Volume 22, No 4 | International Journal of Radiation Research, October 2024

The value of serum HE4 and ESM-1 levels in the evaluation patients with lung cancer receiving chemoradiotherapy

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► ***Original article***

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Received: September 2023
Final revised: March 2024
Accepted: April 2024

Int. J. Radiat. Res., October 2024; 22(4): 1051-1057

DOI: 10.61186/ijrr.22.4.1051

Keywords: *Human epididymis protein 4, endothelial cell specific molecule-1, lung cancer, chemo radiotherapy, molecular targeted therapy.*

ABSTRACT

Background: To analyze the value of serum human epididymis protein 4 (HE4) and endothelial cell specific molecule-1 (ESM-1) in the evaluation of chemoradiotherapy in patients with lung cancer (LC). ***Materials and Methods:*** The patients were treated with chemoradiotherapy alone combined with bevacizumab targeted drug therapy. 45 healthy subjects were selected as the control group. According to different clinical effects, it is divided into progression (PD), stability (SD), partial remission (PR) and complete remission (CR). Among them, PR group + CR group + SD group is regarded as the effective group, and PD group is regarded as the ineffective group, Cr + PR = disease effective rate (RR), SD + PR + CR = disease control rate (DCR). ***Results:*** Compared with the control group, serum HE4 and ESM-1 in the study group was decreased ($P < 0.05$). compared with before treatment, the levels of serum HE4 and ESM-1 in Cr, PR and SD groups decreased ($P < 0.05$), and these in CR group were decreased than those in PR group ($P < 0.05$), the levels of serum HE4 and ESM-1 in PR group were decreased than those in SD group ($P < 0.05$). The best cutoff points of serum HE4 and ESM-1 levels for the diagnosis of therapeutic effect of LC were 69.88 ng/ml and 27.58ng/ml respectively. ***Conclusion:*** The levels of serum HE4 and ESM-1 have obvious diagnostic value for the effect of chemoradiotherapy and targeted drugs in patients with LC, and they play critical role in the evaluation of the effect of drugs in patients with LC.

INTRODUCTION

According to statistics, there are more than 1.2 million new cases of lung cancer (LC) every year, with over 900,000 annual LC-related deaths, ranking first in morbidity and mortality among malignant tumors. The 5-year survival rate for LC patients is only about 16%, significantly impacting their quality of life and overall health [1]. The etiology of LC is multifactorial, and due to the lack of specific symptoms in the early stages and limited means of early detection, the disease often progresses to metastasis. Consequently, finding strategies to extend patient survival and enhance treatment efficacy is a pressing clinical challenge [2]. Current clinical approaches for LC primarily involve surgery combined with chemoradiotherapy; however, postoperative recurrence rates are high, and the aggressive nature of chemoradiotherapy causes considerable damage to patients' tissues and cells [3]. Studies have indicated that targeted drug therapy, when combined with chemoradiotherapy, plays a pivotal role in improving LC patient survival rates [4].

Serum tumor markers serve as crucial indicators in the diagnosis and treatment of LC. Human epididymis protein 4 (HE4) and endothelial cell-specific molecule-1 (ESM-1), identified as serum tumor markers in recent years, exhibit abnormal expression levels in various tumors, including gastric and liver cancers [5,6]. HE4, also identified as whey acidic protein, serves as a precursor to the epididymal secretory protein E4 [7,8]. HE4 exhibits expression in various organs, including lung tissue [9]. A previous examination established a link between elevated serum HE4 levels and advanced stages of epithelial ovarian cancer, predicting an unfavorable prognosis in patients undergoing surgery and platinum-based chemotherapy for this cancer type [10]. Another investigation highlighted the increased serum HE4 levels in lung cancer, signifying its prognostic relevance for individuals with lung cancer [11]. A comprehensive study encompassing cancer patients, including those with lung and ovarian cancer, disclosed that non-small and small cell lung cancer as well as ovarian cancer patients exhibited significantly higher serum HE4 levels compared to healthy controls. Critically, post-chemotherapy, elevated serum HE4 levels correlated closely with diminished overall survival [12].

ESM-1 is a 50-kD soluble dermatan sulfate proteoglycan exclusively secreted by vascular endothelial cells [13]. In response to inflammatory cytokines and proangiogenic growth factors, ESM-1 can undergo up-regulation [14]. Multiple studies have shown ESM-1 to be overexpressed in various malignant tumors, including non-small cell lung cancer (NSCLC) [14-17]. Elevated serum levels of ESM-1 have been identified as diagnostic markers for poor

[DOI: 10.61186/ijrr.22.4.1051]

prognosis in gastric carcinoma and colorectal cancer [18-20]. Furthermore, in NSCLC, both ESM-1 mRNA and circulating ESM-1 levels are significantly elevated, serving as predictors of an adverse prognosis [14].

Recent advancements have identified serum tumor markers, particularly HE4 and ESM-1, as potential indicators for various cancers, including lung cancer. While studies have associated elevated serum HE4 levels with adverse prognoses in epithelial ovarian cancer and lung cancer, and demonstrated the prognostic value of ESM-1 in gastric carcinoma and colorectal cancer, the precise role of these markers in evaluating the therapeutic effect of LC remains uncertain.

This study aims to fill this knowledge gap by analyzing the serum levels of HE4 and ESM-1 in LC patients undergoing treatment at our hospital. The novelty of our investigation lies in its comprehensive assessment of the effects of chemoradiotherapy and targeted drugs on these serum markers, providing valuable insights into their potential as indicators of therapeutic outcomes in LC. This study selected LC patients treated at our hospital from August 2021 to February 2023 to analyze the value of assessing the effects of chemoradiotherapy and targeted drugs. The focus is on detecting changes in serum HE4 and ESM-1 levels among patients with different therapeutic outcomes.

MATERIALS AND METHODS

Study Population

Forty-five LC patients treated in our hospital from August 2021 to February 2023 were randomly selected as the study group. Admission criteria: 1 all patients met the guidelines for diagnosis and treatment of LC [21] and were confirmed by pathology or cytology; 2 all patients were approved by the hospital ethics committee of our hospital; all met the guidelines of medical ethics; 3 patients and their families in this study had informed consent and signed an informed consent form; 4 the estimated survival time of the patients was more than 3 months and could cooperate with treatment. (5) there was no anti-tumor therapy such as radiotherapy and chemoradiotherapy before participating in the study. Exclusion criteria: (1) patients with severe drug allergy history, allergic to the drugs used in this study, (2) complete medical records, and did not drop out, (3) patients with severe cardiac function or liver and kidney function insufficiency, (4) patients with infectious diseases or other malignant tumors, and (5) patients with severe coagulation dysfunction. Our control group consisted of 45 healthy subjects who underwent physical examinations at the same time.

According to the different clinical effects, the patients were divided into PD group (n = 4), SD group (n = 10), PR group (n = 21) and CR group (n = 10). Among them, PR group + CR group + SD group was regarded as effective group (n = 41), PD group as ineffective group (n = 4).

Main instruments and drugs

Cryogenic high-speed centrifuge (Shandong Boko Scientific instrument Co., Ltd., model: TG-18W); -80 ℃ cryogenic refrigerator (Beijing Alice Biotechnology Co., Ltd., model: DW-86L626); Pantoprazole (Shenyang Shengyuan Pharmaceutical Co., Ltd., production batch number: 20177169, specification: 40 mg×10s); Dexamethasone (Guangdong South China Pharmaceutical Group Co., Ltd., production batch number: 44024469, specification: 0.75mg×100 tablets). Oxaliplatin (Zhejiang Haizheng Pharmaceutical Co., Ltd., batch number: 20183487, specification: 50mg/s); gemcitabine (Jiangsu Hausen Pharmaceutical Group Co., Ltd., batch number: 20190104, specification: 0.2g); bevacizumab (RochePharma (Switzerland) Ltd., production batch number: S20190069, specification: 400 mg/ bottle); Radiotherapy unit (RadiantZen Co., China).

Experimental method

The patients in the study group were treated with simple chemoradiotherapy (all patients were given pantoprazole 40mg 24 hours before chemoradiotherapy to protect gastric mucosa, and 30min was given dexamethasone 5mg before chemoradiotherapy to reduce nausea and vomiting. Patients were given oxaliplatin plus fluorouracil regimen: oxaliplatin was added to 5% glucose solution 500 mL every time, intravenous drip for 3 hours, once every 3 weeks; gemcitabine 1000 mg/ m2, intravenous drip of 30 min, once a week for 3 weeks, followed by 1 week rest and repeated every 4 weeks) combined with bevazol single targeted drug therapy, 250mg, once a day. They were treated continuously for 3 months.

Concurrent radiotherapy (TRT) was administered at a dosage of 2 Gy per fraction daily, five days a week, aiming to reach a target dose ranging from 60 to 66 Gy within 30 to 33 fractions. The TRT commenced on the first day of chemotherapy. Field reductions were not allowed during the radiotherapy sessions, ensuring consistent treatment delivery. Each day, the entire planning treatment volume (PTV), with at least 95% coverage receiving a minimum of 93% of the prescribed dose, was treated.

Observation index

All subjects forbidden drinking and fasting for more than 8 hours. The next morning, fasting elbow median venous blood 5mL was drawn and centrifuged at the speed of 3000r/min with a low temperature and high-speed centrifuge. The supernatant was taken and cryopreserved in an ultra-low temperature refrigerator at -80 ℃ for

[DOI: 10.61186/ijrr.22.4.1051]

follow-up study.

Comparison of clinical data: compare the basic clinical data between the study group and the control group, including age, sex, body mass index, cell type, lymph node metastasis, degree of differentiation, history of drinking and smoking, *etc*.

Clinical efficacy test: the clinical efficacy of patients was evaluated according to the evaluation criteria of solid tumor, including progression (PD), stability (SD), partial remission (PR) and complete remission (CR). A PD is defined as the sum of the maximum diameters of the baseline lesions increasing by more than 20% or the appearance of new lesions. Baseline lesion diameters decreased but did not reach PR or increased but not until the PD considered SD. As a PR, the maximum diameters of the baseline lesions decreased by more than 30%, and as a CR, all target lesions disappeared. The disease effective rate (RR) was regarded as imaging remission, RR = CR+PR, disease control rate (DCR) = SD+PR+CR. According to the different clinical effects, the patients were divided into PD group (n = 4), SD group (n = 10), PR group (n = 21) and CR group (n = 10). Among them, PR group + CR group + SD group was regarded as effective group (n = 41), PD group as ineffective group (n = 4).

Detection of serum HE4 and ESM-1 levels: the level of serum HE4 was detected by electrochemiluminescence. Detection of serum ESM-1 level by ELIAS.

The changes of serum HE4 and ESM-1 levels before and after treatment with different clinical effects were compared.

The relationship between serum HE4 and ESM-1 levels and clinicopathological features was analyzed.

ROC curve was established to analyze the diagnostic value of serum HE4 and ESM-1 levels in the treatment of LC.

The relationship between the levels of serum HE4 and ESM-1 and the efficacy of chemoradiotherapy and targeted drugs was analyzed.

Statistical Analysis

SPSS23.0 software was used to analyze the data in this study. The data of sex and clinical curative effect between the study group and the control group were compared by χ 2 and expressed by [n (%)]. The measurement data such as age, serum HE4 and ESM-1 levels of the two groups were compared by independent sample t-test and expressed by ($x \pm s$). ROC curve was established to analyze the diagnostic value of serum HE4 and ESM-1 levels in the treatment of LC.

RESULT

General Characteristic

Overall, 90 patients were included into the study. Forty-five LC patients treated in our hospital from August 2021 to February 2023 were randomly selected as the study group and matched with 45 healthy controls. The study included 52 males and 38 females with 63 patients (70.0%) aged below 55 years old.

There was no difference in age, sex, body mass index, and smoking history between the two groups ($P > 0.05$) (table 1).

Comparison of serum HE4 and ESM-1 levels in each group

The serum levels of HE4 and ESM-1 in the study group were significantly reduced compared to those in the control group (HE4: 109.63 ± 11.15 vs. 31.52 ± 8.41; ESM-1: 49.22 ± 6.13 vs. 12.45 ± 3.29) (table 2).

Comparison of serum HE4 and ESM-1 levels in different clinical effects

The serum HE4 and ESM-1 levels in CR, PR and SD groups are decreased after treatment, and these in CR group were reduced than those in PR group, while these levels in PR group were lower than those in SD group. There was no difference in serum HE4 and ESM-1 levels before and after treatment in PD group (table 3).

Relationship between serum HE4 and ESM-1 levels and clinicopathological features

Serum HE4 and ESM-1 levels were correlated with lymph node metastasis, differentiation, pathological stage and tumor size, but not with age, sex, cell type and tumor location ($P > 0.05$) (table 4).

The ROC curve was established, and it was found that serum HE4 and ESM-1 alone or combined to diagnose the therapeutic effect of LC. The areas under the curve of HE4 and ESM-1 alone or combined were 0.884, 0.901 and 0.949, respectively. The best cut-off points for the diagnosis of the therapeutic effect of LC by serum HE4 and ESM-1 levels were 69.88ng/mL and 27.58ng/mL, respectively, and their decreasing rates were 63.74% and 56.03%, respectively (table 5).

The relationship between the serum level and the efficacy of chemoradiotherapy

The results showed that among the 45 patients, there were 41 patients in the effective group, including 35 patients with HE4 decrease ≥ 63.74%, 30 patients with ESM-1 decrease ≥ 56.03%, and 4 patients with ineffective group, including 1 patient with HE4 decrease ≥ 63.74% and 1 patient with ESM-1 decrease ≥ 56.03%. The decrease of serum HE4 and ESM-1 is significantly related to the efficacy of chemoradiotherapy and targeted drugs (table 6).

[DOI: 10.61186/ijrr.22.4.1051]

Table 1. The ratio of basic clinical data between the study group and the control group (%, x±s).

Group	study group (n=45)	control group (n=45)	χ^2/t	*P*
Age (years old)			0.476	0.490
≤55	33(73.33)	30(66.67)		
>55	12(26.67)	15(33.33)		
Gender (n, %)			0.182	0.770
Male	27(60.00)	25(55.56)		
Female	18(40.00)	20(44.44)		
Body mass index(kg/m$^{2)}$	23.18±1.93	-	-	-
Cell type				
Squamous cell carcinoma	22(48.89)	-	-	-
Adenocarcinoma	18(40.00)	-	-	-
Other	5(11.11)	-	-	-
Lymph node metastasis				
Yes	29(64.44)	-	-	-
No	16(35.56)	-	-	-
Degree of differentiation				
Low differentiation	13(28.89)	-	-	-
Medium differentiation + high differentiation	32(71.11)	-	-	-
History of drinking (n, %)			0.182	0.640
Yes	18(40.00)	20(44.44)		
No	27(60.00)	25(55.56)		
Smoking history (n, %)			0.527	0.468
Yes	10(22.22)	13(28.89)		
No	35(77.78)	32(71.11)		

Table 2. The serum HE4 and ESM-1 levels in each group (%).

Group	n	HE4(ng/mL)	ESM-1(ng/mL)
study group	45	109.63±11.15	49.22±6.13
control group	45	31.52±8.41	12.45±3.29
t		31.518	35.455
P		<0.001	<0.001

Table 3. Serum HE4 and ESM-1 levels in different clinical effects (x±s).

Group	n	Time	HE4(ng/mL)	ESM-1(ng/mL)
CR	10	Before treatment	111.67±25.17	59.30±10.13
		After treatment	34.44±5.12	11.07±2.29
PR	21	Before treatment	107.46±27.26	60.64±4.08
		After treatment	41.59±5.85	19.49±3.47
SD	10	Before treatment	110.84±26.17	58.51±9.25
		After treatment	73.27±19.17	40.63±6.68
PD	4	Before treatment	108.66±27.17	57.49±9.24
		After treatment	97.46±29.41	53.52±10.36

CR: Complete remission, PR: Partial remission, SD: stability, PD: Progression

Table 4. Relationship between serum HE4 and ESM-1 levels and clinicopathological features (x±s).

Group	n	HE4(ng/mL)	ESM-1(ng/mL)
Age (years)			
≤55	33	114.89±26.24	50.73±5.14
>55	12	107.58±23.14	47.41±5.27
Gender (n, %)			
Male	27	120.51±21.14	50.36±5.54
Female	18	117.25±24.16	48.91±4.81
Cell type			
Squamous cell carcinoma	22	109.14±26.22	46.59±8.64
Adenocarcinoma	18	117.24±19.54	51.63±6.71
Other	5	119.46±20.41	53.75±8.20
Lymph node metastasis			
Yes	29	116.15±16.59	52.24±6.24
No	16	54.82±24.72	16.11±4.81
Degree of differentiation			
Low differentiation	13	98.37±21.67	36.27±5.97
Medium differentiation + high differentiation	32	115.84±18.96	45.14±4.96
Pathological staging			
Ⅰ	7	49.16±21.24	24.74±4.95
Ⅱ	9	78.47±29.54	36.17±5.72
Ⅲ	10	96.96±21.14	42.78±4.87
Ⅳ	19	115.46±19.85	52.75±5.85
Tumor location			
Central type	24	106.89±22.46	48.84±6.58
Peripheral type	21	114.33±20.48	47.38±6.73
Tumor size(cm)			
≤3.5	17	116.73±21.27	12.03±6.24
>3.5	28	74.62±21.46	55.18±3.81

Diagnostic value of serum HE4 and ESM-1 levels in the treatment of LC.

[DOI: 10.61186/ijrr.22.4.1051]

Table 5. Diagnostic value of serum HE4 and ESM-1 levels in the treatment of LC.

Index	Area under curve	Specificity (%)	Sensitivity (%)	Accuracy (%)	95%CI		Optimal cut-off point
					Lower limit	Upper limit	
HE4	0.884	92.56	83.51	85.67	0.829	0.937	69.88ng/mL
ESM-1	0.901	91.86	89.81	84.23	0.851	0.951	27.58ng/mL
HE4+ESM-1	0.949	95.91	93.61	89.26	0.899	0.999	

Table 6. The relationship between the decrease of serum HE4 and ESM-1 and the efficacy of chemoradiotherapy and targeted drugs(x±s).

Group	n	HE4dereased≥63.74%	ESM-1 dereased≥56.03%
Effective	41	35（85.37）	30（73.17）
Invalid	4	1（25.00）	1（25.00）
χ^2		8.300	3.946
P		0.004	0.047

DISCUSSION

LC is one of the most common respiratory malignant tumors originating from bronchial mucosa, gland or alveolar epithelium, and its morbidity and mortality ranks first among malignant tumors. Platinum-based chemoradiotherapy is now the standard chemoradiotherapy , which can improve the survival rate of newly treated patients [22]. Although chemoradiotherapy can slow down the spread and metastasis of tumor and prolong the survival time of patients to some extent, the side effects of chemotherapeutic drugs do great damage to the tissues and cells of patients with LC, which may be one of the common reasons for the failure of chemoradiotherapy [23]. Chemoradiotherapy combined with drug targeting therapy plays critical role in killing cancer cells or small lesions that remain after surgery [24]. Early and accurate understanding of the changes in the efficacy of treatment for patients with LC plays critical role in understanding the prognosis and outcome of patients, adjusting the treatment plan in time, further improving the prognosis of patients, and avoiding or reducing adverse reactions caused by improper treatment. it plays critical role in reducing the economic burden of patients' families and even society.

With the deepening of molecular biology research, some studies have found that the level of serum tumor markers and the clinical treatment effect of patients play an important role. Serum HE4 is a secretory glycoprotein with anti-inflammatory, antibacterial and other functions [25], The expression level of serum HE4 in ovarian cancer was significantly increased. It can be used as an important index for early diagnosis and prognosis evaluation of ovarian cancer. Some studies have found that the expression level of serum HE4 in LC cells is significantly increased [26]. Additionally, the level of serum HE4 in patients with benign LC was lower than that in patients with malignant tumor. The serum HE4 level was lower in patients with benign LC than in patients with malignant tumor [27]. The results showed that the level of serum HE4 in the study group was lower than that in the control group. After treatment, the level of serum HE4 in CR, PR and SD groups decreased, and the higher the treatment effect was, the lower the serum HE4 level was. Serum HE4 may play critical role in the progression of LC, and it is reflecting the clinical treatment effect of patients. Similarly, a study by Lan *et al.* [28] indicated that serum HE4 levels can distinguish between patients exhibiting favorable and unfavorable responses to CRT. Elevated serum HE4 is strongly linked to an augmented risk of non-responsiveness to CRT. Moreover, the level of serum HE4 is correlated with the prognosis of patients following CRT. Individuals with elevated HE4 levels experienced shorter RFS and OS compared to those with lower HE4 levels. Another study by Mo et al. also showed higher serum levels of HE4 is a predictor of poor prognosis in NSCLC patients, especially in patients with adenocarcinoma [29].

ESM-1 is a newly discovered dermatan sulfate proteoglycan in recent years [6,30], serum ESM-1 is expressed in breast cancer, renal cell carcinoma and other malignant tumors, and it can combine with hepatocyte growth factor/dissemination factor, vascular endothelial growth factor and other pro-angiogenic molecules to regulate tumor invasion and migration, change the microenvironment of tumor cells, and then regulate tumor growth. The results showed that the level of serum ESM-1 in the control group was increased than that in the study group. After treatment, it in CR, PR and SD groups decreased, and the higher the treatment effect was, the lower the serum ESM-1 level was. Serum ESM-1 may be a marker for the progression of LC and an important target for the treatment of LC. Similarly, a study by Lu et al. on prognostic values of ESM-1 with malignant pleural effusions showed the diagnostic performance of ESM-1 in identifying MPE yielded accuracy, sensitivity, and specificity rates of 82.5%, 81.4%, and 84.0%, respectively. Additionally, among NSCLC patients, those with pleural fluid ESM-1 levels below 19.58 ng/ml exhibited significantly longer overall survival (OS) compared to patients with higher ESM-1 levels [31]. A study by Yang et al. in patients with oral squamous cell carcinoma (OSCC), showed that Plasma ESM-1 emerges as a novel biomarker with the potential to predict the tumor status in these patients [32].

A number of domestic and foreign studies have confirmed [33,34], the specificity and sensitivity of single serum tumor marker in the diagnosis of diseases is low, and the diagnosis rate of many

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diseases is low, which may delay the treatment of patients and increase the treatment burden of patients. The results of this study found that serum HE4 and ESM-1 alone or combined diagnosis of LC has a certain value, while the combination of the two has a higher diagnostic value. In addition, the decrease of serum HE4 and ESM-1 levels were related to the efficacy of chemoradiotherapy and targeted drugs. The detection of serum HE4 and ESM-1 levels plays critical role in effectively evaluating the efficacy of chemoradiotherapy and targeted drugs in LC.

CONCLUSION

In conclusion the levels of serum HE4 and ESM-1 have obvious diagnostic value for chemoradiotherapy and targeted drugs in patients with LC, and they play critical role in evaluating the efficacy of chemoradiotherapy in patients with LC. The detection of serum HE4 and ESM-1 levels is of great significance to evaluate the prognosis, guide clinicians to take effective treatment measures and reduce the mortality rate of patients.

Fundings: None.

Conflict of interest: None.

Ethical considerations: Approval from the hospital ethics committee was obtained, aligning with medical ethics guidelines. Furthermore, informed consent, along with signed consent forms, was obtained from patients and their families, ensuring their understanding and willingness to participate.

Author contributions: D-X.W.: Conceptualization, Methodology, Data Collection, Writing - Original Draft; H.L.: Methodology, Data Analysis, Writing - Review & Editing; J-Q.Y.: Project Administration, Funding Acquisition, Writing - Review & Editing.

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[DOI: 10.61186/ijrr.22.4.1051]