carcinoma (WHO type III) [11]. Nyoman in his research also concluded that EGFR was expressed differently in various head and neck cancers, but there was no relationship between EGFR expression with clinicopathological characteristics and tumor location.[21] In line with previous studies in this study, a histopathological assessment also showed that the expression of EGFR titer had no significant relationship with histopathological profile, meaning that this titer expression was not determined by profile histopathological.

The findings of this study and comparison with the results of previous studies can be used as a reference for the treatment of nasopharyngeal cancer through the EGFR work system approach. Another basis for consideration is that an increased EGFR titer is correlated with a decrease in patient survival [22]. Recent data have proposed EGFR as a new target for cancer therapy In addition, EGFR is the first receptor as a target therapy in cancer therapy with various anti-EGFRs through the principle of prevention and anti-cancer mechanisms through molecular target therapy and immunotherapy [23].

5. CONCLUSION

All subjects of nasopharyngeal carcinoma had different expression of egfr titers based on stage and histopathological profile. EGFR titer quantity has a positive relationship with nasopharyngeal carcinoma stage and there is no relationship between EGFR titer and histopathological profile of nasopharyngeal carcinoma. Further studies with more samples are needed to see the correlation effect. Stage and histopathological profile with incidence of nasopharyngeal cancer.

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