Correlations between Expression of Epidermal Growth Factor Receptor (EGFR), Phosphorylated EGFR, Cyclooxygenase-2 and Clinicopathological Variables and Treatment Outcomes in Nasopharyngeal Carcinomas

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Background: To evaluate immunoexpression of epidermal growth factor receptor (EGFR), phosphorylated EGFR (pEGFR^{Tyr1068}), and cyclooxygenase-2 (COX-2) and analyze their prognostic utility in nasopharyngeal carcinomas (NPC).

Methods: We used a retrospective review of charts and tissue specimens. The immunoexpression levels of EGFR, pEGFR^{Tyr1068}, and COX-2 were semiquantitatively assessed by the H-score method for 170 NPC samples from patients treated with radiotherapy (RT) alone.

Results: The ranges of immunohistochemical H-scores were 0-510 (median 225) for EGFR, 0-395 (median 25) for pEGFR^{Tyr1068}, and 0-460 (median 170) for COX-2. None of these 3 markers were significantly associated with one another, clinicopathological factors, or the rates of locoregional control (LRC), distant metastasis-free survival (DMFS), or overall survival (OS). In multivariate analysis, the independent adverse prognosticators were T-stage for LRC, N-stage for DMFS, and T-stage, N-stage, and age > 60 years for OS.

Conclusions: Immunoexpression levels of EGFR, pEGFR^{Tyr1068}, and COX-2 were not related to clinicopathological variables and not predictive of outcomes of NPC patients treated with RT alone.

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Key words: nasopharyngeal carcinoma, EGFR, pEGFR, COX-2

Nasopharyngeal carcinoma (NPC) represents an endemic disease strongly associated with Epstein-Barr virus infection in Taiwan. Recent advances in radiotherapy (RT) and chemotherapy (CT) have improved locoregional control and reduced distant metastasis. However, approximately 20%-50% of patients still suffer from relapses or metastases, and the majority of these patients die from this disease. It is therefore highly desirable to search for molecular markers to correlate with actual clinical outcomes and to be used as references for molecular targeted therapy in NPC patients.

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Epidermal growth factor receptor (EGFR), a 170 kD surface receptor with intrinsic tyrosine kinase activity, belongs to the erbB growth factor receptor family.[1] Cyclooxygenase-1 (COX-1) and COX-2 catalyze prostanoid synthesis from arachidonic acid.[2] In contrast to the constitutive expression of COX-1, COX-2 is barely detectable in normal tissues and rapidly induced in response to inflammatory and mitogenic stimuli. EGFR and COX-2 have been separately shown to mediate pleiotropic carcinogenic processes, including cell survival, proliferation, angiogenesis, and invasiveness. In addition, both proteins have been reported to be overexpressed and associated with poor prognoses in a variety of human carcinomas, including NPC, although the conclusions were not consistent among different series.[1-7] There is mounting evidence suggesting the tight interaction between these two signaling pathways, which upholds the rationale for combining inhibitors of both COX-2 and EGFR tyrosine kinase at lower doses to minimize drug toxicity and resistance.[1,3]

It has become clear that ionizing radiation (IR) can induce a dose-dependent, cytoprotective activation and/or increased expression of EGFR as well as its downstream effectors, such as mitogen-activated protein kinase (MAPK) and the serine-threonine kinase, protein kinase B/Akt. These alterations can further mediate the proliferative signaling of cancer cells after IR with consequent radioresistance. Similarly, exposure to IR was also found to increase the in vitro expression of COX-2 and the synthesis of prostaglandins in normal and tumor cells. In this context, inhibition of EGFR represents an attractive approach to enhance radiosensitization in cancers showing EGFR overexpression. Recently, many in vivo and clinical studies have reported the radiation-enhancing effects of EGFR inhibiting agents, e.g. IMG-C225 (cetuximab), and tyrosine kinase inhibitor ZD 1839 (gefitinib, Iressa).[8] Some in vivo studies have reported radiation-potentiating effects in cancer cells by selective COX-2 inhibitors.[9,10] To our knowledge, the prognostic utility of EGFR and COX-2 in NPC remains controversial, and has only been examined in some series with limited and selected cases. Furthermore, little is known about the prognostic value of the activated (phosphorylated) form of EGFR (pEGFR). In this study, we aimed to assess the expression patterns of EGFR, pEGFR, and COX-2 oncoproteins by immunohistochemistry (IHC) and analyze their correlations with clinical outcomes in a sufficiently large, well-defined cohort treated at a single institution in southern Taiwan.

METHODS

Study population

From January 1996 to December 1999, there were 431 consecutively diagnosed NPC patients treated with RT at Kaohsiung Chang Gung Memorial Hospital. Patients were excluded from the study if they had distant metastasis (n = 23) at diagnosis, did not complete the prescribed RT schedule (n = 9), or had RT combined with CT (n = 53). In this cohort (n = 346), immunohistochemical expression of EGFR, pEGFR^{Tyr1068}, and COX-2 could be assessed in 170 (49%) cases having paraffin-embedded blocks from pretreatment biopsy specimens, which formed the study group in this series. To exclude a potential selection bias, the patient, tumor, treatment, and survival data were compared with those of the remaining 176 control cases not subjected to EGFR, pEGFR^{Tyr1068}, and COX-2 staining. The study group had a median age of 46 years (range, 15 to 72 years), and there were 109 (64%) males. Using the 2002 American Joint of Cancer Committee (AJCC) system, 18 (11%) cases were classified as stage I-IIa, 53 (31%) as Stage IIb, 69 (41%) as Stage III, and 30 (17%) as either Stage IVa or IVb. Two pathologists (H.Y.H & C.F.L) jointly reappraised the histological types of NPC according to the updated World Health Organization classification and identified 76 (45%) nonkeratinizing, differentiated (i.e., former type II) and 94 nonkeratinizing, undifferentiated (i.e., former type III) carcinomas. The method of RT for NPC was generally uniform within this period as previously reported.[5] All patients were regularly monitored after RT until death or their last appointment according to the intervals and protocols of follow-up as detailed in our prior studies.[11,12] Locoregional failure was determined based on the pathologic diagnosis or progression shown on consecutive image studies. To identify distant metastasis, patients were scrutinized by chest radiograph yearly and by abdominal sonogram or bone scan whenever indicated. The mean follow-up time was 68 months (range, 3-128). As summarized in Table 1, no significant disparity was found between the study and control groups with respect to treatment outcomes and established con-

Table 1. Characteristics of Patients with and without Immunohistochemistry (IHC) Study

	Without IHC (n = 176)	With IHC (n = 170)	*p*
Median age (range), yrs	47 (17-81)	46 (15-72)	0.10
Gender			
Female	48 (27%)	61 (36%)	0.11
Male	128 (73%)	109 (64%)	
Histology			
differentiated	83 (47%)	76 (45%)	0.67
undifferentiated	93 (53%)	94 (55%)	
AJCC stage			
I-IIa	21 (12%)	18 (11%)	0.10
IIb	65 (37%)	53 (31%)	
III	54 (31%)	69 (41%)	
IV	36 (20%)	30 (17%)	
T stage			
T1-2a	65 (37%)	62 (36%)	0.18
T2b	61 (35%)	63 (37%)	
T3	19 (11%)	27 (16%)	
T4	31 (17%)	18 (11%)	
N stage			
N0	45 (25%)	38 (22%)	0.15
N1	76 (43%)	64 (38%)	
N2	41 (24%)	56 (33%)	
N3	14 (8%)	12 (7%)	
RT technique			
2DRT	76 (43%)	74 (44%)	1.00
2DRT+3DCRT	100 (57%)	96 (56%)	
5-y LRC	85.9%	85.7%	0.67
5-y DMFS	86.8%	80.7%	0.23
5-y OS	73.7%	66.9%	0.19

Abbreviations: AJCC: American Joint of Cancer Committee published in 2002; RT: radiotherapy; 2DRT: two dimensional radiotherapy; 3DCRT: three dimensional conformal radiotherapy; LRC: locoregional control; DMFS: distant metastasis free survival; OS: overall survival.

ventional prognosticators, such as AJCC stage, T stage, N stage, or age.

Staining and assessment of immunohistochemical expression of EGFR, pEGFR^{Tyr1068}, and COX-2

Tissue sections were cut onto precoated slides from paraffin-embedded tissue blocks at 3-μm thickness. Slides were routinely deparaffinized with xylene and rehydrated with ethanol washes. For antigen retrieval, slides were heated by microwave treatment in a 10 mM citrate buffer (pH 6) for 7 min. Endogenous peroxidase was quenched by 3% H_2O_2 treatment. Slides were washed with TBS for 15 minutes and then incubated with anti-EGFR (31G7, monoclonal, prediluted, Zymed, San Francisco, CA, U.S.A.), anti-pEGFR^{Tyr1068} (ZMD.310, monoclonal, 1: 50, Zymed) and anti-COX-2 (COX229, monoclonal, 1: 100, Zymed). Primary antibodies were detected using the ChemMate DAKO EnVision kit (DAKO, K5001, Carpinteria, CA, U.S.A.). The slides were incubated with the secondary antibody for 30 minutes, developed with 3,3-diaminobenzidine for 5 minutes, and then counterstained with Gill's hematoxylin. Omission of the primary antibodies and substitution with normal serum were used for the negative control. The positive controls were colorectal adenocarcinomas previously known to be positive for COX-2 and lung cancer specimens positive for EGFR and pEGFR^{Tyr1068}.

Two pathologists (H.Y.H & C.F.L) blindly evaluated the expression level of the 3 markers tested without prior knowledge of clinical and follow-up data. Scoring of the immunoreactivity was evaluated based on a combination of both the percentage and intensity of positively stained tumoral cytoplasm to generate an H-score, which was calculated using the following equation: H-score = $\Sigma Pi\ (i + 1)$, where i is the intensity of the stained tumor cells (0 to 4 +), and Pi is the percentage of stained tumor cells for each intensity varying from 0% to 100%.[13]

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 12.0 for MS Windows (SPSS Inc., Chicago, IL, U.S.A.). All baseline clinicopathological characteristics of the study and control groups were compared using the chi-square test, except for age, which was examined by *t* test. Pearson's correlation coefficient was used to assess the correlations among the three markers and between individual markers and clinicopathological variables. The endpoints analyzed were locoregional control (LRC), distant metastasis-free survival (DMFS), and overall survival (OS), calculated from the starting date of RT to the date of the event. Patients lost to follow-up were censored on

the latest follow-up date. Univariate and multivariate analysis of LRC, DMFS, and OS were performed using the Cox proportional hazards model. For all analyses, two-sided tests of significance were used with $p < 0.05$ considered significant.

RESULTS

Immunoexpression of EGFR, pEGFR^{Tyr1068}, and COX-2 in NPC cases assessed by the H-score method

Among the 170 cases tested, both EGFR and COX-2 showed a wide range of distribution in H-scores, varying from 0 to 510 (median 225, Fig. 1A) for EGFR and from 0 to 460 (median 170, Fig. 1B) for COX-2. The H-score of pEGFR^{Tyr1068} ranged from 0 to 395 (median 25), and tended to skew toward the low end of expression (Fig. 1C). Furthermore, expression of pEGFR^{Tyr1068} was not detected in 41 cases (24.1%), although the vast majority of NPC cases (n = 167, 98.2%) showed at least focal expression of EGFR. Immunostains of representative cases with low, intermediate, and high expression of EGFR, COX-2, and pEGFR^{Tyr1068} are shown in Fig. 2. These findings suggest that a subset of NPC cases with EGFR overexpression did not necessarily have phosphorylated activation at the residue of tyrosine 1068. However, the expression of all three markers, determined by H-scores, did not correlate with one another or with any clinicopathological factor (Table 2).

Expression of EGFR, pEGFR^{Tyr1068}, and COX-2 showed no prognostic significance

In the study cohort, the 5-year rates of LRC, DMFS, and OS were 85.7%, 80.7%, and 66.9%, respectively. In both univariate and multivariate analyses (Tables 3 and 4), all three markers tested were unable to effectively predict treatment outcomes with respect to all three endpoints analyzed, no matter whether the H-scores were considered as a continuous variable or dichotomized using the medians of individual markers as cutoffs. In multivariate analysis, the independent adverse prognosticators

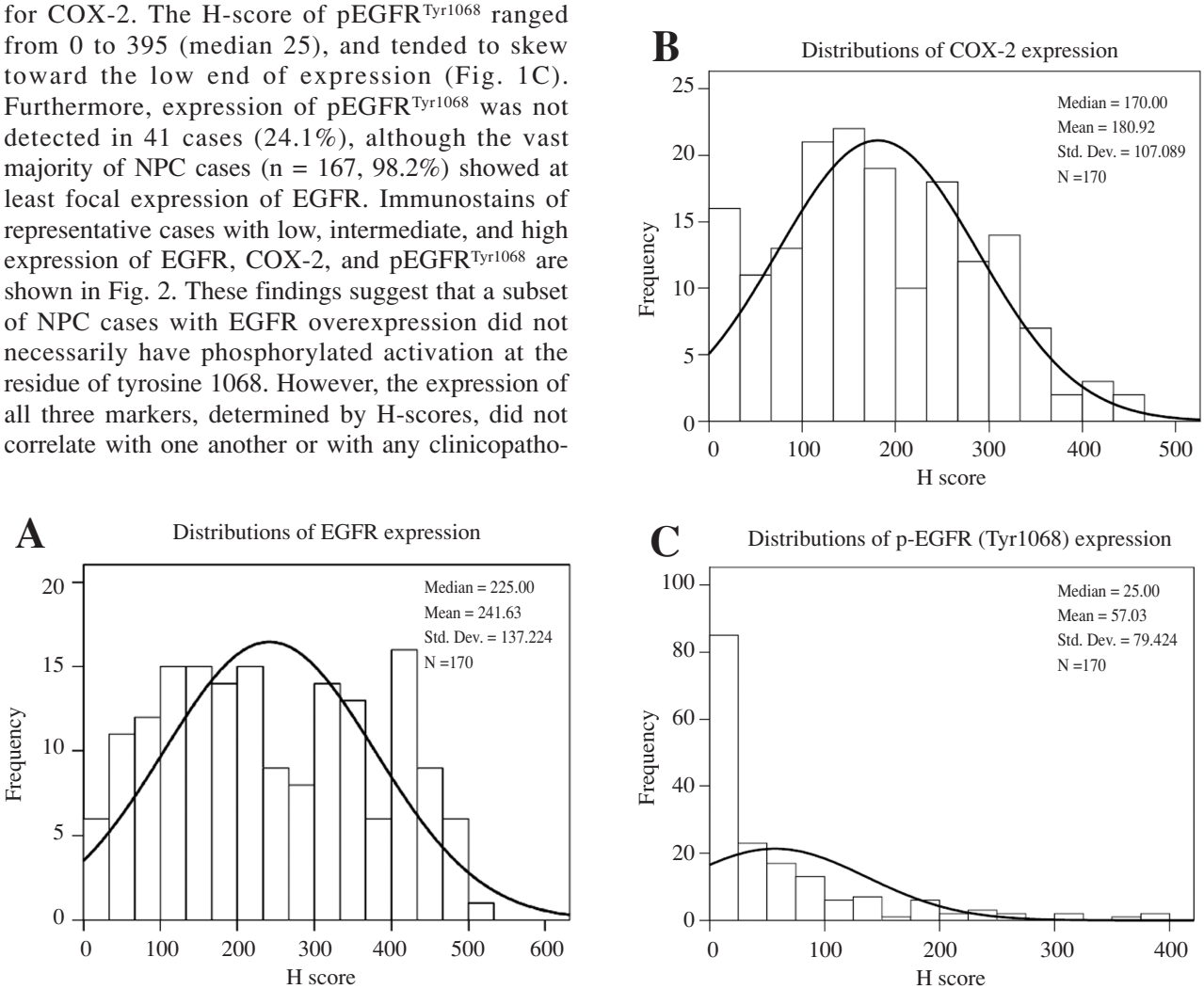

Fig. 1 Histogram illustrating the distribution of H-scores. (A) for EGFR; (B) for Cox-2; (C) for pEGFR^{Tyr1068}.

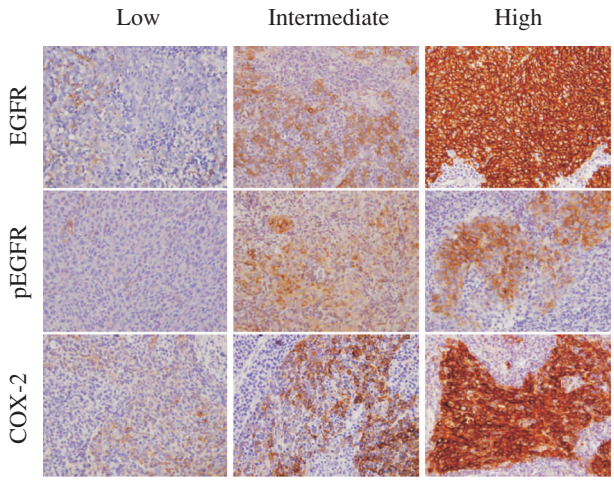

Fig. 2 Immunostains of representative cases with low, intermediate, and high expression of EGFR, COX-2, and pEGFR^{Tyr1068}.

were T-stage for LRC, N-stage for DMFS, and T-stage, N-stage, and age > 60 years for OS. In the subcohort analyses, the prognostic implications of all three markers still remained insignificant among cases at various T stages and AJCC stages.

DISCUSSION

Using immunohistochemistry, we analyzed the relationship between EGFR, pEGFR^{Tyr1068}, and COX-2 expression and their correlations with clinicopathologic factors and patient survival. The expression levels of these three markers were evaluated by the H-score method, a semiquantitative scheme incorporating both the intensity and extent of specific stains. The rates of positive expression were higher than 95% for EGFR and COX-2 in our cohort, similar to prior series showing that both oncoproteins were expressed in a high proportion of NPC patients.[3-6] A lower expression level (75%) of pEGFR^{Tyr1068} was observed, similar to that reported in another series from China which found 100% expression of EGFR and 60% of pEGFR in NPC.[14] In this study, the expression levels of EGFR, pEGFR^{Tyr1068}, and COX-2 did not correlate with each other. However, Soo et al found a significant correlation between EGFR and COX-2 in NPC specimens, which was in agreement with in vitro evidence of a molecular link between the two markers.[3] In contrast to previously reported data,[5,6] we did not identify a correlation of EGFR overexpression with any of the clinicopathological variables, including histologic subtype, T stage, N stage, and AJCC stage. This discrepancy might result from small numbers of selected cases in earlier series, since Putti et al demonstrated a significantly higher expression of EGFR in T4 tumors and cases with advanced AJCC stages than in less advanced tumors using the identical scoring scheme.[6] Recently, it has been shown that COX-2 overexpres-

Table 2. Correlations among H Scores of EGFR, pEGFR, and COX-2 Expression and Clinical Parameters

Correlation coefficient (95% CI)	EGFR	pEGFR	COX-2
Age	–0.05 (–0.20 ~ 0.11)	–0.11 (–0.25 ~ 0.04)	–0.03 (–0.18 ~ 0.12)
Gender	0.08 (–0.07 ~ 0.23)	–0.10 (–0.24 ~ 0.05)	–0.07 (–0.21 ~ 0.09)
Histology	0.02 (–0.14 ~ 0.17)	–0.05 (–0.20 ~ 0.10)	–0.05 (–0.20 ~ 0.11)
AJCC stage	–0.05 (–0.20 ~ 0.10)	0.01 (–0.15 ~ 0.16)	–0.11 (–0.26 ~ 0.04)
T stage	0.15 (0.00 ~ 0.30)	–0.02 (–0.17 ~ 0.14)	–0.08 (–0.23 ~ 0.07)
N stage	–0.22 (–0.36 ~ –0.07)	0.05 (–0.11 ~ 0.19)	0.01 (–0.14 ~ 0.16)
RT technique	0.06 (–0.09 ~ 0.21)	0.13 (–0.02 ~ 0.28)	0.12 (–0.04 ~ 0.26)
pEGFR	0.13 (–0.02 ~ 0.28)	--	0.24 (0.09 ~ 0.38)
COX-2	0.04 (–0.11 ~ 0.19)	0.24 (0.09 ~ 0.38)	--

Abbreviations: EGFR: epidermal growth factor receptor; pEGFR: phosphorylated EGFR; COX-2: cyclooxygenase-2; AJCC: American Joint of Cancer Committee published in 2002; RT: radiotherapy; CI: confidence interval.

sion was more frequently seen as nasopharyngeal epithelium progressed from normal through dysplastic to carcinomatous stages, suggesting its role in the multistep carcinogenesis of NPC.[3] However, the current study and a larger series by Tan et al both revealed a lack of association of COX-2 expression with TNM staging.[7]

Only few published reports have systematically evaluated the prognostic significance of EGFR and COX-2 expression in NPC.[5-7,14,15] In a small series of stage III-IV NPC treated with induction CT plus RT, Chua et al identified the extent of EGFR staining as an independent adverse factor for locoregional control, relapse-free survival, and disease-specific survival when using 25% positive cells as the cutoff. Intriguingly, neither the extent nor intensity of EGFR

Table 3. Univariate Analysis of H Scores of EGFR, pEGFR, and COX-2 Expression with LRC, DMFS, and OS Rates

	LRC		DMFS		OS	
	p	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
EGFR						
continuous	0.33	0.999 (0.996-1.001)	0.30	0.999 (0.998-1.002)	0.09	0.998 (0.996-1.000)
≤ *vs.* > median	0.64	1.205 (0.546-2.656)	0.21	0.557 (0.272-1.140)	0.15	0.698 (0.427-1.140)
pEGFR						
continuous	0.67	0.999 (0.994-1.004)	0.39	0.998 (0.993-1.003)	0.12	0.997 (0.993-1.001)
≤ *vs.* > median	0.54	0.779 (0.353-1.719)	0.91	0.961 (0.481-1.923)	0.08	0.699 (0.469-1.103)
COX-2						
continuous	0.56	0.999 (0.995-1.003)	0.57	0.999 (0.996-1.002)	0.11	0.998 (0.996-1.000)
≤ *vs.* > median	0.58	0.799 (0.361-1.767)	0.85	1.069 (0.535-2.138)	0.29	0.768 (0.469-1.256)

Abbreviations: LRC: locoregional control; DMFS: distant metastasis free survival; OS: overall survival; EGFR: epidermal growth factor receptor; pEGFR: phosphorylated EGFR; COX-2: cyclooxygenase-2; HR: hazard ratio; CI: confidence interval.

Table 4. Multivariate Analysis of H Scores of EGFR, pEGFR, and COX-2 Expression with LRC, DMFS, and OS Rates

	LRC		DMFS		OS	
	p	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
EGFR (≤ *vs.* > median)	0.94	1.03 (0.45-2.36)	0.17	0.59 (0.28-1.25)	0.16	0.69 (0.42-1.25)
pEGFR (≤ *vs.* > median)	0.38	0.69 (0.30-1.57)	0.81	0.91 (0.44-1.91)	0.11	0.65 (0.39-1.19)
COX-2 (≤ *vs.* > median)	0.83	0.91 (0.39-2.11)	0.79	1.11 (0.53-2.29)	0.93	0.98 (0.58-1.64)
Age (≤ *vs.* > 60 yrs)	0.78	1.15 (0.42-3.13)	0.18	0.43 (0.13-1.48)	0.01	1.78 (1.18-3.04)
Gender (female *vs.* male)	0.37	0.68 (0.29-1.58)	0.69	1.16 (0.54-2.45)	0.50	1.21 (0.69-2.14)
Histology (differentiated *vs.* undifferentiated)	0.73	1.16 (0.50-2.67)	0.97	0.99 (0.48-2.04)	0.14	1.76 (0.92-3.02)
T stage (T1-2 *vs.* T3-4)	0.002	1.95 (1.29-2.96)	0.20	1.43 (0.83-2.48)	0.001	1.73 (1.32-2.27)
N stage (N0-1 *vs.* N2-3)	0.36	1.34 (0.72-2.480	0.001	2.52 (1.61-3.94)	0.003	3.97 (1.16-2.09)
RT technique (2DRT *vs.* 2DRT + 3DCRT)	0.64	1.21 (0.53-2.76)	0.17	0.59 (0.23-1.36)	0.11	0.52 (0.25-1.34)

Abbreviations: LRC: locoregional control; DMFS: distant metastasis free survival; OS: overall survival; EGFR: epidermal growth factor receptor; pEGFR: phosphorylated EGFR; COX-2: cyclooxygenase-2; RT: radiotherapy; 2DRT: two dimensional radiotherapy; 3DCRT: three dimensional conformal radiotherapy; HR: hazard ratio; CI: confidence interval.

expression was found correlated with T or N stage in that series.[5] In the prospective study of Ma et al, similar results were also found, wherein strong EGFR intensity in stage III-IV cases was not only associated with shorter time to tumor relapse but also with inferior OS.[15] Nevertheless, EGFR overexpression was not related to the LRC, DMFS, or OS rates in Leong's or our studies.[16] In a pilot study evaluating the prognostic utility of COX-2, Chen et al found that the 5-year OS rate significantly decreased from 60% to 27% in cases with COX-2 overexpression among 37 patients with T4N0-3 NPC.[4] Nevertheless, prognostic values for EGFR and COX-2 were not identified in any subgroup of our large, well-characterized cohort of NPC cases stratified by T stage or AJCC stage.

Phosphorylated EGFR stimulates a variety of signaling pathways, such as the Ras/MAPK, PI3K/Akt, and phospholipase-Cγ/protein kinase C pathways. The activation of these signaling intermediates by pEGFR is known to play critical biological roles in various oncogenic cellular processes, such as cell proliferation, migration, and apoptosis.[17,18] There appear to be conflicting results among prior studies on the prognostic impact of EGFR versus pEGFR expression in various epithelial malignancies, such as breast, lung, and oral carcinomas.[12,19,20] For instance, Magkou et al reported that pEGFR^{Tyr1173} was positively related to the Akt pathway and appeared to participate in metastasis among 154 invasive breast carcinomas tested.[19] On the contrary, Nieto et al identified EGFR expression, instead of pEGFR^{Tyr1068}, as an independent adverse prognostic factor among 225 patients with locally advanced breast cancesr.[12] In a study of 52 oral squamous cell carcinomas, Hiraishi et al found that the pEGFR^{Tyr1173} expression level did not correlate with the tumor stage, nodal metastasis or distant dissemination.[20] Specifically for NPC, a series of 110 patients from southern China demonstrated that the 5-year DMFS rate at the univariate level was significantly lower in cases with high pEGFR expression than in those with low expression (72.2% vs. 91.0%, $p = 0.012$).[14] However, we, in our larger series, could not substantiate the prognostic relevance of pEGFR^{Tyr1086} with respect to any survival endpoint examined.

The aforementioned controversies in the prognostic utility of EGFR and/or pEGFR are likely related to the fact that different antibodies against various residues of phosphorylated tyrosine of EGFR were used in previous series. Alternatively, in the absence of protein overexpression, other molecular mechanisms modulating EGRR activation may still operate to activate relevant downstream signaling intermediates upon ligand binding, thereby transducing proliferative stumuli.[21] The latter hypothesis was supported by the fact that anti-EGFR antibodies have shown clinical benefits in the absence of overexpression of EGFR in some malignancies.[22]

There are some limitations in this study. The IHC was retrospectively reviewed and measured semiquantitatively, although there was high agreement (kappa value: 0.77) in the H-scores calculated by the two pathologists. Furthermore, we did not try different antibodies from other vendors in the samples, although the antibodies used in the current study have been used in samples reported in our previous report.[23]

In conclusion, the prognostic utility of overexpressed EGFR, pEGFR^{Tyr1086}, and COX-2 could not be validated in our well-characterized, large cohort of patients with NPC. However, the high prevalence of these oncoproteins still provides a basis for combined targeted therapy by specific pharmacological inhibitors to enhance the effects of RT or CT.

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上皮生長因子接受器 (EGFR)，磷酸化上皮生長因子接受器 (pEGFR) 及環化氧化酶-2 (COX-2) 在鼻咽癌的表現與其臨床病理因子及治療結果之相關性

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背 景： 探討上皮生長因子接受器 (EGFR)，磷酸化上皮生長因子接受器 (pEGFR^{Tyr1068}) 及環化氧化酶-2 (COX-2) 的免疫組織表現程度對鼻咽癌預後之影響。

方 法： 病例回溯及免疫組織化學檢驗 170 例單獨接受放射治療鼻咽癌病人的組織切片，利用H-記分法半定量分析 EGFR，pEGFR^{Tyr1068}，COX-2 的免疫表現程度。

結 果： 依據H-記分法，EGFR，pEGFR^{Tyr1068}，COX-2 在鼻咽癌之免疫組織表現範圍分別爲 0-510 (平均值 225)，0-395 (平均值 25)，0-460 (平均值 170)。這三個標記，沒有任一個標記與臨床病理因子，癌症局部控制率，無遠端轉移存活率及整體存活率有顯著相關；在多變數分析中，影響癌症局部控制率的獨立不良預後因子爲 T 分期；無遠端轉移存活率的獨立不良預後因子爲 N 分期；整體存活率的獨立不良預後因子爲 T 分期，N 分期及病人年齡大於 60 歲。

結 論： 接受放射治療的鼻咽癌病人，其病理組織切片 EGFR，pEGFR^{Tyr1068}，COX-2 的免疫表現與臨床病理因子並無相關性，無法預測其臨床結果。

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關鍵詞： 鼻咽癌，上皮生長因子接受器，磷酸化上皮生長因子接受器，環化氧化酶-2

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