MTA1: A Prognosis Indicator of Postoperative Patients with Esophageal Carcinoma

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Abstract

Background To investigate the overexpression of Metastasis-associated gene 1(MTA1) protein and its relationship to the prognosis in esophageal squamous cell cancer after esophagectomy.

Methods 174 patients with middle third squamous cell carcinoma of the esophagus underwent complete resection in Provincial Hospital Affiliated to Shandong University between January 2002 and January 2005. The overexpression of MTA1 protein was detected by immunohistochemistry. Kaplan–Meier method was performed to calculate the survival rate, Cox regression multivariate analysis was performed to determine independent prognostic factors.

Results MTA1 protein overexpression rate in T1, T2, and T3 patients was separately 25.0, 31.9, and 53%, the difference of MTA1 protein overexpression between them was statistically significant ($p = 0.017$). The overexpression of MTA1 protein in patients with lymph node metastasis was significantly higher than those without metastasis ($p = 0.042$). MTA1 protein overexpression correlated with significantly worsened 5-year survival for all patients as well as those with T2 and T3 tumors, N0 nodal status or N1 nodal status. However, no significant correlations with T1 patients ($p = 0.061$). The result of Cox analysis demonstrated that N stage and MTA1 protein overexpression were independent prognostic factors.

Conclusion MTA1 protein overexpression was detected in esophageal squamous cell carcinoma and was found to be significantly associated with the T stage. The patients with MTA1 protein overexpression had a significantly lower 5-year survival rate than without MTA1 protein overexpression. Lymph node metastasis and MTA1 protein overexpression were independent prognostic factors.

Keywords

- esophageal neoplasms
- lymphatic metastasis
- surgical procedures
- metastasis-associated gene 1

Introduction

Esophageal carcinoma is one of the most common malignant tumors worldwide, and its incidence is very high in China. Surgical resection is the primary treatment but its effect nowhere near the level required, with the overall 5-year survival rate of only 30–50%. To improve the overall cure rate of patients with esophageal cancer, it should be emphasized that we should not only remove the tumor completely but also take targeted measures as postoperative adjuvant treatment. However, after complete resection of esophageal squamous cell carcinoma, patients whether should adopt adjuvant therapy is still controversial. In 2009, NCCN esophageal cancer treatment guidelines pointed out that patients of esophageal squamous cell carcinoma after complete resection do not require postoperative adjuvant therapy. Our previous reports indicated that even if patients with esophageal squamous cell

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carcinoma achieved a complete resection, there were still some patients with relapse, metastasis,[1,2] and further study found that postoperative radiotherapy can reduce local recurrence rate.[3] Accordingly, we cannot fully agree with the views of NCCN.

Except for clinical and pathological indicators, such as TNM staging, a new molecular biomarker which can identify the patients with poor prognosis has great clinical value as the indicator of that whether a postoperative adjuvant therapy is needed. Metastasis associated gene 1 (MTA1) was discovered recently as a tumor invasion and metastasis-related gene whose overexpression showed positive correlation with tumor invasion and metastasis.[4] We previously found that MTA1 protein overexpression of pN0 patients with midthoracic esophageal squamous cell carcinoma was related to poor prognosis.[5] To further explore the relationship between MTA1 overexpression and the prognosis of patients, the retrospective analysis of esophageal squamous cell carcinoma of different stages patients with MTA1 overexpression, and prognosis factors of multiple regression analysis, aimed at exploring the value of MTA1 in forecasting the prognosis after complete resection in patients with mid thoracic esophageal cancer.

Materials and Methods

Materials

From January 2002 to January 2005, we have analyzed retrospectively the midthoracic esophageal squamous cell carcinoma patients who underwent complete resection (R0 resection) with intact clinical information. The specimens consisted of 130 male and 44 female patients aged 38 to 76 years (average 56.7) (►**Table 1**), including 100 patients who underwent Ivor-Lewis esophagectomy and other 74 patients underwent esophagectomy through the left chest with esophagogastrostomy above the aortic arch (Left chest incision). Preoperative radiotherapy or chemotherapy was not taken to all cases. The tumor location and the TNM classification were determined according to the International Union Against Cancer (UICC) in 1997; and the two-field lymph node section criteria was based on the lymph node introduction from the American Joint Committee on Cancer (AJCC)/UICC.

The patients with serious postoperative complications and perioperative mortality were not enrolled in the study. After 5 years, follow-up data were obtained by telephone or mail from the patients or his or her family. The last check on follow-up of all patients was performed in June 2010. They were evaluated by clinical history, physical examination, laboratory analysis, barium esophagram, computed tomography, ultrasound examination, and fiberoptic esophagoscopy if necessary. The median follow-up period was 47 months.

Surgical Procedure

Ivor-Lewis esophagectomy: With a right anterolateral thoracotomy, the chest was entered through the fourth intercostal space. The azygos vein arch was cut off, and the esophagus was dissected from esophagogastric junction to the apex of the chest. When the tumor invaded significantly outside, the thoracic duct was routinely ligated above the diaphragm. Then an upper midline abdominal incision was made, and the abdomen was explored. During the mobilization of the stomach, the right gastroepiploic vessels and arcades must be preserved. The left gastric artery was cut off at its origin. Subsequently, the hiatus was enlarged and the stomach was carried to the right chest. An end-to-side esophagogastric mechanical anastomosis was performed in the apex of the chest. 2R, right upper paratracheal nodes; 3P, posterior mediastinal nodes; 4R, right lower paratracheal nodes; 7, subcarinal nodes; 8M, middle paraesophageal lymphnodes; 9, pulmonary ligament nodes; 16, paracardial nodes; 17, left gastric nodes were dissected.

Left chest incision: Left posterolateral thoracotomy incision through the sixth intercostal space. The thoracic esophagus was liberated to the apical pleura. When the tumor invasion obviously extended outside the esophagus, the thoracic duct was routinely ligated above the diaphragm. The greater and lesser curvatures of the stomach were liberated through the radial incision of the diaphragm. The right gastroepiploic vessels and arcades should be preserved, but the left gastric artery and vein should be ligated at the origin. The stomach was then pulled to the chest above the aortic arch, and the mechanical anastomosis was performed within the left apex of the chest. The fields of lymph nodes dissection were as follows: 4L, left lower paratracheal nodes; 7, subcarinal nodes; 8M, middle paraesophageal lymphnodes; 9, pulmonary ligament nodes; 16, paracardial nodes; 17, left gastric nodes. And 2L, left upper paratracheal nodes were dissected selectively.

This paper has no further analysis of postoperative adjuvant therapy because postoperative chemotherapy programs and chemotherapy cycle were not unified, and also due to the lack of balance and comparability.

MTA1 Detection

Anti-MTA1 goat polyclonal antibody was raised against a peptide mapping at the C-terminus of MTA1 of human origin (sc-9446, Santa Cruz Biochemistry, Santa Cruz, California, United States). Immunohistochemical staining for MTA1 protein was performed using the avidin–biotin peroxidase complex method with 3,30-diaminobenzidine as a chromogen using an LSAB kit (Dako, Carpenteria, California, United States). Slides were deparaffinized and rehydrated with xylene and graded alcohol. The slides were then incubated in 3% hydrogen peroxide for 10 minutes to inactivate the endogenous peroxidase. Optimal antigen retrieval was performed in citrate buffer (pH = 6.0) for 10 minutes with a steam oven to enhance the immunoreactivity. The primary antibody against MTA1 was used at a dilution of 1:100. Subsequently, the secondary biotinylated antibody and avidin-biotin complex reagent were applied, and the slides were counterstained. The positive cells of the MTA1 protein staining was the brown particles appeared in the nucleus, and with the positive outcome assessed by the percentages of the positive cells. For MTA1 protein assessment, immunoreactivity was

Table 1 The correlations between MTA1 protein overexpression and clinicopathologic factors

Characteristics	Numbers	5-year survival (%)	P^*	MTA1(−)	MTA1(+)	χ^2	P^{**}
Gender			0.928			0.11	0.732
Male	130	34.6		70	60		
Female	44	31.8		25	19		
Age (y)			0.931			0.21	0.644
≤0	38	34.2		22	16		
>0	136	33.8		73	63		
Size of tumor			0.096			2.74	0.253
<3 cm	41	51.2		27	14		
3–5 cm	70	30.0		36	34		
>5 cm	63	27.0		32	31		
Operation			0.754			0.64	0.424
Ivor-Lewis	100	34.0		52	48		
Left chest incision	74	33.8		43	31		
TNM staging			0.000			5.93	0.052
Stage I ($T_1N_0M_0$)	10	80.0		8	2		
Stage II ($T_{2,3}N_0M_0$) ($T_{1,2}N_1M_0$)	95	37.9		56	39		
Stage III ($T_3N_1M_0$)	69	21.7		31	38		
T status			0.017			8.17	0.017
T1	12	66.7		9	3		
T2	47	40.0		32	15		
T3	115	27.8		54	61		
N status			0.000			4.15	0.042
Yes	91	22.0		43	48		
No	83	47.0		52	31		
Loss of weight			0.482			0.70	0.042
Yes	24	29.2		15	9		
No	150	34.7		80	70		
Differentiation			0.366			0.00	0.967
Well/moderately	139	35.3		76	63		
Poorly	35	28.6		19	16		
MTA1 overexpression			0.000				
Yes	79	19.0					
No	95	46.3					

*Log-rank test; ** χ^2 test.

evaluated using a semiquantitative scoring system for both staining intensity (0, negative staining; 1, weak staining; 2, moderate staining; 3, intense staining) and percentage of positively stained cancer cells (0, 0–5%; 1, 6–25%; 2, 26–50%; 3, 51–75%; 4, C76%). The final staining score was the sum of the scores of staining intensity and percentage of positive cells, and was further graded as follows: (-), 0 to 1; (+), 2 to 3; (++), 4 to 5; (+++), 6 to 7. Tumors with final staining score ≥4 were defined as overexpressing MTA1 protein[6] (►**Fig. 1**). All sections were judged by two pathologists together in blind principle and the agreement was reached by negotiation when inconsistent cases emerged.

Statistical Methods

All statistics analyses were performed with SPSS 10.0 statistical software. The Kaplan–Meier method was used to calculate the survival rate, and the log-rank test was performed to identify the difference of survival. Cox regression multivariate analysis was performed to judge the independent prognostic factors.

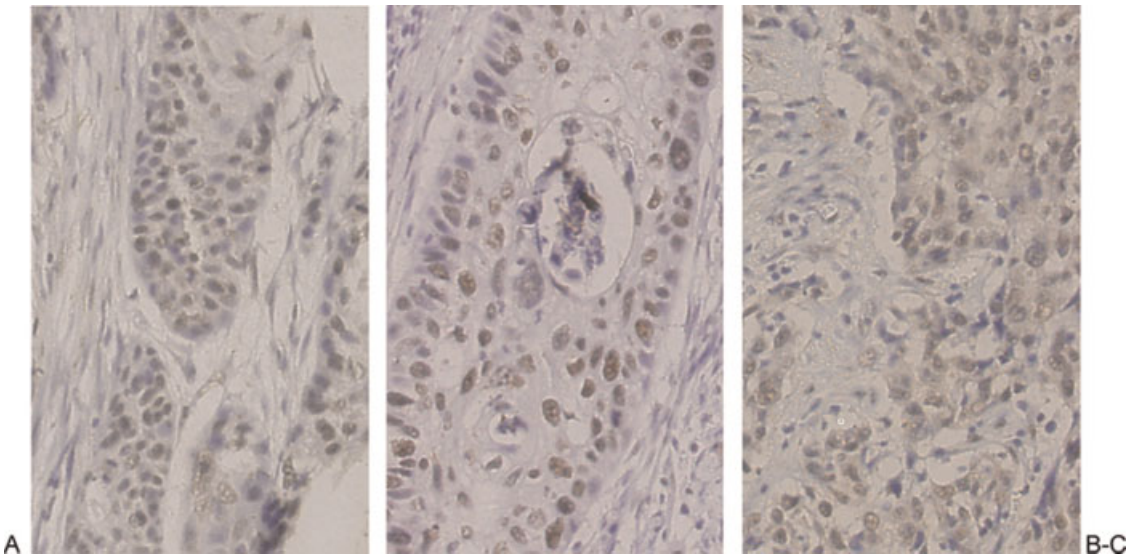

Fig. 1 MTA1 protein expression in esophageal carcinoma. (A) Well differentiated; (B) medium differentiated; (C) poorly differentiated (IHC ×200).

Results

The overall 5-year survival rates of 174 patients was 33.9%, and the rates of stageI, stage II and stage III was 80.0, 37.9, and 21.7%, respectively (survival curve depicted in ►**Fig. 2**).

Of the 174 patients in this study, recurrence was recognized in 89 patients (51.1%) in the first 3 years after operation. The distribution of the sites of tumor recurrence is shown in ►**Table 2**; 51 patients (26.5%) developed a locoregional recurrence; 38 patients (22.4%) developed a hematogenous recurrence, including 8 patients (5.1%) with simultaneous locoregional and hematogenous recurrence.

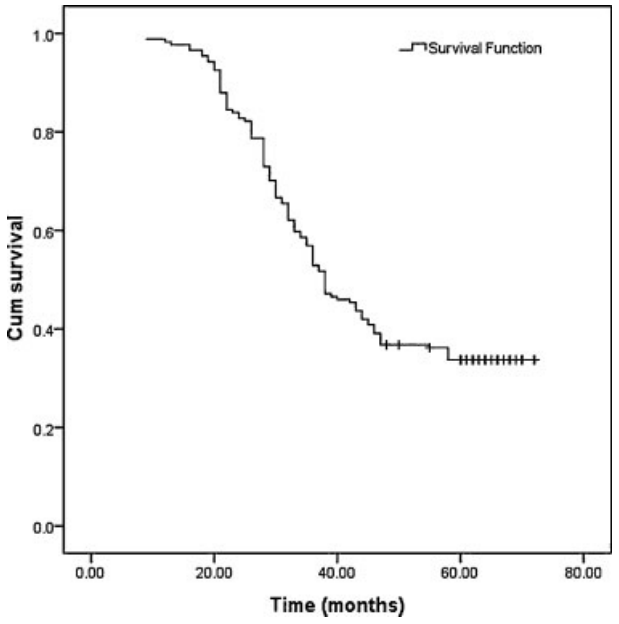

Fig. 2 Kaplan-Meier survival curves for 174 patients.

MAT1 Overexpression

Of all the 174 esophageal cancer specimens, MTA1 protein overexpression was present in 79 (45.4%) specimens. The overexpression rates of MTA1 protein in stage I, stage II and stage III were 20.0% (2/10), 41.1% (39/95), and 55.0% (38/69), respectively. The difference of MTA1 protein overexpression between them was not statistically significant ($\chi^2 = 5.9$, $p = 0.052$). The overexpression rates of MTA1 protein in T1, T2, and T3 were 25.0% (3/12), 31.9% (15/47), and 53.0% (61/115), respectively. The difference of MTA1 protein overexpression between them was statistically significant ($\chi^2 = 8.1$, $p = 0.017$). The overexpression rates of MTA1 protein in patients with lymph node metastasis and without metastasis were 52.7% (48/91) and 37.3% (31/83), respectively. It was statistically significant between them ($\chi^2 = 4.1$, $p = 0.042$).

The Relationship between MTA1 Overexpression and Prognosis

In this group specimens, 79 cases of MTA1 protein overexpression in patients with 5-year survival rates were 19.0%, 95 patients without MTA1 overexpression with 5-year survival rates were 46.3%, difference between them was statistically significant ($\chi^2 = 14.3$, $p = 0.000$, ►**Fig. 3**).

In the similar TNM stage because of different MTA1 overexpression, there were also differences in the prognosis of patients. Stage II patients, with or without MTA1 protein overexpression in 5-year survival rates were 25.6 and 47.4%, the difference between the two groups was statistically significant ($\chi^2 = 4.7$, $p = 0.031$); stage III patients, with or without MTA1 protein overexpression in the 5-year survival rates were 10.5 and 35.5%, the difference between them was statistically significant ($\chi^2 = 4.1$, $p = 0.042$); however, stage I patients, with or without MTA1 protein overexpression in 5-year survival rates were 50.0 and 87.5%, the difference between

Table 2 Site of recurrence in 89 patients

Site of recurrence	Number of patients (%)
Locoregional recurrence	51/89 (57.3)
Mediastinal node	30/51 (58.8)
Cervical/supraclavicular node	9/51 (17.6)
Multiple nodes[a]	9/51 (17.6)
Abdominal node	3/51 (5.9)
Hematogenous recurrence	30/89 (33.7)
Liver	13/30 (43.3)
Bone	6/30 (20.0)
Lung	5/30 (16.7)
Multiple organs[b]	4/30 (13.3)
Brain	1/30 (3.3)
Pleura	1/30 (3.3)
Locoregional and hematogenous[c]	8/89 (8.9)

[a]Mediastinal and cervical node recurrence in six patients; mediastinal and abdominal node recurrence in three patients.
[b]Liver and bone recurrence in three patients; liver and brain recurrence in one patient.
[c]Liver recurrence in four patients; lung recurrence in three patients; bone recurrence in one patient.

the two groups was not statistically significant ($\chi^2 = 1.8$, $p = 0.176$).

Different TNM stages of patients have different prognosis due to different MTA1 overexpression. T2 patients with or without MTA1 protein overexpression in 5-year survival rates were 20.0 and 50.0%, the difference between them was statistically significant ($\chi^2 = 5.0$, $p = 0.025$); T3 patients with or without MTA1 protein overexpression in 5-year survival rates were 18.0 and 48.9%, difference between the two groups was statistically significant ($\chi^2 = 3.9$, $p = 0.048$);

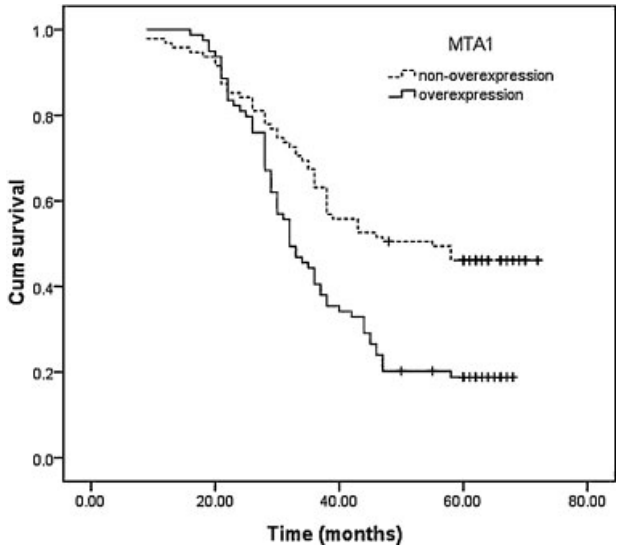

Fig. 3 Kaplan-Meier survival curves for patients with and without MTA1 expression.

but T1 patients with or without MTA1 protein overexpression in 5-year survival rates were 33.3 and 37.8%, the difference between them was statistically significant ($\chi^2 = 3.5$, $p = 0.061$).

In patients with and without lymph node metastasis because of different reason of MTA1 overexpression, there were differences in the prognosis of patients also. In pN0 patients with or without MTA1 protein overexpression in 5-year survival rates were 29.0 and 57.7%, respectively, the difference between them was statistically significant ($\chi^2 = 6.8$, $p = 0.009$); pN1 patients with or without MTA1 protein overexpression in 5-year survival rates were 12.5 and 32.6%, the difference between them was statistically significant ($\chi^2 = 4.5$, $p = 0.032$).

According to the univariate analyses, the overexpression of MTA1 is correlative with T and N classifications, and the multivariate analyses of these factors that may be correlative with the MTA1 indicated that the T classification is the independent pathologic risk factor of MTA1 overexpression (►**Table 3**).

Cox Regressive Analysis for Prognostic Risk Factor

The Cox regression analysis revealed (►**Table 4**) that N status and MTA1 protein overexpression were independent prognostic factors.

Discussion

Middle third thoracic esophagus is the predilection site of esophageal squamous cell carcinoma, and the tumors of this part are always accompanied with lymph nodes metastasis in the mediastinum, abdominal cavity, and neck. There were ~40% of patients with lymph node metastasis by immunohistochemical and molecular biological methods for further examination even though they were diagnosed pN0 in the routine pathological examination previously.[7] It seems that subtotal esophagectomy with three-field lymph nodes dissection is an ideal surgical procedure for local control or even cure of the esophageal carcinoma. Theoretically, the surgical procedure has many advantages, but its overall effect for esophageal carcinoma patients is not so satisfactory. Many patients still die of local recurrence and/or hematogenous metastasis. So this surgical procedure has not been widely adopted at home and abroad, besides the serious surgical trauma and latent complications cannot be ignored.[8–10] Currently, there are many different surgical procedures for midthoracic esophageal carcinoma, and we always take Ivor-Lewis esophagectomy and esophagectomy through the left chest with esophagogastrostomy above the aortic arch.

We have analyzed the prognosis of the patients with midthoracic esophagus cancer undergone Ivor-Lewis esophagectomy,[11,12] and found that the first tumor recurrence of 28.7% patients was mediastinal or cervical lymph node metastasis within 3 years after the operation, the postoperative adjuvant radiation therapy for mediastinum, bilateral supraclavicular fossa and the root of the neck can significantly reduce the incidence of lymph node metastasis. Based on the results of previous studies, we cannot fully agree with the

Table 3 Logistic regression analysis for MTA1 overexpression

Characteristics	B	Wald	*P*	OR	95% CI
Gender	0.037	0.010	0.920	1.038	0.502–2.147
Age	−0.088	0.052	0.820	0.916	0.431–1.949
Size of tumor	0.110	0.259	0.611	1.116	0.731–1.704
T status	0.634	4.820	0.028	1.885	1.070–3.321
N status	0.445	1.888	0.169	1.560	0.827–2.943
Differentiation	0.032	0.006	0.936	1.032	0.477–2.235

Abbreviations: B, regression coefficient; Wald, Wald value; OR, odds ratio; CI, confidence interval.

Table 4 Cox regression analysis of the risk factor on esophageal cancer after esophagectomy

Characteristics	B	Wald	*P*	OR	95% CI
Gender	0.009	0.002	0.969	1.009	0.655–1.554
Age	0.106	0.214	0.644	1.112	0.709–1.743
Size of tumor	0.018	0.018	0.894	1.018	0.783–1.324
T status	0.230	1.613	0.204	1.259	0.883–1.795
N status	0.710	11.942	0.001	2.033	1.359–3.040
MTA1 overexpression	0.564	8.186	0.004	1.758	1.194–2.587
Operation	0.169	0.748	0.387	1.184	0.808–1.735
Differentiation	0.205	0.764	0.382	1.227	0.775–1.942

Abbreviation: CI, confidence interval.

view of NCCN: "the postoperative adjuvant radiation therapy is not necessary for the complete resection of esophageal squamous cell carcinoma patients." In our opinion, middle third thoracic esophageal carcinoma patients of high-risk tumor recurrence and metastasis, even though have accepted complete resection, should adopt targeted auxiliary treatment measures. Prognosis of esophageal cancer patients is always predicted by TNM staging in clinic but sometimes lack of sensitivity. The prognosis prediction has great potential clinical value, and therefore it will be of great significance to detect the molecular biology signs, furthermore, identification of novel biomarker that could be utilized as a possible therapeutic target or prognostic predictor may be employed as an adjunct to the staging system and contribute to optimize treatment for esophageal cancer patients.

MTA1 gene encodes a protein with 703 amino acids, molecular mass of 79.4 kDa, its amino acid sequence contains multiple tyrosine kinase, protein kinase C, and casein kinase-2 phosphorylation sites.[4,13] The MTA1 protein is a component of the nucleosome remodeling and histone deacetylation (NURD) complex, which is associated with ATP-dependent chromatin remodeling and histone deacetylase activity. Metastasis-associated protein 1 functions in conjunction with other components of NURD to mediate transcriptional repression as it facilitates the association of repressor molecules with the chromatin.[13–16] MTA1 along with its protein product overexpression was closely associated with tumorigenesis and aggressiveness of a wide range of human malignant tumors.[17–24] The study showed that MTA1 protein overexpression was common in early-stage NSCLC and was significantly associated with tumor angiogenesis and poor survival.[6] Haili Qian's research showed that the MTA1 expression associates with the invasion and migration of esophageal cancer cells in vitro.[25] In Y Toh's study, esophageal tumors overexpression of MTA1 mRNA showed significantly higher frequencies of adventitial invasion and lymph node metastasis.[26] We have had studied the prognostic significance of the MTA1 protein overexpression in pN0 esophageal cancer patients and found that overexpression of MTA1 protein is an independent prognostic risk factors, patients with MTA1 protein overexpression have shorter disease-free survival and lower 5-year survival rate. In this paper, we studied the midthoracic esophageal cancer with different TNM staging and found that there were significant differences in MTA1 protein overexpression of different TNM classification of tumors. The patients with MTA1 protein overexpression have a lower 5-year survival rate, patients of stage II and stage III with or without MTA1 protein overexpression have significant statistically differences in 5-year survival rate; Cox regression analysis confirmed that MTA1 protein overexpression was an independent adverse prognostic factor. Except for the analysis of the selected various prognostic factors, the postoperative adjuvant radiotherapy and chemotherapy may affect the local recurrence and long-term survival of cancer

patients. This paper has no further analysis of postoperative adjuvant therapy because the study of this group is retrospective and postoperative adjuvant treatment programs are not unified, and it lacks balance and comparability.

Given that there is no well-accepted standardized surgical method for midthoracic esophageal cancer, Ivor-Lewis esophagectomy and esophagectomy through the left chest with esophagogastrostomy above the aortic arch could be an optional operation method for midthoracic esophageal cancer. Even though these two methods can accomplish the complete resection of tumor, the overall 5-year survival rate was just 33.9%, so the targeted postoperative adjuvant treatment measure for patients is necessary. This study showed that the patients with MTA1 protein overexpression have a lower 5-year survival rate, we concluded that MTA1 gene overexpression can be used as a molecular biological marker to predict the prognosis of middle esophageal squamous cell carcinoma, and it is recommended that we should suggest the patients with MTA1 gene overexpression to take positive postoperative adjuvant therapy.

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