Original Article

The role of prostaglandin E receptor 2 and epidermal growth factor receptor in esophageal squamous cell carcinoma patients with (pN+) regional lymph node metastasis

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: To find the relationship between prostaglandin E receptor 2 (EP_2) and epidermal growth factor receptor (EGFR) in esophageal squamous cell carcinoma (ESCC) patients with regional lymph nodes metastasis (pN+) who had undergone curative resection, and to analyze them in the role of judging prognosis.

Methods: Sixty-three patients with ESCC who underwent attempted curative esophagectomy with lymph node metastasis were collected. Immunohistochemistry (IHC) was used to analyse the expression of EP_2 and EGFR in tumor tissues. We analyzed the relationship between the two markers. Furthermore, we analyzed the role of EP_2 and EGFR in disease-free survival (DFS) and overall survival (OS).

Results: The expression rate of EP_2 and EGFR in this study were 73.0%, 85.7%, respectively. And the EP_2 status was closely related with the expression of EGFR in tumor tissues (χ^2=0.260, P=0.011). The patients with EP_2 or EGFR positive expression had a shorter DFS and OS than the negative group. Further analysis found EGFR is an important prognostic factor for DFS and OS (P<0.001), the expression of EP_2 was related with PFS (P=0.048), but it was not an independent influencing factors for OS (P>0.05).

Conclusions: The expression of EP_2 and EGFR were high in tumor tissues of (pN+) ESCC, and they are playing a key role in the prognosis of ESCC patients with local lymph node metastases.

Keywords: Esophageal squamous cell carcinoma (ESCC); regional lymph nodes metastasis; prostaglandin E receptor 2 (EP_2); epidermal growth factor receptor (EGFR); disease-free survival (DFS); overall survival (OS)

Submitted Dec 11, 2018. Accepted for publication Jun 24, 2019.
doi: 10.21037/tcr.2019.06.51
View this article at: http://dx.doi.org/10.21037/tcr.2019.06.51

Introduction

Esophagus cancer (EC) is one of most common cancers in the world, among which esophageal squamous cell carcinoma (ESCC) is the most common histological type in China (1,2). Although the detailed examinations and treatment strategies have made great progress in recent years, it is still insufficiently studied. Recently, albeit a proportion of patients were taken operative treatment, most patients were marred by distant metastasis, local relapse (3,4). Given the high morbidity and mortality, especially for those patients with regional lymph node metastases, it is important to find the etiopathogenesis of the cancer and develop tools for early detection.

Prostaglandin E receptor 2 (EP_2) is one of four kind

prostaglandin E receptors (EP), and it plays an essential role in the regulation of inflammatory cytokine and chemokine expression in many different cell types, including tumor cells. In the recent years, researchers had found EP_2 were play an important role in various human cancers, such as colon cancer (5), gastric cancer (6), breast cancer and non-small cell lung cancer (NSCLC), etc. The esophagus is often damaged by the excitant food, and manifested by persistent local inflammation response, which may induce the development and metastasis of the ESCC. However, some studies have demonstrated EP_2 as a promising marker for EC (7-10), few were reported about the expression of EP_2 in (pN+) ESCC and the way it worked. Epidermal growth factor receptor (EGFR), is a cell membrane tyrosine kinase (TK) receptor, is widely expressed on the surface of solid human malignancies (11), and it can be recognized as a target for the treatment of many cancer. Many studies reported overexpression of EGFR in ESCC, which may predict a trend of poor prognosis (12), and may predict a trend of poor prognosis. EP and EGFR signaling pathway was studied in many kinds of tumors, such as colon cancer, NSCLC, and hepatocellular carcinoma (HCC) (13-15). Some studies had also reported the prostaglandin E2 (PGE2) mediated the EGFR by the way of trans-activation, and this mechanism may relevant the way it works in ESCC, through the trans-activation of EGFR by EP_2 and the relevant mechanism on works on ESCC cells (16). But there were few studies about the EP_2 and EGFR in (pN+) ESCC.

In this study, we try to find the relationship between the expression of EP_2 and EGFR in ESCC with local lymph node metastasis by IHC assay. We further analyze the correlation between the two markers expressions and clinical prognosis.

Methods

Patients

Between June 2004 and June 2012, 63 patients, who underwent R0 radical operation for ESCC in The First Affiliated Hospital of University of Science and Technology of China, were included in the study. Approaches for esophagectomy include tri-incisional esophagectomy, abdominothoracic esophagectomy (Ivor-Lewis procedure). The patients with serious postoperative complications were excluded. During the surgery, the number of lymph node dissection should be more than 15. All patients were diagnosed with limited disease without distance metastasis. Preoperative chemotherapy and/or radiotherapy were not permitted. But at least one local lymph node metastasis was presenting in postoperative pathology of all cases. That means the pTNM stage is pT14N13M0. None of these patients received previous anti-inflammatory treatment within one week, nor did they have previous or concomitant other cancer in preoperative assessments. The primary analysis data consisted of age, gender, smoking/drinking history, and tumor size/location/differentiation, postoperative treatment. Postoperative treatments include 2 cycles chemotherapy (platinum-based chemotherapy) at least and/or more than 30 Gy dose of radiotherapy. For the patients who received postoperative treatments, systemic examinations of computed tomography scanning every 2 treatments cycles were used to follow up. And for other patients it performed every 3 months for the first 2 years after surgery and thereafter every 6 months up to death or the end of the study for patients without death. American Joint Committee on Cancer (AJCC) staging system (7th edition, 2010) was used to classify disease progression. disease-free survival (DFS) was measured from the date of operation to the date of first evidence of relapse or death, whichever was observed first. For patients who had not relapsed or died, DFS was censored at the last date that the absence of relapse was confirmed. Overall survival (OS) was measured from the date of surgery to the date of death or last follow-up for surviving patients. And the ultimate time of follow-up was June 2017. The present study was authorized by the Ethics Committee of Anhui Provincial Hospital (The First Affiliated Hospital of University of Science and Technology of China West District) and all patients signed the informed consent.

IHC

Three paraffin-embedded blocks included tumor tissue, para-cancerous tissue, and the normal tissue in anastomosis were collected of each case. Expressions of EP_2 and EGFR in the above-mentioned 3 tissues were detected by immunohistochemical method for each of the 63 cases. All the samples were fixed by formalin within 6–8 h after leaving the body. Paraffin embedded tissue sections (thickness, 4 μm) of ESCC were deparaffinized, heated in an oven for 2 h at 60 ℃, natural cool completely 30 min. Steeped the slides in milk (whole milk: distilled water =1:6) for 15 min. Then immunohistochemically stained using IHC autostainer (Benchmark XT, Roche Pharmaceutical Ltd., Basel, Switzerland). Specific monoclonal rabbit

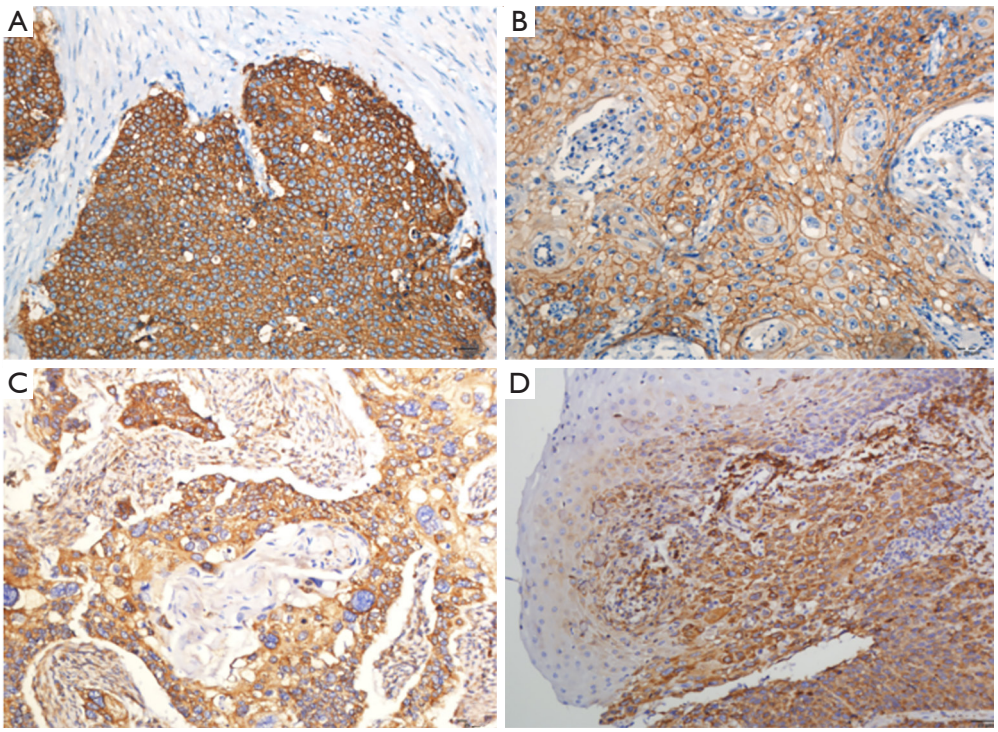

Figure 1 The expression of (A,B) EGFR and (C,D) EP_2 in ESCC with brown staining, ×100. EGFR, epidermal growth factor receptor; EP_2, prostaglandin E receptor 2; ESCC, esophageal squamous cell carcinoma.

antibody against EP_2 (ab167171, Abcam Inc., USA) and Anti-EGFR rabbit monoclonal primary antibody (5B7, Roche Diagnostics Ltd., Switzerland) were used at a dilution of 1:500 and applied to tissue sections. All the secondary antibodies were purchased from Roche Diagnostics Ltd.

Immunohistochemical evaluation

Positive EP_2 and EGFR staining were indicated by the presence of tan-colored particles in the cytoplasm and cell membranes, respectively. The immunohistochemical evaluation was independently performed by two pathologists who were blinded to the clinical data. Decision was made after the discussion of the two pathologists if the result disagreement among the experts. Each pathological slice was observed in 6 visual fields from different areas (×200), take the average value as the result of each glass evaluation of immunohistochemical result by immunoreactive score (IRS). IRS = staining intensity (SI) × percentage of positive cells (PP). SI was divided into four degrees: 0 is negative, 1 is weak, 2 is moderate, and 3 is strong. PP was defined as 0 is negative; 1 is 10% positive cells; 2 is 11–50% positive cells; 3 is 51–80% positive cells; and 4 is more than 80% positive cells. IRS >3 was defined as positive immunoreactive (17,18).

Statistical analysis

Statistical analysis was conducted with SPSS (SPSS 16.0, Inc., Chicago, IL, USA). Spearman test was used to analyze the correlation and difference of EP_2 and EGFR in different tissues. The DFS and OS were calculated by the Kaplan-Meier method, and compared by log-rank test. Cox's proportional hazards regression model were performed to evaluate the prognostic factors for DFS and OS. All statistical tests were two-sided, and P values <0.05 was considered statistically significant in all tests.

Results

In the present study, IHC showed that EP_2 was expressed in ESCC cytoplasm with brown staining and the positive rate was 73.0% (*Figure 1*). The DFS and OS of EP_2 positive group were shorter than the control group (*Figure 2*). The

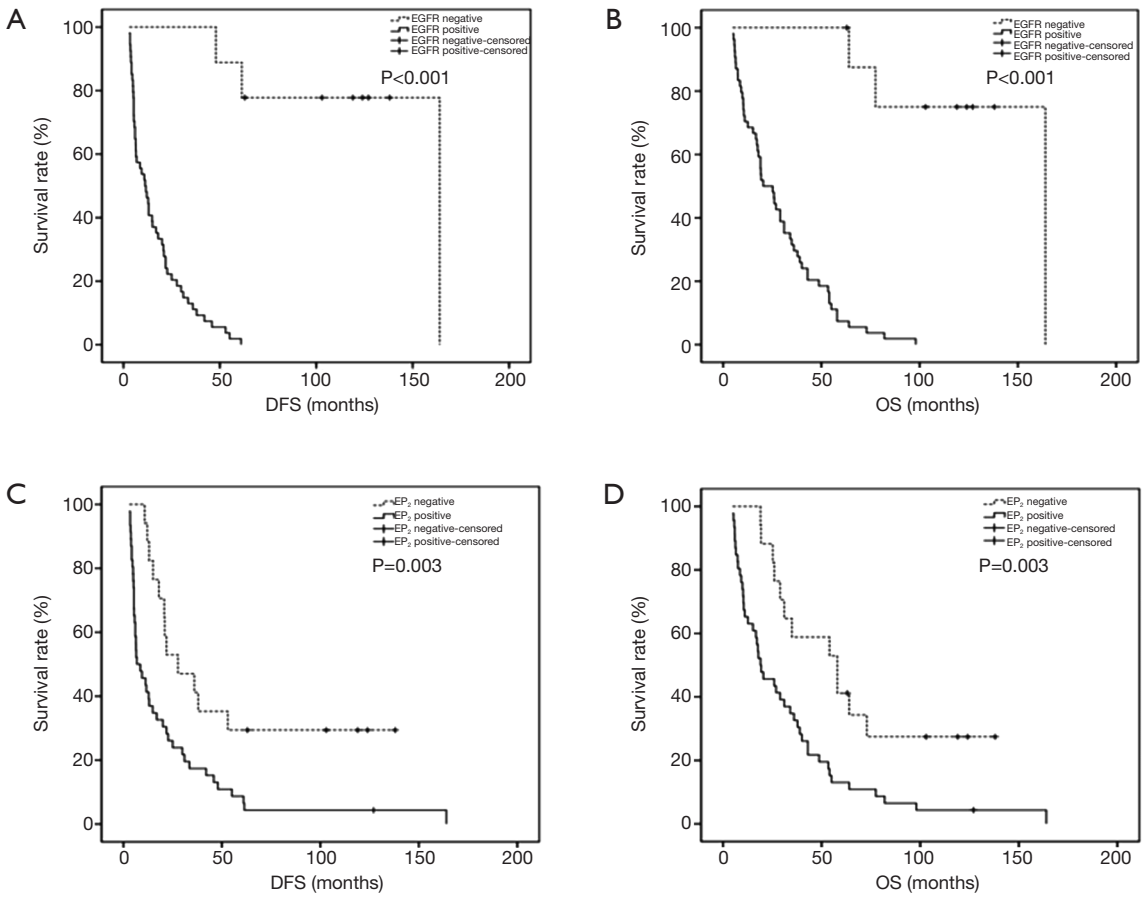

Figure 2 The Kaplan-Meier survival analysis of EP_2 and EGFR in the study. There are 42 patients had EP_2 and EGFR positive expresses on the same tissue, this means the 66.7% patients had the two markers over-express at the same time. But the Pearson Chi-square test did not find there was a relationship between the express of EP_2 and EGFR in these patients (Pearson correlation coefficient =3.102, P=0.078). EGFR, epidermal growth factor receptor; EP_2, prostaglandin E receptor 2; DFS, disease-free survival; OS, overall survival.

high expression of EP_2 was closely associated with the poor differentiation (P=0.036) and younger patients (P=0.029). But sex, smoking, drinking, tumor size, tumor location, tumour stage showed no correlation with the expression of EP_2 (P>0.05) (*Table 1*). EGFR staining was detected in the cell membrane in 54 of 67 cases (*Figure 1*). We found the smoker had a high rate of EGFR expression. The expression of EGFR was closely related to DFS and OS (P<0.05) (*Figure 2*). In multivariate analysis, the age (P=0.032), gender (P=0.026), EP_2 (P=0.045), EGFR (P=0.001) and postoperative treatment (P=0.005) were the independent factors that could impact on the DFS (P<0.05). For the OS, we found the younger patients (P=0.016), EGFR positive (P=0.001) or without postoperative treatment (P=0.018) had a shorter OS, and the above factors are all the independent factors for OS (*Tables 2,3*).

Discussion

The most type of EC in China is squamous cell carcinoma. The most common and effective way to treat early esophageal cancer patients is operation. In the data reported by many studies, the survival decreased with presence of regional lymph node metastases (19), and the lymph nodes involvement has been shown to be a strong independent predictor of poor survival with surgery alone. The great majority of such patients are relapsed or metastasized in the short time after operation. So, these patients are therefore considered for induction therapy followed by surgery. But there had no precise set of indicators to predict the disease,

Table 1 The difference of EP_2 and EGFR in different clinical features' patients of 63 (pN+) ESCC

Clinical characteristics	Case	EP_2				EGFR			
		+	–	χ^2	P	+	–	χ^2	P
Age (years)									
≤60	29	25	4	4.746	0.029	27	2	2.396	0.122
>60	34	21	13			27	7		
Gender									
Male	52	36	16	2.166	0.141	44	8	0.294	0.588
Female	11	10	1			10	1		
Stage									
II	19	13	6	0.292	0.589	15	4	1.017	0.313
III	44	33	11			39	5		
Length of tumor (cm)									
<3	9	6	3	0.215	0.643	9	0	1.750	0.186
≥3	54	40	14			45	9		
Location of tumor									
Middle	37	29	8	1.309	0.253	33	4	0.884	0.347
Low	26	17	9			21	5		
Differentiation									
High or middle	53	36	17	4.393	0.036	45	8	0.178	0.673
Poor	10	10	0			9	1		
Smoking									
No	35	26	9	0.064	0.800	27	8	4.725	0.030
Yes	28	20	8			27	1		
Drinking									
No	36	26	10	0.027	0.870	30	6	0.389	0.533
Yes	27	20	10			24	3		

EP_2, prostaglandin E receptor 2; EGFR, epidermal growth factor receptor; ESCC, esophageal squamous cell carcinoma.

so it is in bad need of finding indicator which can predict the prognosis.

EP_2 was one of the four EP coupling receptors which mediate PGE2 signaling. Many tumors that intensely express COX-2 enzyme have also been found to contain high levels of PGE2 (20-22). Previous studies have well established that human ESCC frequently overexpress COX-2 and produce high levels of PGE2 (23,24). So that, it is indicated that EP_2 plays a role in esophageal cancer. EP_2 receptor performs its function by combining with the PGE2 that stimulates cell proliferation (25). Until recently, several studies have been focused on the association of EP_2 expression with survival of patients with esophageal cancer. Kuo *et al.* used immuno-histochemical staining and Western blot to find that EP_2 overexpression was associated with worse prognosis from 226 patients with ESCC. And they observed that EP_2 overexpression was in 43.4% (98/226) of ESCC (7). Xu *et al.* also found EP_2 positive expresses was more observed in ESCC than the control group (52.9% *vs.* 4.88%), with a significant difference (P<0.001). What's more, overexpression of EP_2 exhibited significant correlation with worse 5-year OS than those with negative result

Table 2 Multivariate analysis of DFS in 63 middle and lower (pN+) ESCC

Prognostic factor	DFS		
	Odds ratio	95% CI	P value
Age	0.476	0.242–0.936	0.032
Gender	2.777	1.127–6.842	0.026
EGFR	46.713	5.241–416.340	0.001
EP_2	2.332	1.019–5.338	0.045
Postoperative treatment	0.359	0.175–0.736	0.005
Stage	0.949	0.470–1.918	0.884
Length of tumor	1.160	0.457–2.943	0.755
Differentiation	0.638	0.262–1.555	0.323
Smoking	0.901	0.369–2.201	0.819
Drinking	0.779	0.326–1.858	0.573

DFS, disease-free survival; ESCC, esophageal squamous cell carcinoma; EGFR, epidermal growth factor receptor; EP_2, prostaglandin E receptor 2.

Table 3 Multivariate analysis of OS in 63 middle and lower (pN+) ESCC

Prognostic factor	OS		
	Odds ratio	95% CI	P value
Age	0.425	0.212–0.852	0.016
Gender	2.215	0.935–5.248	0.071
EGFR	16.572	3.229–85.053	0.001
EP_2	1.974	0.898–4.342	0.091
Postoperative treatment	0.452	0.234–0.871	0.018
Stage	1.437	0.702–2.942	0.321
Length of tumor	1.112	0.459–2.697	0.814
Differentiation	0.769	0.305–1.939	0.578
Smoking	1.090	0.408–2.911	0.863
Drinking	0.617	0.237–1.609	0.324

OS, overall survival; ESCC, esophageal squamous cell carcinoma; EGFR, epidermal growth factor receptor; EP_2, prostaglandin E receptor 2.

(10.9% *vs.* 34.1%, P<0.001) (8). Piazuelo *et al.* found EP_2 may play important roles in the development of esophageal adenocarcinoma (EAC) induced by gastroduodenal reflux in the rat (9). In Barrett's esophagus adenocarcinoma and EAC, they also found the EP_2 was overexpressed, and they thought it might be used as a new method to treat Barrett's esophagus in the future (10). In a word, EP_2 is an important marker in EC, But the role of EP_2 in (pN+) ESCC is not available, and the way it works is still unknown.

In this study, we found EP_2 was overexpression in (pN+) ESCC, and it was directly related to prognosis. DFS and OS were shorter in (pN+) ESCC patients with EP_2 positive expression in tumor tissues than control group (6.8 *vs.* 27.7 months, P=0.003; 19.0 *vs.* 58.0 months, P=0.003). COX multivariate survival analysis also found that EP_2 was an independent prognostic risk factor for DFS in (pN+) ESCC patients (P=0.045, 95% CI: 1.019–5.338). However, further analysis showed that the condition of EP_2 did not affect

OS. This may suggest that EP_2 played an important role in recurrence of (pN+) ESCC. But the mechanism of EP_2 was used to achieve its role in ESCC is no unified conclusion.

As we know, EP_2 is an inflammatory marker. The study found that the activation of EGFR under inflammatory conditions might be positively attributed to the transformation of normal esophageal epithelia to squamous cell cancer (26). EGFR is a cell membrane TK receptor and is recognized as a target for the treatment of many cancers, including esophageal cancer. The role of EGFR in esophageal carcinoma had been studied for a long time. In the previous studies, the detection of the expression rate of EGFR in ESCC tissue was ranging from 40% to 80% (27). At the present time there are many research results concerning EGFR and esophageal cancer. As it was mentioned above in the part of results, most studies showed that over expression of EGFR was an independent adverse prognostic factor in esophageal cancer (8). In our study, EGFR was highly expressed in ESCC tumor tissues (54/63, 85.7%), and we can find that the 42 (66.7%) patients had EP_2 and EGFR positive expresses at the same tissue. But the Pearson Chi-square test did not find there was a relationship between the express of EP_2 and EGFR in the tissues of tumor (Pearson correlation coefficient =3.102, P=0.078). However, EP_2 and EGFR expressions were both found in the same tissue from most patients. there is must be a relationship between the two markers. In our study, we did not find the statistical relationship between EP_2 and EGFR, which might be due to the limited number of patients.

Therefore, we consider that there might be a connection between the EP_2 and EGFR in ESCC. The exactly signaling pathway between the two markers was unavailable now. Of course, there might be more than one signaling pathway between them in ESCC. In the previous studies, we can find some clues. Donnini *et al.* found PGE2 as the selective stimulation of the EP_2 receptor subtype, leading to EGFR transactivation via protein kinase (PK) A and c-Src activation in ESCC (28). Another path way between EP_2 and EGFR was via PKC/extracellular signal regulated kinase pathway-dependent induction of c-Myc expression in human ESCC (29). What's more, they might also exist EP_2/EGFR/PI3 kinase-Akt signaling in cervical cancer (30). In addition to the above, Chun *et al.* found EP_2 played a part in UVB-exposed mouse skin via an EGFR/STAT3 pathway (31). Cheng *et al.* reported that PGE2 could upregulate the expression level of Snail protein through the EP_2/Src/EGFR/Akt/mTOR pathway in Huh-7 cells, which promotes HCC cell invasion and migration (32). EP a_2nd EGFR may also work by immune escape. NSCLCs harboring EGFR mutations is associated with low overall response rate to PD-1/PD-L1 inhibitors, this immunosuppression phenomenon maybe caused by EP_2-EGFR signal way. As you know the above mechanisms were in different cancers, they might exist in ESCC.

In this study, we found the DFS of (pN+) ESCC patients with EP_2 or EGFR expresses was remarkably decreased as compared with the negative group. But for the OS, we did not find the EP_2 was an independent of influential factors of prognosis. So, the EP_2-EGFR signaling pathway may play a key role in the recurrence of the disease. The high-risk of relapse was found in (pN+) ESCC patients in the clinical practice. One possible reason may be the activating of this signaling pathways. So, we thought the EP_2-EGFR may one reason cause the disease recurrence. Tumor recurrence may be delayed by inhibiting the single way. So, this may give us some inspiration for the treatment of postoperative therapy.

Some limitations should be interpreted in our study. First, the sample size is too small to cover these too many parameters. Second, this study did not go further in analysis the relation between EP_2 and EGFR, the exact mechanisms involved are still mysterious. So, the further study is needed.

In conclusion, the expression of EP_2 and EGFR were important independent prognostic factor for the DFS. So we proposed hypothesis that it exits a signal pathway about EP_2-EGFR playing an important role in the occurrence and development of (pN+) ESCC. The limitation of this study is that we did not perform further work to confirm the signaling pathway between EP_2 and EGFR in this study. This work was performed in the laboratory, and the full statistical results will be available soon.

Acknowledgments

Funding: This study was supported by Natural Science Foundation of Anhui Province, China.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.06.51). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The present study was authorized by the Ethics Committee of Anhui Provincial Hospital (2018-16) (The First Affiliated Hospital of University of Science and Technology of China West District) and all patients signed the informed consent.

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Cite this article as: Luo HQ, He YF, Yan Y, Wu SS, Hu XX, Ke LH, Niu JY, Li HM, Xu HJ. The Role of prostaglandin E receptor 2 and epidermal growth factor receptor in esophageal squamous cell carcinoma patients with (pN+) regional lymph node metastasis. Transl Cancer Res 2019;8(4):1233-1241. doi: 10.21037/tcr.2019.06.51

