Original Article

Clinical and prognostic significance of MUC1 expression in patients with esophageal squamous cell carcinoma after radical resection

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Abstract

Background/Aim: To investigate the clinical and prognostic significance of MUC1 expression in patients with esophageal squamous cell carcinoma (ESCC) after radical resection.

Materials and Methods: A total of 108 ESCC specimens were evaluated by reverse transcriptase-polymerase chain reaction (RT-PCR) to detect MUC1 at the mRNA level and were evaluated by immunohistochemistry (IHC) to detect MUC1 at the protein level.

Results: MUC1 mRNA was found in 74 cases by RT-PCR and MUC1 protein expression was found by IHC in 70 cases. Both MUC1 mRNA and protein expression correlated with pT (<0.05), pN ($P < 0.01$), and pTNM (<0.01). The 5-year survival rates of the patients were 39.8%. In univariate analysis, the 5-year survival rate in the ESCC patients was significantly associated with pT ($P < 0.01$), pN ($P < 0.01$), pTNM stage ($P < 0.01$), and MUC1 mRNA and protein expression ($P < 0.05$). In multivariate analysis, pN and MUC1 expression were the independent relevant factors.

Conclusion: MUC1 expression can become a useful marker to predict poor prognostic factors for 5-year survival rate in patients with ESCC after radical resection.

Keywords: Esophageal cancer, immunohistochemistry, MUC1, prognosis, reverse transcriptase-polymerase chain reaction

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INTRODUCTION

Esophageal cancer is one of the ten malignant tumors in China, and the major histological type is esophageal squamous cell carcinoma (ESCC). The major treatment method for ESCC is esophagectomy. However, the prognosis is not satisfactory, and the 5-year survival rate of the patients with ESCC is only 30–50%.[1] The tumor-node-metastasis (TNM) staging system, according to histopathologic findings, lacks sufficient predictive value as significant differences in survival are often observed for the same TNM stage. Recently, some molecular biomarkers combined with TNM staging system have become valuable in accurately distinguishing ESCC patients' prognosis.

MUC1 (Mucin1) is a transmembrane mucin and can be present on the apical surface of normal glandular epithelial

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cells in normal tissues.[2,3] In cancer tissues, MUC1 can be upregulated and the whole cell surface can show MUC1 expression.[4] It has been reported that MUC1 plays important roles in the invasion and metastasis of some cancers and is an important prognostic factor in some malignant tumors. However, only few studies have confirmed the prognostic value of MUC1 in ESCC. Thus, we designed the present study to investigate the clinical and prognostic significance of MUC1 expression in ESCC patients after curative resection by both univariate and multivariate analysis. We also aimed to detect MUC1 expression at the mRNA level by reverse transcriptase-polymerase chain reaction (RT-PCR) and detect MUC1 expression at the protein level by immunohistochemistry (IHC).

MATERIALS AND METHODS

Patients

One hundred and sixty-two consecutive patients with ESCC underwent resection at the department of Thoracic Surgery, Jinan Central Hospital Affiliated to Shandong University and the department of Thoracic Surgery East Ward, Provincial Hospital Affiliated to Shandong University from August 2008 to July 2009. A total of 108 patients were enrolled in this study. The inclusion criteria were as follows: (1) patients who underwent complete resection and in whom postsurgical pathology proved ESCC; (2) patients who were diagnosed as pathologic stage I–III postoperatively. The TNM staging was determined by the criteria established by the International Union Against Cancer (UICC) in 2009; (3) patients who did not undergo preoperative radiotherapy or chemotherapy, without surgical contraindication; (4) Cases that were well preserved. The clinicopathological characteristics of the 108 patients are listed in Table 1. This study was carried out in strict accordance with the recommendations listed in the Guide for the Chinese Ethics Review Committees. The protocol was approved by the Shandong University Ethics Committee.

Samples

We obtained ESCC specimens from 108 patients. Each specimen was divided into two parts. At least 0.5 cm × 0.5 cm × 0.5 cm ESCC specimens were used to detect MUC1 mRNA expression by RT-PCR. The other ESCC specimen was used for histopathologic examination. To prevent cross-contamination of MUC1 mRNA, we handled specimens with a fresh set of instruments. Each ESCC specimen was wrapped in foil quickly after being labeled and then snap frozen in liquid nitrogen for one minute and kept at −80°C until RNA extraction. Normal esophagus specimen were used as controls.

According to the manufacturer's protocol, we used Trizol one-step procedure to extract total RNA from each specimen. We used standard UV spectrophotometric assay to determine RNA purity and concentration. Primers were designed as follows: MUC1:5'-end primer: 5'-CGTCGTGGACATTGATGGTACC-3', 3'-end prime: 5'-GGTACCT CCT CTC AC CTCCTCCAA-3. The primers of MUC1 yielded 288 bp products. The primers of β-actin yielded a 539 bp product as follows: 5'-end primer: 5'-GTG GGGCGCCCCAGGCACCA-3', 3'-end primer: 5'-CTCCTTAAT GT CACGCACGATTTC-3'. The samples followed an initial denaturation for 5 minutes at 95°C, and were amplified by thirty cycles of denaturation for 1 minute at 94°C, annealing for 1 minute at 58°C, extending for 1 minute at 72°C, and finally extending for 7 minutes at 72°C. PCR products were visualized by electrophoresis through 1% agarose gels and stained with ethidium bromide. We obtained gel images from AlphalmagerTM 2200 UV-image analyzer (Alpha Innotech Corp., USA).

Immunohistochemistry

We detected MUC1 expression by IHC according to previous reports.[5] IHC analysis was performed using mouse immunoglobulin monoclonal antibody against human *MUC1* gene (MAB-0581; 1:100 dilution; Fuzhou Maxim Inc., Fuzhou, Fujian, China). A secondary antibody was applied using the Elivision plus kit (Dako, Glostrup, Denmark) according to the manufacturer's instructions. MUC1 was located in the cytoplasm of tumor cell. The expression of MUC1 is shown by bright yellow, brown yellow, or brown diffusively distributed or granules focally. MUC1 expression was scored semi-quantitatively as follows: 0, 1= <5% of cells; 2 = 5–29% of cells; 3 = 30–60% of cells; 4= >60% of cells. If the score was =>3, we regarded MUC1 expression as positive.[6,7]

Follow-up

Forty-four patients received chemotherapy, 12 patients received postoperative radiotherapy, and 26 patients received combined chemoradiotherapy. We examined the patients every 3 to 4 months during the first 3 years and every 6 months thereafter. Patients who succumbed to mortality due to the tumor were included in the prognostic analysis.

Statistical methods

Fisher's exact probability test or chi-sqaure test were used to calculate the correlation between MUC1 expression and clinicopathological factors. Univariate analysis was carried out using Kaplan–Meier survival curves. Multivariate analysis was performed using the Cox proportional hazard

Table 1: Correlation between MUC1 expression and clinical features of the ESCC patients

Clinical characteristics	Patients 108	MUC1 expression (RT-PCR) 34 74		*P* Value[a]	MUC1 expression (IHC) 38 70		*P* Value[a]
		(-)	(+)		(-)	(+)	
Gender				0.111*			0.290*
Male	89	25	64		29	60	
Female	19	9	10		9	10	
Age, years				0.305*			0.548*
<60	52	19	33		20	32	
≥60	56	15	41		18	38	
Smoking				0.539*			1.000*
Yes	49	17	32		17	32	
No	59	17	42		21	38	
Tumor length, cm				>0.05			>0.05
< 3	12	6	6		6	6	
3-5	52	17	35		21	31	
>5	44	11	33		11	33	
Tumor location				0.138*			0.100*
Middle	66	17	49		19	47	
Lower	42	17	25		19	23	
Weight, kg				0.599*			0.130*
≤ 5	88	29	59		33	54	
> 5	20	5	15		4	16	
Differentiation				>0.05			>0.05
Well	15	7	8		8	7	
Moderate	70	24	46		25	45	
Poor	23	3	20		5	18	
pT				<0.05			<0.05
pT1	10	7	3		7	3	
pT2	59	16	43		20	39	
pT3	39	11	28		11	28	
pN				0.006*			0.004*
-	65	27	38		30	35	
+	43	7	36		8	35	
pTNM				<0.05			<0.01
pI	37	18	19		21	16	
pII	48	12	36		13	35	
pIII	23	4	19		4	19	

P Value[a]: x^2 test, *Fisher's exact probability test

model. When the *P* value was less than 0.05, we considered the differences significant. We obtained the statistical data using SPSS software package (SPSS 13.0 Inc., Chicago, IL, USA).

RESULTS

As shown in Table 1, MUC1 mRNA was found in 74 cases by RT-PCR and was significantly correlated with pT (<0.05), pN ($P < 0.01$), and pTNM (<0.01). MUC1 protein expression was found by IHC in 70 cases and was also significantly correlated with pT (<0.05), pN ($P < 0.01$) and pTNM (<0.01) [Figures 1 and 2]. No other clinicopathological parameter was related to MUC1 expression. Among the follow-up of 108 ESCC patients, the 5-year survival rates were 39.8%. In univariate analysis by the log-rank test [Table 2], the 5-year survival rate in ESCC patients was significantly associated with pT ($P < 0.01$), pN ($P < 0.01$), pTNM stage ($P < 0.01$), and MUC1 mRNA and protein expression ($P < 0.05$) [Figure 3]. In multivariate analysis by Cox regression, pN, and MUC1 expression were the independent relevant factors [Tables 3 and 4].

DISCUSSION

MUC1 is a structural membranous bound mucin, and was shown on secretory epithelial cell apical borders.[8] In cancer tissues, the expression of MUC1 can be upregulated and expressed on the entire cell surface. It has been reported that MUC1 can increase invasion and metastasis in some cancers. MUC1 can reduce the E-cadherin mediated cell–cell adhesion through steric hindrance,[5] and can also reduce the integrin-mediated cell adhesion through the extracellular matrix. In addition, MUC1 participating in carcinogenesis progression by interacting with the epidermal growth factor receptor (EGFR) family, act as a signal transducer.[9] Therefore, MUC1 has been studied in some cancers, such as breast,[10] lung,[8] pancreatic,[11] colorectal,[12] gastric,[13] ovarian cancer,[14] and even lymphoma[15] because of its potential role as a prognostic biomarker.

However, the correlation between MUC1 expression and prognosis in patients with esophageal carcinomas remains controversial. MUC1 plays an important role in proliferative, invasive and metastatic properties of esophageal Barrett's adenocarcinoma.[16,17] Mariette *et al.*[18] found that the induction of MUC1 by bile acids could increase the invasive and metastatic potential of esophageal adenocarcinoma cancer cells. Piessen *et al.*[19] found MUC1 expression was strong in patients with primary esophageal adenocarcinoma using IHC. However, no correlation was found between MUC1 expression and survival. Our previous study showed that MUC1 can be used to

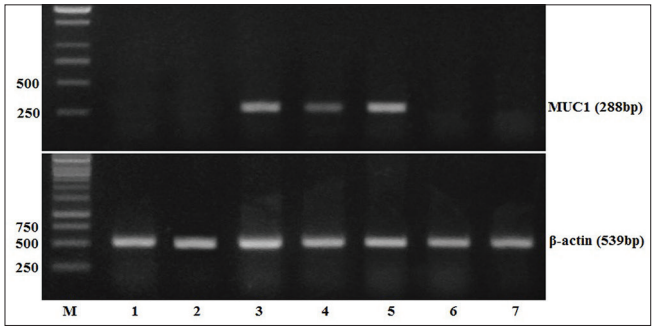

Figure 1: Expression of MUC1 mRNA detected by polymerase chain reaction (PCR). Lane 1-2: corresponding adjacent normal epithelium tissues; lane3-5: cancer tissues MUC1 mRNA(+); lane 6-7: cancer tissues MUC1 mRNA(-). M molecular marker (bp)

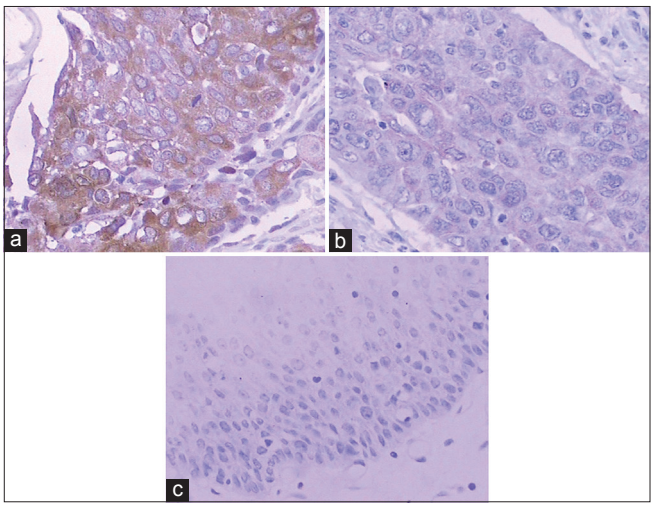

Figure 2: (a) Immunohistochemical staining of human ESCC tissue sections demonstrating MUC1 protein. The MUC1 staining was confined to the cytoplasm, and photomicrographs showed human ESCC specimen with high MUC1-positive tumor cells (>3). Original magnification ×200 (b) Photomicrographs showing ESCC specimen with low MUC1-positive tumor cells(<3). Original magnification ×200. (c) Photomicrographs showing the corresponding normal tissue specimen with no MUC1-positive tumor (-). Original magnification ×200

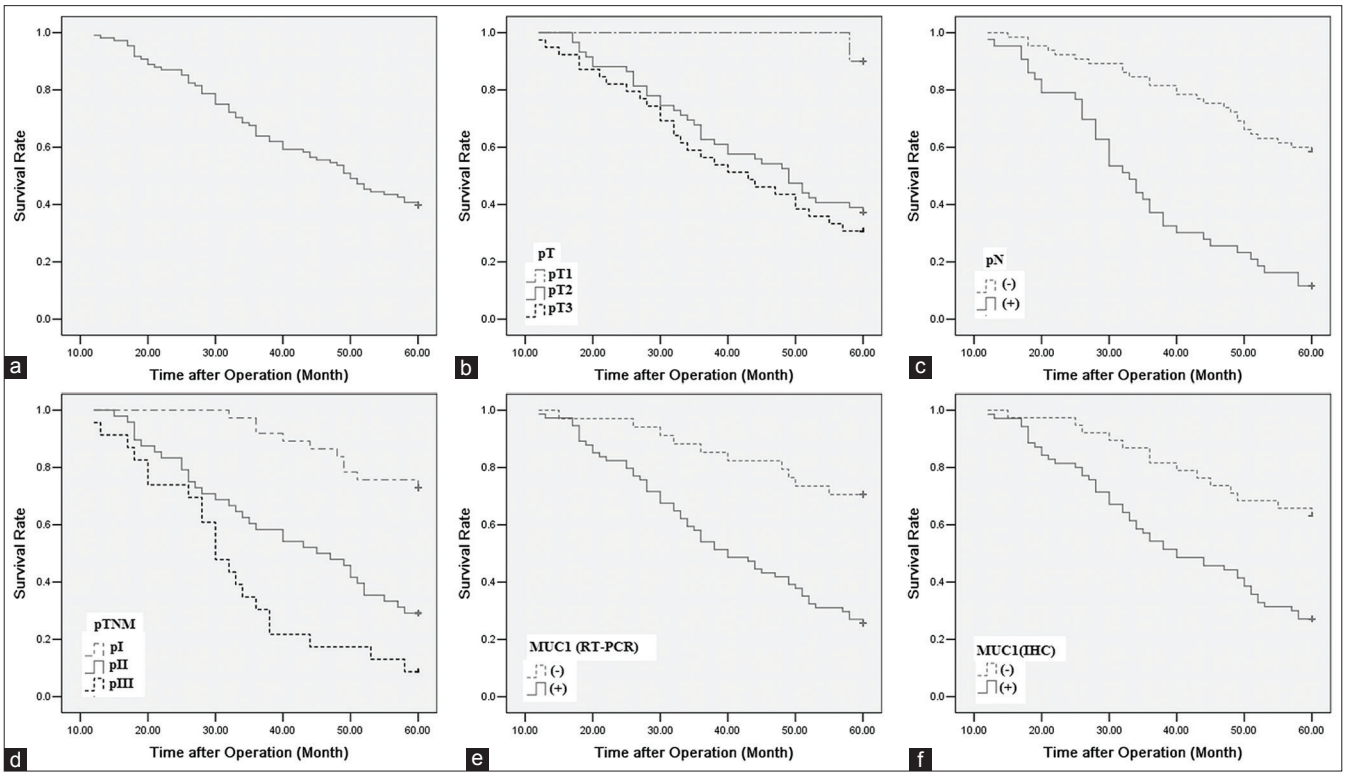

Figure 3: (a) Kaplan-Meier analysis of the overall survival after operation (b) Kaplan-Meier analysis of the overall survival rate after operation in patients with pT stage. (c) Kaplan-Meier analysis of the overall survival rate after operation in patients with pN(-) and pN(+) (d) Kaplan-Meier analysis of the overall survival rate after operation in patients with pTNM stage (e) Kaplan-Meier analysis of the overall survival rate after operation in patients with positive and negative expression of MUC1 mRNA, respectively. (f) Kaplan-Meier analysis of the overall survival rate after operation in patients with positive and negative expression of MUC1 protein, respectively

Table 2 Univariate analysis with respect to 5-year survival

Clinical characteristics	Patients 108	5-year survival (%) 43 (39.8)	Patients Rate (%)	*P*
Gender				0.133
Male	89	33	37.1	
Female	19	10	52.6	
Age, years				0.940
<60	52	21	40.4	
≥60	56	22	39.3	
Smoking				0.634
-	59	24	40.7	
+	49	19	38.8	
Tumor length, cm				0.083
<3	12	8	66.7	
3-5	52	20	38.5	
>5	44	15	34.1	
Tumor location				0.695
Middle	66	25	37.9	
Lower	42	18	42.9	
Weight, kg				0.249
≤5	88	36	40.9	
>5	20	7	35.0	
Differentiation				0.184
Good	15	9	60.0	
Moderate	70	26	38.6	
Poor	23	7	30.4	
pT				0.009
pT1	10	9	90.0	
pT2	59	22	37.3	
pT3	39	12	30.8	
pN				<0.01
-	65	38	58.5	
+	43	5	11.6	
pTNM				<0.01
pI	37	27	73.0	
pII	48	14	29.2	
pIII	23	2	8.7	
Chemotherapy				0.605
-	38	17	44.7	
+	70	26	37.1	
Radiotherapy				0.982
-	70	31	44.3	
+	38	12	31.6	
MUC1expression (RT-PCR)				<0.01
-	34	24	70.6	
+	74	19	25.7	
MUC1expression (IHC)				<0.01
-	38	24	63.2	
+	70	19	27.1	

P Value[c]: Log-rank test

Table 3 Results of Cox regression multivariate 5-year survival analysis (RT-PCR)

	B	SE	Wald	P	HR	95.0% CI for HR
Gender	0.028	0.396	0.005	0.944	1.028	0.473-2.236
Age	-0.246	0.264	0.869	0.351	0.782	0.466-1.312
Smoking	0.033	0.279	0.014	0.906	1.034	0.598-1.786
Weight	0.034	0.355	0.009	0.923	1.035	0.516-2.077
Tumor length	0.143	0.212	0.457	0.499	1.154	0.762-1.747
Tumor location	-0.352	0.306	1.321	0.250	0.704	0.386-1.281
Differentiation	0.191	0.257	0.553	0.457	1.210	0.732-2.001
pT	0.679	0.363	3.498	0.061	1.972	0.968-4.016
pN	1.094	0.548	3.982	0.046	2.986	1.020-8.743
pTNM	0.323	0.405	0.638	0.424	1.382	0.625-3.054
Chemotherapy	-0.682	0.398	2.940	0.086	0.505	0.232-1.103
Radiotherapy	-0.390	0.312	1.561	0.212	0.677	0.368-1.248
MUC1 expression	1.080	0.365	8.758	0.003	2.944	1.440-6.018

B: Regression coefficient, SE: Standard error, Wald: Wald value, HR: Hazard ratio, CI: Confidence interval

Table 4: Results of Cox regression multivariate 5-year survival analysis (IHC)

	B	SE	Wald	P	HR	95.0% CI for HR
Gender	0.068	0.393	0.030	0.862	1.070	0.496-2.310
Age	-0.261	0.262	0.993	0.319	0.770	0.461-1.287
Smoking	0.023	0.278	0.007	0.934	1.023	0.593-1.764
Weight	-0.049	0.348	0.020	0.888	0.952	0.481-1.884
Tumor length,cm	0.142	0.211	0.452	0.502	1.153	0.762-1.744
Tumor location	-0.389	0.304	1.630	0.202	0.678	0.373-1.231
Differentiation	0.222	0.259	0.734	0.392	1.249	0.751-2.075
pT	0.657	0.359	3.347	0.067	1.929	0.954-3.900
pN	1.191	0.540	4.862	0.027	3.291	1.142-9.489
pTNM	0.283	0.406	0.488	0.485	1.328	0.599-2.940
Chemotherapy	-0.294	0.302	0.950	0.330	0.745	0.412-1.347
Radiotherapy	-0.351	0.305	1.327	0.249	0.704	0.387-1.279
MUC1 expression	0.681	0.322	4.485	0.034	1.976	1.052-3.713

B: Regression coefficient, SE: Standard error, Wald: Wald value, HR: Hazard ratio, CI: Confidence interval

detect lymph node micrometastasis. MUC1 expression in lymph node was significantly associated with lymph node metastatic recurrence and poor prognosis in patients with pN0 ESCC.[20] Only three studies have confirmed the clinicopathological characteristics and the prognostic value of MUC1 in patients with ESCC. In a study by Song,[21] MUC1 expression was shown in 78.9% of ESCC patients and correlated with lymph node metastasis by IHC. They found that a high expression of MUC1 correlates with a poor survival and is an independent prognostic factor in ESCC patients. In Kahkhaie's study,[22] MUC1 mRNA expression was evaluated in patients with ESCC. They found that Specific MUC1 splice variants were correlated with ESCC progression. Ye *et al*.[23] found that MUC1 expression and MMP13 expression are correlated with lymph node metastasis in ESCC patients. MUC1 can lead to increased cell migration and metastasis by stimulating MMP13 expression. Their findings indicate that MUCI may be used as a novel diagnostic biomarker and therapeutic target in ESCC. However, in Kijima's study,[24] MUC1 was found in (32.1%) ESCC by IHC, MUC1 expression was detected in the intramucosal part in 28.3% (15 out of 53) and in the invasive part in 32.6% (14 out of 43) of the esophageal carcinomas (no significant difference). These observations suggested that expression of MUC1 is an early event in cancer progression, but that it is not significantly associated with metastasis of human esophageal carcinomas. These results might be explained by using different analytic methods and different treatments. A conclusive effectiveness should be further verified by a large-scale randomized clinical study.

In our study, MUC1 expression was detected both by RT-PCR at mRNA level and IHC at protein level.

MUC1 expression correlated with tumor invasion (pT), lymph node metastasis (pN), and pTNM both at the mRNA and protein levels. In a univariate analysis, the 5-year survival rate of ESCC patients without MUC1 expression was significantly higher than that of the ESCC patients with MUC1expression. In multivariate analysis, MUC1 expression and lymph node metastasis (pN) were independent relevant factors for 5-year survival rate.

In our study, all patients underwent complete resection, and we detected MUC1 expression at different levels. To eliminate the impact of mixed factors on statistical analysis, we used both univariate and multivariate analysis to determine prognostic factors. Consequently, it made the results more objective. The present study had several limitations. First, in China, the indications for treatment not only depend on doctors' preferences but also on patients' willingness and economic status. These factors may have influenced the relatively poor survival rate observed. The study sample was relatively small. Finally, all the patients' histologic type is squamous cell carcinoma in the study. SCC is one of the most common malignant diseases in China. This implies that the patients enrolled in the study might not be representative of the population in the world and some conclusions might be relevant to the Chinese population only.

In conclusion, MUC1 expression is related to pT, pN, pTNM stage and poor survival in ESCC patients. The examination of MUC1 expression in ESCC would become a useful marker to predict a poor prognostic factor. Our study suggests that MUCI may be used as a novel diagnostic biomarker and therapeutic target for ESCC patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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