Original Article

The Role of Epidermal Growth Factor Receptor in Head and Neck Squamous Cell Carcinoma in Thai Patients

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Background: *EGFR*, a member of the type 1 tyrosine kinase family of receptors, plays a crucial role in several types of cancer especially in squamous cell carcinoma of the head and neck (HNSCC).

Objective: This study aims to determine the frequency of *EGFR* overexpression in HNSCC and to find a possible correlation with various clinical pathological parameters and patient outcomes.

Materials and Methods: Fresh cancerous tissue samples and matched normal mucosa were collected from 78 previously untreated HNSCC patients after obtaining informed consent. All patients had no detectable distant metastases at presentation. *EGFR* mRNA expression was examined using quantitative real-time RT-PCR analysis. Data were correlated with both clinicopathological characteristics and survival outcome.

Results: Overexpression of *EGFR* mRNA was found in 21 of 78 patients. *EGFR* expression was significantly correlated with lower overall survival.

Conclusion: *EGFR* expression plays an important role in the pathogenesis and progression of HNSCC.

Keywords: EGFR, Head and neck cancer, Squamous cell carcinomas

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Head and neck cancer is the fifth most common type of cancer worldwide and it is considered to be a significant cause of morbidity and mortality with an estimated 650,000 new cases and 350,000 cancer-related deaths every year[1,2]. Epidermal growth factor receptor (EGFR) is a member of the tyrosine kinase family of receptors[3-5] and overexpression of EGFR is found in 90% of head and neck tumors[6-9]. Upregulation of this factor occurs early in the progression of dysplasia to HNSCC in the upper aerodigestive tract[3,4,10]. Overexpression of the EGFR gene has been proposed as a key determinant of head and neck tumor pathogenesis. Using RT-PCR, Jin et al quantified the EGFR mRNA levels in tumor tissue samples and compared them to normal mucosa, and demonstrated that 49% of specimens overexpressed EGFR in the tumor samples compared with normal mucosa[11]. Several other studies also report EGFR protein overexpression in 25% to 95% of HNSCC tumors when analyzed using immunohistochemical techniques[12]. Schartinger et al demonstrated EGFR overexpression in 44.7% (51 of 114 cases) of HNSCC[13].

Other studies have investigated whether or not there is a correlation between expression of EGFR in HNSCC and any clinicopathological parameters or tumor behavior patterns[12]. Although most studies suggest prognostic implications of EGFR expression in HNSCC, the sometimes-contradictory results are currently under debate. There are currently reported correlations between EGFR overexpression with advanced tumor stage[14-16], tumor differentiation[16,17], nodal metastasis[14,15,17,18], disease-free survival[19,20], and overall survival[20,21]. In contrast, others studies into HNSCC showed no correlation between EGFR overexpression and tumor size[21-23], tumor differentiation[22-25], tumor site[22,24], tumor stage[18,21,22,24,26], nodal stage[21-23,25,26], clinical stage[17,21,26], tumor thickness[22,26], and survival[17,22,26].

In the present study, the authors characterized the expression and prognostic value of EGFR receptors in Thai patients and their relationship with clinicopathological characteristics.

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Materials and Methods

Patients

Total RNAs were extracted from frozen sections of HNSCC tumors from 78 patients undergoing surgical resection for HNSCC at the Division of Head-Neck & Breast

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Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, from January 28, 2002 through January 4, 2004 after obtaining informed consent and following guidelines established by the Siriraj Ethical Committee on Research Board (491/2553(EC4)). All patients had no detectable metastases to distant organs at presentation and all of them were selected using the following inclusion criteria: patients diagnosed with HNSCC (primaries of the oral cavity, oropharynx, hypopharynx, pharynx and larynx) with no prior chemo- or radio-therapy. Patients with recurrent disease, incomplete standard treatment, or lost to follow-up were excluded.

Reverse transcription

Tissue samples and head and neck cancer cell lines were prepared for total RNA extraction using Trizol® reagent (Invitrogen). DNase treatment was employed, in order to eliminate DNA contamination in RNA samples. The cDNA synthesis was performed using Omniscript RT Kit® (Qiagen).

Real time PCR

Real-time PCR was performed in the LightCycler PCR device (Roche Diagnostics, Mannheim, Germany). The Quantitect SYBR-Green PCR kit (Qiagen) together with 0.5 µmol/L of each primer was used as a master mix (total volume, 20 µl). Eighteen microlitres of master-mix were filled in the glass capillaries and 2 µl volume of cDNA was added as PCR template. Cycling condition were 95°C for 15 min, 45 cycles of 95°C 15 s, 57°C 20 s, 72°C 10 s). β-actin was used as a reference gene. A calibrator sample was included in every run and used for normalization of final results. Sequences of PCR primer sets for EGFR receptors were as follow: EGFR forward, TCCCAGTGCCTGAATACATA; EGFR reverse, TGGACAGTGTTGAGATACTCG, product size = 150 bps; β-actin forward, CACTCT TCCAGCCTTCCTTCC and β-actin reverse, CTGTGTTG GCGTACAGGTCT, product size = 114 bps. An efficiency curve for each primer was constructed by using various dilutions of cDNA. After quantification, an efficiency curve was generated by Light cycle software and efficiency of each primer was calculated. The data were analyzed and compared using a relative quantification method:

$$\text{ratio} = \frac{(E_{\text{ref}})^{\text{CP Sample}}}{(E_{\text{target}})^{\text{CP Sample}}} \div \frac{(E_{\text{ref}})^{\text{CP Calibrator}}}{(E_{\text{target}})^{\text{CP Calibrator}}}$$

where ratio is relative amount of EGFR relative to β-actin;
E = Efficiency of primer; cp = cycle threshold of PCR product

Statistical analysis

All statistical analyses were performed using the SPSS statistical software system® (SPSS for Windows, version 16.0). The association between the different clinicopathological and biological characteristics was studied by the Pearson χ^2 test. Survival was measured in months from the date of surgery to the date of death or to the last follow-up. Cancer specific survival curves and median survival times were calculated by the method of Kaplan and Meier, and differences in survivor function due to prognostic factors were calculated by the log-rank test. A *p*-value of less than 0.05 was considered statistically significant. The predictive values of various biological markers and clinicopathologic parameters were assessed with univariate and multivariate logistic regression analysis.

Results

Clinicopathological features of 78 patients with HNSCC

In each case, a portion of tumor was resected near the advancing edge of the tumor, avoiding its necrotic center. After excision, the tissues were immediately snap-frozen and stored in liquid nitrogen until the prospective utility and the adjacent tissues were submitted for histopathological study which revealed that most of the cells were malignant. Tumors were staged according to the TNM classification 7th edition and graded as follows: well, moderately and poorly differentiated. The T stage was evaluated according to tumor size in the case of tumors from the oral cavity or the oropharynx, and of tumor size and extensiveness in the case of tumors from the hypopharynx. The mode of cancer invasion was divided into perineural and perivascular invasion (Table 1).

Expression of EGFR mRNA in HNSCC tissues

To examine the expression of EGFR in head and neck cancer patients, quantitative real time RT-PCR analysis of EGFR mRNA derived from head and neck cancer tissues (n = 78) and normal adjacent mucosae (n = 17) of Thai HNSCC patients was performed. EGFR mRNA was examined using SYBR green dye and the fluorescence signal was detected by the Light Cycler instrument. Relative mRNA expression levels of the EGFR in head and neck cancer tissue were normalized to the level of β-actin mRNA expression in the respective sample. A value above the mean of fibroblasts+2 SD was implemented as a cut of point to show EGFR expression positivity. The EGFR mRNA was detected by real time RT-PCR in 27% (21 of 78) of tumor, in 45% (9 of 20) of metastatic lymph nodes, in 35% (6 of 17) of normal adjacent mucosae. EGFR mRNA was not found positive in normal fibroblasts (0 of 4). The mean of mRNA expression of EGFR was greater in tumor (0.3261), metastatic lymph node (0.2908) and normal adjacent mucosae (0.3174) when compared with normal fibroblasts (0.1016). However, the expression levels among groups were not significantly different (Figure 1).

Correlations between clinicopathological parameters and overall survival

During the period of follow-up, 38 patients (48.7%) were alive and 40 patients (51.3) were deceased. As shown in Table 2, tumor stage (p = 0.004), N stage (p = 0.024), overall stage (p = 0.002), perivascular invasion (p = 0.007), and post-operative radiotherapy (p = 0.009) were correlated

Table 1. Clinicopathological features of 78 patients with HNSCC

Parameters	Number of patients [n (%)]
Age (years)	
<60	31 (40)
≥60	47 (60)
Median, range	64.5, 27 to 100
Gender	
Males	37 (47)
Females	41 (53)
Alcohol drinking	
Yes	44 (56)
No	33 (42)
Unknown	1 (2)
Smoking	
Yes	40 (51)
No	37 (47)
Unknown	1 (2)
Betel nut chewing	
Yes	26 (33)
No	52 (67)
Tumor Sites	
Oral cavity	72 (91)
Oropharynx	4 (6)
Oropharynx and Hypopharynx	2 (3)
Histological grade	
Well differentiated	36 (46)
Moderately differentiated	35 (44)
Poorly differentiated	4 (6)
Unknown	3 (4)
T stage	
T1	13 (16)
T2	18 (23)
T3	18 (23)
T4	28 (36)
Unknown	1 (2)
N stage	
N0	42 (54)
N1	8 (10)
N2	19 (24)
N3	2 (3)
Unknown	7 (9)
Overall stage	
1	13 (16)
2	10 (13)
3	12 (15)
4	32 (41)
Unknown	11 (15)
Perineural invasion	
Yes	25 (31)
No	42 (54)
Unknown	11 (15)
Perivascular invasion	
Yes	16 (21)
No	53 (68)
Unknown	9 (11)
Post-operative radiotherapy	
Yes	44 (56)
No	32 (41)
Unknown	2 (3)
Post-operative chemotherapy	
Yes	5 (6)
No	70 (90)
Unknown	3 (4)

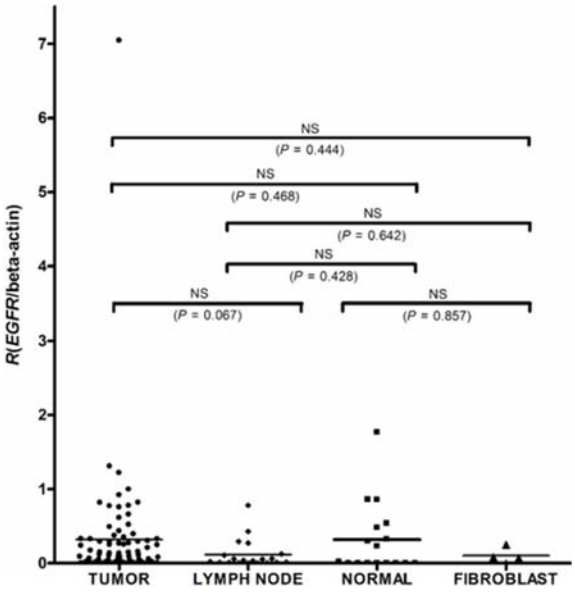

Figure 1. EGFR mRNA expression by real time RT-PCR in HNSCC tissue samples.

with mortality. However, other clinical variables including age, gender, alcohol drinking, smoking, betel nut chewing, tumor site, histological grade, nodal stage, perineural invasion, post-operative chemotherapy, had no significance associated with overall survival.

Correlations between level of EGFR mRNA and clinicopathological parameters

The relationship between the level of EGFR mRNA expression in HNSCC tumors (n = 78) and clinicopathological parameters was analyzed. The data from Table 3 illustrated that EGFR mRNA expression in HNSCCC tumors showed no statistically significant correlation with clinicopathological parameters. On the other hand, overexpression of EGFR mRNA was correlated with lower overall survival according to Figure 2 ($p = 0.034$).

Discussion

In the present study, the mean mRNA levels of *EGFR* among primary tumors, metastatic lymph nodes, and normal adjacent mucosae did not differ significantly. In addition, *EGFR* mRNA in tumors demonstrated overexpression in around 27% (21/78) of cases. This is a lower percentage when compared with previous reports that showed 49% of specimens overexpressed EGFR in tumor compared with normal adjacent mucosae[11]. The mean mRNA levels of EGFR from normal adjacent mucosae were not different and tended to be higher than those of primary tumors. A possible explanation for this is that the normal adjacent mucosae from patients are exposed to carcinogens (smoking and alcohol) which lead to genetic changes due to 'field cancerization'. These findings have been found in previous studies that also

Table 2. Clinicopathological parameters of HNSCC according to overall survival

Parameters	Dead, n (%)	Alive, n (%)	Odds ratio	95% CI	*p*-value
Age(years)					
<60	12 (39)	19 (61)			
≥60	27 (60)	18 (40)	2.375	0.931 to 6.062	0.070
Gender					
Females	15 (43)	20 (57)			
Males	24 (59)	17 (41)	1.882	0.755 to 4-692	0.275
Alcohol drinking					
No	14 (44)	18 (56)			
Yes	25 (57)	19 (43)	2.000	0.796 to 5.024	0.321
Smoking					
No	15 (42)	21 (58)			
Yes	24 (60)	16 (40)	2.100	0.840 to 5.243	0.240
Betel nut chewing					
No	26 (50)	26 (50)			
Yes	13 (57)	10 (43)	1.300	0.484 to 3.490	0.736
Tumor Sites					
Oral cavity	35 (69)	16 (31)			
Oropharynx and Hypopharynx	4 (16)	21 (84)	0.087	0.026 to 0.296	0.216
Histological grade					
Well differentiated	28 (62)	17 (38)			
Moderately-Poorly differentiated	31 (61)	20 (39)	0.941	0.413 to 2.146	0.913
T stage					
T1 to T2	9 (26)	26 (74)			
T3 to T4	30 (65)	16 (35)	5.417	2.051 to 14.302	0.004
N stage					
N0	18 (45)	22 (55)			
N1 to N3	21 (58)	15 (42)	1.711	0.689 to 4.249	0.024
Overall stage					
1 to 2	6 (26)	17 (74)			
3 to 4	33 (62)	20 (38)	4.675	1.582 to 13.818	0.002
Perineural invasion					
No	21 (40)	31 (60)			
Yes	18 (75)	6 (25)	4.429	1.508 to 13.005	0.007
Perivascular invasion					
No	28 (47)	32 (53)			
Yes	11 (69)	5 (31)	2.514	0.718 to 8.121	0.105
Post-operative radiotherapy					
No	11 (34)	21 (66)			
Yes	28 (64)	16 (36)	3.341	1.287 to 8.670	0.009
Post-operative chemotherapy					
No	36 (51)	35 (49)			
Yes	3 (60)	2 (40)	1.458	0.230 to 9.263	0.645
EGFR mRNA					
Negative	24 (44)	31 (56)			
Positive	15 (71)	6 (29)	3.229	1.090 to 9.570	0.034
HER2 DNA					
Negative	12 (41)	17 (59)			
Positive	3 (43)	4 (57)	0.438	0.075 to 2.552	0.943
HER2 mRNA					
Negative	23 (51)	22 (49)			
Positive	16 (52)	15 (48)	1.020	0.409 to 2.548	0.966
HER2 protein					
Negative	13 (68)	6 (32)			
Positive	12 (43)	17 (57)	0.326	0.096 to 1.101	0.071

Table 3. Correlation between *EGFR* mRNA expression and clinicopathological parameters

Parameters	*EGFR* mRNA expression		*p*-value
	Positive	Negative	
Age (years)			0.081
<60	5	26	
≥60	16	31	
Gender			0.623
Males	12	29	
Females	9	28	
Alcohol drinking			0.851
Yes	13	31	
No	8	26	
Smoking			0.853
Yes	10	30	
No	11	27	
Betel nut chewing			0.588
Yes	8	18	
No	13	39	
Tumor Sites			0.630
Oral cavity	19	53	
Oropharynx	2	2	
Oropharynx and hypopharynx	0	1	
Histological grade			0.302
Well differentiated	9	27	
Moderately-poorly differentiated	10	29	
Unknown	2	1	
T stage			0.135
T1-T2	25	26	
T3-T4	16	31	
N stage			0.853
N0-N1	14	36	
N2-N3	6	15	
Unknown	1	6	
Overall stage			0.632
1-2	5	18	
3-4	14	30	
Unknown	2	9	
Perineural invasion			0.381
Yes	8	17	
No	12	30	
Unknown	1	10	
Perivascular invasion			0.156
Yes	5	11	
No	16	37	
Unknown	0	9	

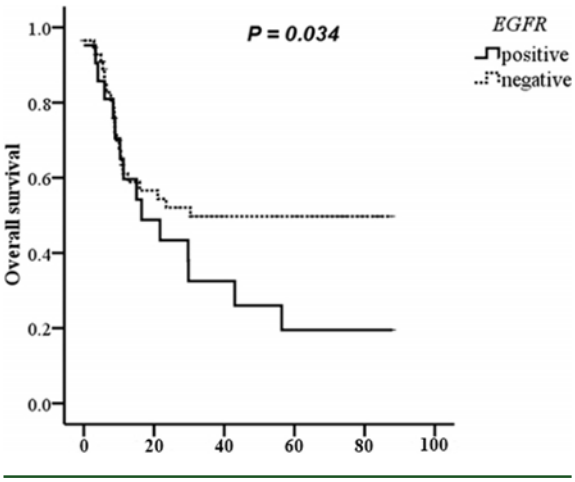

Figure 2. Kaplan-Meier curves for the overall survival of HNSCC patients were calculated according to *EGFR* mRNA expression (positive versus negative).

demonstrated EGFR gene overexpression in the normal mucosa of patients. Grandis et al demonstrated that EGFR mRNA and protein levels in tumor tissues as well as histologically normal mucosae of HNSCC patients were greater than in the normal mucosae of control patients without cancer[27]. Jin et al also detected EGFR mRNA in both squamous cell carcinomas specimens and normal mucosa adjacent to carcinoma[11]. Therefore, these findings suggest that the normal adjacent mucosae in cancer patients may not be an ideal normal control.

Several studies have demonstrated the relationship between the EGFR overexpression and adverse clinicopathological parameters in HNSCC, but the results in Thai patients were unknown. The results of the present study illustrate that EGFR mRNA overexpression in HNSCC tumors showed no statistically significant correlation with clinicopathological parameters. This is in contrast to other studies which have demonstrated correlations between EGFR expression with tumor size[16], tumor stage[14,15], nodal stage[14,17], lymph node metastasis[15,18] and tumor differentiation[16,17].

However, the results of this study have indicated statistically significant correlations between overall survival and tumor stage, overall stage, perivascular invasion, post-operative radiotherapy or EGFR mRNA. Univariate and multivariate analysis were used to evaluate the correlation between these clinicopathological parameters and overall survival. In addition, multivariate analysis of the 8 categories demonstrate that tumor stage, nodal stage and overall stage are independent predictors for overall survival. This is in concordance with similar findings observed in previous studies that showed EGFR overexpression correlated with overall survival[20,21].

Conclusion

The results of this clinical study demonstrate that EGFR expression shows a significant correlation with overall survival representing a poor prognosticator and may be used as a potential target for additional therapy.

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What is already known on this topic?

Epidermal growth factor receptor (EGFR) is a member of the tyrosine kinase family of receptors. Overexpression of *EGFR* mostly found in 90% of head and neck tumors. Upregulation of this factor occurs early in the progression of dysplasia to HNSCC in the upper aerodigestive tract.

What this study adds?

EGFR expression plays a crucial role in the pathogenesis and progression of HNSCC. The clinical study of EGFR expression showed significant correlation with overall survival.

Potential conflicts of interest

The authors declare no conflict of interest.

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บทบาทของ Epidermal Growth Factor Receptor ในมะเร็งศีรษะและลำคอชนิดสเควมัสเซลล์ที่เกิดในผู้ป่วยชาวไทย

ดุลยพัฒน์ สงวนรักษา, หทัยฉันท์ ศิริเขตต์, อิงค์ โอเจริญรัตน์, ฐณวัฒน์ ธำรงธราดล, สุรัตน์ พุ่มพวง

ภูมิหลัง: EGFR เป็นตัวรับการเกาะจับของสารกระตุ้นการเติบโตในตระกูล type 1 tyrosine kinase ซึ่งมีหน้าที่สำคัญในการควบคุมมะเร็งหลายชนิดโดยเฉพาะมะเร็งศีรษะและลำคอชนิดสแควมัสเซลล์

วัตถุประสงค์: งานวิจัยนี้มีวัตถุประสงค์ที่จะคำนวณค่าความถี่ในการแสดงออกที่เพิ่มสูงขึ้นของจีน EGFR ในมะเร็งศีรษะและลำคอชนิดสแควมัสเซลล์และหาความเชื่อมโยงระหว่างตัวแปรทางพยาธิวิทยาคลินิกและผลตรวจผู้ป่วย

วัสดุและวิธีการ: ตัวอย่างชิ้นเนื้อเยื่อมะเร็งสดและเยื่อบุปกติถูกเก็บมาจากผู้ป่วยมะเร็งศีรษะและลำคอชนิดสแควมัสเซลล์ที่ยังไม่ได้รับการรักษาหลังจากลงนามในใบยินยอมเข้าร่วมการวิจัยแล้วจำนวน 78 ราย โดยจะไม่พบการแพร่กระจายไปอวัยวะอื่นในผู้ป่วยทุกราย ณ วันที่เข้าร่วมโครงการ หลังจากนั้นการแสดงออกของจีน EGFR mRNA จะถูกวิเคราะห์โดย quantitative real-time RT-PCR โดยข้อมูลจะมีความเกี่ยวข้องกับลักษณะทางพยาธิวิทยาคลินิกและอัตราการมีชีวิตรอด

ผลการศึกษา: พบการแสดงออกที่เพิ่มสูงขึ้นของจีน EGFR mRNA ในผู้ป่วย 21 ราย จาก 78 ราย ซึ่งการแสดงออกของจีน EGFR มีความสัมพันธ์กับอัตราการรอดชีวิตที่แย่กว่า

สรุป: การแสดงออกของจีน EGFR มีบทบาทสำคัญในการเกิดโรคมะเร็งศีรษะและลำคอชนิดสแควมัสเซลล์ รวมถึงการพัฒนาของโรคเช่นกัน