

Correlation of serum alkaline phosphatase with clinicopathological characteristics of patients with oesophageal cancer

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الترابط بين الفسفاتاز القلوية في المصل والخواص الباثولوجية السريرية للمرضى المصابين بسرطان المريء

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الخلاصة: يتوطن سرطان المريء في بعض مناطق جمهورية إيران الإسلامية، وتبذل الجهود لاكتشاف العوامل التي تؤثر في إنذاره (مآله). وقد أجرى الباحثون تفحصاً استعادياً للترابط بين مستويات الفسفاتاز القلوية في المصل وبين عدد من الخواص الباثولوجية السريرية لدى 207 من المرضى المصابين بسرطان المريء. وكان متوسط مستوى الفسفاتاز القلوية في المصل في المرضى الذين أصيبت عقدهم اللمفية بالسرطانات أعلى بدرجة يُعتدُّ بها إحصائياً [141 (±77) وحدة/ل] مقارنة بمن كانت نتائج عقدهم سلبية [116 (±63) وحدة/ل]. وكان المرضى الذين تجاوزت مستويات الفسفاتاز القلوية في المصل عندهم 165 وحدة/ل أكثر احتمالاً بمقدار 3.29 ضعفاً لأن تتعرض عقدهم اللمفية للإصابة، مقارنة بالمرضى الذين كانت مستويات الفسفاتاز القلوية في المصل لديهم ≥ 165 وحدة/ل. ولم يشاهد أي ترابط يُعتدُّ به إحصائياً بين مستوى الفسفاتاز القلوية في المصل والجنس، أو العمر، أو النمط الهستولوجي للورم، أو موقع الورم، أو حجمه، أو عمق اختراقه، أو وجود نقائل بعيدة، ولا بين مستوى الفسفاتاز وبين درجة التمايز، أو حدوث غزو للعقد اللمفية، ووجود سرطانات متعددة في وقتٍ معاً. ويدل ذلك على أن ارتفاع مستوى الفسفاتاز القلوية في مصل المرضى المصابين بسرطان المريء يمكن الاستئناس للنتيجة باكتشاف العقد اللمفية.

ABSTRACT Oesophageal cancer is endemic in some regions of the Islamic Republic of Iran and efforts have been made to find factors that play a role in its prognosis. We retrospectively examined the correlation of serum alkaline phosphatase (ALP) levels with several clinicopathological characteristics of 207 cases of oesophageal carcinoma. The mean ALP level in patients with lymph node involvement was significantly higher [141 (SD 77) U/L] than with node negative cancers [116 (SD 63) U/L]. Patients with ALP levels > 165 U/L were 3.29 times more likely to have lymph node involvement than patients with ALP levels ≤ 165 U/L. There was no statistically significant correlation between ALP level and sex, age, tumour histological type, site and size of tumour, depth of penetration, distant metastasis, degree of differentiation, presence of lymphatic invasion and presence of simultaneous multiple cancers. Elevated ALP in patients with oesophageal cancer may predict lymph node involvement.

Corrélation entre la phosphatase alcaline sérique et les caractéristiques clinicopathologiques des patients atteints d'un cancer de l'œsophage

RÉSUMÉ Le cancer de l'œsophage étant endémique dans certaines régions de la République islamique d'Iran, des efforts ont été déployés pour identifier les facteurs qui jouent un rôle dans son pronostic. Nous avons examiné rétrospectivement la corrélation entre le taux de phosphatase alcaline sérique et plusieurs caractéristiques clinicopathologiques de 207 cas de carcinome de l'œsophage. Le taux moyen de phosphatase alcaline sérique chez les patients souffrant d'un cancer de l'œsophage avec atteinte des ganglions était significativement supérieur [141 (E.T. 77) U/l] au taux des autres patients [116 (E.T. 63) U/l]. Les patients ayant un taux de phosphatase alcaline sérique supérieur à 165 U/l avaient 3,29 fois plus de risque de présenter une atteinte ganglionnaire que les autres. Aucune corrélation statistiquement significative n'a été trouvée entre le taux de phosphatase alcaline sérique et le sexe, l'âge, le type histologique de la tumeur, sa localisation et sa taille, sa profondeur de pénétration, la présence de métastases à distance, le degré de différenciation, et la présence d'une atteinte des ganglions et de cancers multiples simultanés. Un taux élevé de phosphatase alcaline sérique chez les patients atteints d'un cancer de l'œsophage peut être un facteur prédictif d'une atteinte ganglionnaire.

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Introduction

Cancer of the oesophagus is the sixth most common cause of cancer-related mortality worldwide [1,2]. Oesophageal cancer is endemic in some regions of Islamic Republic of Iran [3,4] and efforts have been made to find factors that play role in the prognosis of this disease.

Alkaline phosphatase (ALP) comprises a group of enzymes that catalyse the hydrolysis of phosphate esters in an alkaline environment, generating an organic radical and inorganic phosphate [5,6]. As with other enzymes, ALP has different isoenzymes. ALP is mainly derived from the liver and bones and in lesser amounts from intestines, placenta, kidneys and leukocytes.

Increases in serum ALP levels have been associated with a variety of hepatic and bone diseases, such as cholestasis, hepatitis and infiltrative liver disease [6]. Serum ALP levels are elevated in patients with primary and metastatic tumours of liver and bone, such as hepatic metastasis of colorectal cancer and bone and liver involvement in breast cancer [6]. In patients with malignancies, therefore, an elevated serum ALP level may be an indicator of metastatic disease. However, the association of ALP with other clinicopathological characteristics of cancers, such as the status of lymph node involvement, has not been fully evaluated.

In this study we examined the correlation of serum ALP level with several clinicopathological characteristics of oesophageal carcinoma.

Methods

Sample

A sample of 420 cases with oesophageal cancer undergoing oesophagectomy in a referral cancer institute in Tehran,

Islamic Republic of Iran during a 5-year period (2001–06) were studied retrospectively. The level of preoperative serum ALP was available in 207 cases. Neoadjuvant therapy and presence of other malignancies were considered as exclusion criteria. Patients with lower oesophageal tumours underwent transhiatal resection (Orringer technique) and those with mid- and upper-third oesophageal tumours had transthoracic oesophagectomy (Ivor Lewis or McKeown procedures).

Data collection

Data were collected retrospectively from patients' charts. The following information was recorded: pre-operative ALP level; patient's age and sex; site of tumour; presence of multiple cancers; and clinicopathologic characteristics including histology type, tumour size, depth of penetration (T according to TNM classification), lymph node involvement (N according to TNM classification), distant metastasis (M according to TNM classification), degree of differentiation, presence of vascular, lymphatic and perineural invasion, post-operative complications and in-hospital death.

Because there were a limited number of cases in penetration subgroups T_1 and T_2 , the cases were classified as less penetrating tumours (T_1 and T_2) and more penetrating tumours (T_3 and T_4).

Analysis

Levels of ALP in U/L are presented as the mean and standard deviation (SD).

The relation between ALP level and clinicopathological characteristics was assessed with chi-squared, Student t-test and Pearson correlation tests. In all cases the probability of type 1 error < 0.05 was taken as the criterion of significance. All statistical analyses were conducted using SPSS, version 11 computer program.

Results

The mean age of the 207 patients with oesophageal cancer was 63.3 (SD 11.4) years. Squamous cell carcinoma constituted 95% and adenocarcinoma 5% of cases. Most cancers were in stage III, followed by stage II. Most tumours were located in the lower part of the oesophagus (59%). The details of the clinicopathological findings are summarized in Table 1.

The overall mean ALP level was 126 (SD 70) U/L, range 53–438 U/L. The mean ALP level in patients with lymph node involvement was significantly higher [141 (SD 77) U/L] than in patients with node negative cancers [116 (SD 63) U/L], with a mean difference of 25 (SD 10) U/L ($P = 0.022$).

The cut-off point for maximum specificity and sensitivity was established as 165 U/L using receiver operating characteristic curve analysis. Patients with ALP level > 165 U/L were > 3 times more likely to have lymph node involvement than patients with ALP level ≤ 165 U/L (OR = 3.29, 95% confidence interval 1.58–6.84) ($P < 0.001$). Additionally, the level of ALP was significantly higher in the presence of vascular invasion ($P < 0.001$) and perineural invasion ($P = 0.023$) (Table 1).

There was no statistically significant correlation between the ALP level and sex, age, tumour histological type, site and size of tumour, depth of penetration (T), distant metastasis (M), degree of differentiation, presence of lymphatic invasion and presence of simultaneous multiple cancers (Table 1).

Table 2 summarizes the association between the ALP level and clinicopathological parameters in the subgroup of patients with squamous cell carcinoma ($n = 185$). In this subgroup analysis, the ALP level was also significantly higher in the presence of lymph node metastasis ($P = 0.018$) and vascular invasion ($P < 0.001$). We observed poor agreement between

Table 1 Alkaline phosphatase (ALP) level and clinicopathological variables in patients with oesophageal carcinoma (n = 207)

Variable	No.	%	ALP level (U/L) Mean (SD)	P-value
Sex				0.508
Male	106	51	122 (69)	
Female	101	49	129 (71)	
Type				0.848
Squamous cell carcinoma	185	95	125 (70)	
Adenocarcinoma	9	5	120 (68)	
Anatomical location				0.091
Upper	4	2	94 (19)	
Middle	70	39	115 (63)	
Lower	105	59	137 (76)	
Degree of differentiation				0.349
Good	47	27	118 (67)	
Moderate	95	53	124 (66)	
Poor	36	20	139 (72)	
Depth of penetration				0.735
T ₁ and T ₂	44	25	127 (79)	
T ₃ and T ₄	129	75	123 (68)	
Lymph nodes metastasis				0.022
Positive	78	44	141 (77)	
Negative	101	56	116 (63)	
Distant metastasis				0.429
Present	7	4	107 (42)	
Absent	170	96	128 (71)	
Lymphatic invasion				0.104
Present	68	41	134 (80)	
Absent	99	59	115 (63)	
Vascular invasion				0.001
Present	76	43	144 (68)	
Absent	101	57	106 (58)	
Perineural invasion				0.023
Present	42	25	136 (60)	
Absent	123	75	111 (63)	
Multiple cancers				0.213
Present	7	4	94 (17)	
Absent	173	96	129 (73)	

SD = standard deviation.

lymph node involvement and vascular invasion ($\kappa = 0.112$, $P = 0.145$). In the cross tabulation with chi-squared tests there was no significant association between these 2 parameters.

No association was found between ALP level and early post-operative morbidity and mortality of oesophageal cancer surgery (Table 3).

Discussion

Although the association between serum level of ALP and systemic metastases in malignancies have been demonstrated [7–15], the correlation between elevation of ALP and lymph node involvement has not been studied before [5,6].

Pretreatment staging of patients with oesophageal cancer has a major role in decision-making about care. This is generally achieved by using imaging techniques. Local lymph nodes are generally the first site of tumour cell involvement outside the primary malignant focus in most solid tumours. Lymph node involvement plays a major

role in the prognosis of patients with oesophageal cancer. Current imaging techniques, however, are not accurate enough to detect the presence and extent of lymph node involvement in many patients with oesophageal cancer. Additionally, no serum marker predictive of lymph node involvement has been suggested yet.

Correlation between elevation of ALP and lymph node involvement in solid tumours has not been studied before. In our study patients with serum ALP > 165 U/L had a significantly higher (> 3 times) probability of having metastatic lymph node involvement. Saif et al. reported that patients with colorectal cancer and ALP level > 160 U/L were 12 times more likely to have a liver metastasis than patients with an

ALP level < 160 U/L [6]. The significant elevation of ALP in the presence of lymph node involvement in cases of oesophageal cancer for which no enzymatic or antigenic markers have been described may prove to be useful in the estimation of the extent of the tumour.

We conclude that elevated ALP in patients with oesophageal cancer may predict lymph node involvement.

Table 2 Alkaline phosphatase (ALP) level and clinicopathological variables in patients with oesophageal squamous cell carcinoma (n = 185)

Variable			ALP level (g/dL)	P-value
	No.	%	Mean (SD)	
Sex				0.458
Male	96	51	121 (69)	
Female	89	49	129 (71)	
Anatomical location				0.104
Upper	4	2	94 (19)	
Middle	66	40	114 (64)	
Lower	95	58	136 (77)	
Degree of differentiation				0.306
Good	47	29	118 (67)	
Moderate	86	52	125 (67)	
Poor	31	19	142 (74)	
Depth of penetration				0.969
T ₁ and T ₂	42	26	125 (78)	
T ₃ and T ₄	120	74	125 (69)	
Lymph nodes metastasis				0.018
Positive	72	44	143 (78)	
Negative	93	56	115 (64)	
Distant metastasis				0.276
Present	6	4	96 (34)	
Absent	156	96	128 (72)	
Lymphatic invasion				0.095
Present	64	41	134 (79)	
Absent	91	59	114 (64)	
Vascular invasion				0.0001
Present	70	43	144 (69)	
Absent	91	57	105 (57)	
Perineural invasion				0.071
Present	36	24	133 (61)	
Absent	114	76	111 (63)	
Multiple cancers				0.229
Present	7	4	94 (17)	
Absent	160	96	127 (73)	

SD = standard deviation.

Table 3 Alkaline phosphatase (ALP) level and clinical morbidity and mortality after surgery in patients with oesophageal squamous cell carcinoma (n = 207)

Variable	No.	%	ALP level (U/L) Mean (SD)	P-value
Complications				0.754
Present	50	28	124 (77)	
Absent	128	72	128 (70)	
Pulmonary complications				0.749
Present	22	11	121 (63)	
Absent	184	89	126 (71)	
Cardiovascular complications				0.312
Present	4	2	161 (106)	
Absent	203	98	125 (69)	
Anastomotic leakage				0.713
Present	25	12	121 (84)	
Absent	182	88	126 (68)	
Death				0.288
Yes	10	6	100 (33)	
No	168	94	125 (72)	

SD = standard deviation.

Moreover, a cut-off level of 165 U/L may be considered as a major risk factor for lymph node involvement

in patients with oesophageal cancer. Obviously these findings should be confirmed in further studies to provide

more evidence for their application in clinical practice.

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