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Postoperative transient elevation of serum cancer antigen 125 in non-small cell lung cancer patients

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SUMMARY

OBJECTIVE: The aim of this retrospective study was to investigate the correlation of transiently elevated postoperative serum cancer antigen 125 levels and prognosis in patients with non-small cell lung cancer.

METHODS: A total of 181 non-small cell lung cancer patients with normal levels of preoperative serum cancer antigen 125 were statistically summarized in this study.

RESULTS: Out of the analyzed patients, 22 (12.2%) showed elevation of serum cancer antigen 125 within one month after surgery. Serum cancer antigen 125 level decreased to normal at three months postoperation. Serum cancer antigen 125 was positively correlated with pro-brain natriuretic peptide in non-small cell lung cancer postoperative patients (p=0.00035). Univariate analysis did not find significant difference in disease progression survival between those who experienced cancer antigen 125 elevation in the early postoperation and those who did not (p=0.646).

CONCLUSIONS: In conclusion, transient elevation of cancer antigen 125 is associated to pro-brain natriuretic peptide increase after pulmonary surgery in non-small cell lung cancer patients.

KEYWORDS: Carcinoma, non-small-cell lung. CA-125 antigens. Biomarkers. Neoplasms. Natriuretic peptide, brain.

INTRODUCTION

Cancer antigen 125 (CA-125) is a glycoprotein antigen commonly produced by epithelial serous cells in fetal tissues but in mesothelial cells in adults[1]. It has been used as a clinical tumor marker for prognosis and therapy monitoring in ovarian and breast cancer patients[2,3]. High serum levels of the CA-125 have also been reported in heart failure, nephrotic syndrome, liver cirrhosis, tuberculosis and pelvic inflammatory diseases[4-11]. The CA-125 levels were positively correlated with pro-brain natriuretic peptide (pro-BNP) in patients with coronary heart disease. Some studies also reported CA-125 as a marker for worse prognosis in lung cancer[12-14]. Preoperative CA-125 measured in serum in operable patients has been suggested as a prognostic factor in NSCLC in some studies[15-17]. Nuñez et al.[18] reported two cases of elevated serum CA-125 levels in postoperated NSCLC patients and it regressed spontaneously in three and eight months post-operation. However, no other studies reported this drop in CA-125. In this study, we have systemically investigated the relationship between transient elevation of serum CA-125 status in early postoperative NSCLC patients with clinical data and pro-BNP.

METHODS

Patients

This study was approved by the ethics committee of the Peking University Shenzhen Hospital. We enrolled 181 patients with normal levels of serum CA-125, who underwent surgeries from January 2016 to May 2019 in the Thoracic Surgery Department of Peking University Shenzhen Hospital (Shenzhen, China).

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Among these patients, 22 of them were found to have elevation of serum CA-125 within one month after operation. We have analyzed clinicopathological features, including age, gender, smoking, history of hypertension, other nonmalignant diseases (heart failure, nephrotic syndrome, liver cirrhosis, tuberculosis, and pelvic inflammatory disease), location, surgical approach, type of resection, operation time, postoperative pleural effusion (in one month after surgery), histological type, classification system stage, pro-BNP, and survival outcomes. We adopted the staging system of the Union for International Cancer Control (UICC), eighth edition, 2018.01. Most of these NSCLC patients underwent lobectomy plus systematic mediastinal lymphadenectomy, while some patients with pure ground-glass opacity (pGGO) less than 1 cm underwent segmentectomy or wedge resection plus systematic mediastinal lymphadenectomy or mediastinal lymph node sampling.

Initial assessment and follow-up

Initial evaluation included complete medical history and physical examination, with extra attention to symptoms often associated with lung cancer. Chest computed tomography (CT) scan or positron emission tomography – computed tomography (PET/CT) and laboratory tests were performed, including CA-125 level.

Serum CA-125 was tested half a month before and one month after operation, and the following tests were conducted at three months, six months, and then every year after operation. All tests were performed according to the manufacturer's instructions. The cutoff point for CA-125 was 30 ng/mL, as determined by the manufacturer (Abbott, ARCHITECT i40000).

Pro-BNP was tested half a month before operation and within one day after surgery, and repeated one month after operation. All tests were performed according to the manufacturer's instructions. The cutoff point for pro-BNP, as determined by the manufacturer, was 125 pg/mL.

Recurrences were evaluated by physical examination, CT, PET/CT, magnetic resonance imaging and/or histological biopsy.

Statistical analyses

Statistical analyses were carried out using the software SPSS 25.0 (IBM Corp, Armonk, NY, USA). The statistical endpoint of analyses was disease-free survival (DFS) from the date of surgery. Group distributions for each clinicopathological trait were compared using the two-tailed Fisher's exact procedure and the χ^2 test. Univariate analysis was performed using the Cox proportional hazards model. Statistical significance was defined as $p<0.05$.

RESULTS

Patient characteristics

The patient characteristics are given in Table 1. All 181 patients were diagnosed with NSCLC and have normal preoperative serum CA-125 level. The average age was 55.5 years and the subjects were predominately male (female to male ratio 84:97).

Table 1. Baseline characteristics of non-small lung cancer patients with normal preoperation cancer antigen 125 level.

		n
Age (years)	<70	166
	≥70	15
Gender	Male	84
	Female	97
Smoking	Yes	51
	No	130
Operation time (hours)	<3	148
	≥3	33
Surgical approach	Thoracotomy	14
	Video-assisted thoracic surgery	167
Type of resection	Lobectomy/ pneumonectomy	142
	Segmentectomy/ wedge resection	39
Tumor location	Upper lobe	107
	Middle lobe/low lobe	74
Hypertension	Yes	37
	No	144
Postoperative pleural effusion	Yes	27
	No	154
Stage	I	112
	II/III	69
Histology	Adenocarcinoma	137
	Squamous cell carcinoma/other type	44
Other nonmalignant diseases	Heart failure	0
	Nephrotic syndrome	0
	Liver cirrhosis	0
	Tuberculosis	5
Pro-brain natriuretic peptide elevated postoperatively	Yes	38
	No	143

A total of 112 patients (61.9%) were classified as stage I, and other 69 patients (30.1%) as stage II or III. A total of 137 cases were of lung adenocarcinoma, and other 44 cases of lung squamous cell carcinoma or other type of NSCLC. Thirty-seven patients had history of hypertension and blood pressure control well before surgery. As for other nonmalignant diseases (heart failure, nephrotic syndrome, liver cirrhosis, tuberculosis, and pelvic inflammatory disease), only 5 patients had history of tuberculosis. Serum pro-BNP levels were in normal range in all 181 patients pre-operatively, and raised above normal level (>125pg/mL) in 38 patients within one day after surgery and decreased to normal level in one month follow-up.

Levels of cancer antigen 125

Levels of serum CA-125 were found to be transiently elevated in one month after surgery in 22 patients (12.2%), and it returned to normal level in the follow-up examination after three months (Figure 1A). On the other hand, in the rest of the 159 patients, the levels of CA-125 were found to be normal in three months postoperation.

Transient elevation of serum cancer antigen 125 postoperative and clinical characteristics

The baseline characteristics of patients were considered, including age, gender, operative time, tumor stage, tumor differentiation, hypertension, and pro-BNP. Compared to the normal group, patients with transient elevation of CA-125 had significantly correlated transient elevation of pro-BNP (p=0.00035) (Table 2, Figure 1B). There were no significant differences within other data with transient elevation of serum CA-125 in post-operative patients. All of the tuberculosis patients' postoperative CA-125 levels were normal.

Cancer antigen 125 status and pattern of disease progression survival in non-small cell lung cancer patients

Within a median follow-up period of 23 months (range 4–34 months), 42 patients had died or had cancer-recurring incidents. By univariate analysis, comparison of disease progression survival (DFS) between the two groups (CA-125 elevated and not elevated in the early postoperated patients) did not reach statistically significant levels (MST: 31.0 vs. 31.0 months, p=0.646) (Figure 2). The factor influencing DFS in the univariate analysis was stage (95%CI 1.539–5.632; HR=2.944) (Table 3).

DISCUSSION

CA-125, a high molecular weight glycoprotein determinant recognized by murine monoclonal antibody (OC125), is a tumor marker for ovarian cancer, and is usually used to monitor the clinical course of patients with advanced ovarian cancer[1,9].

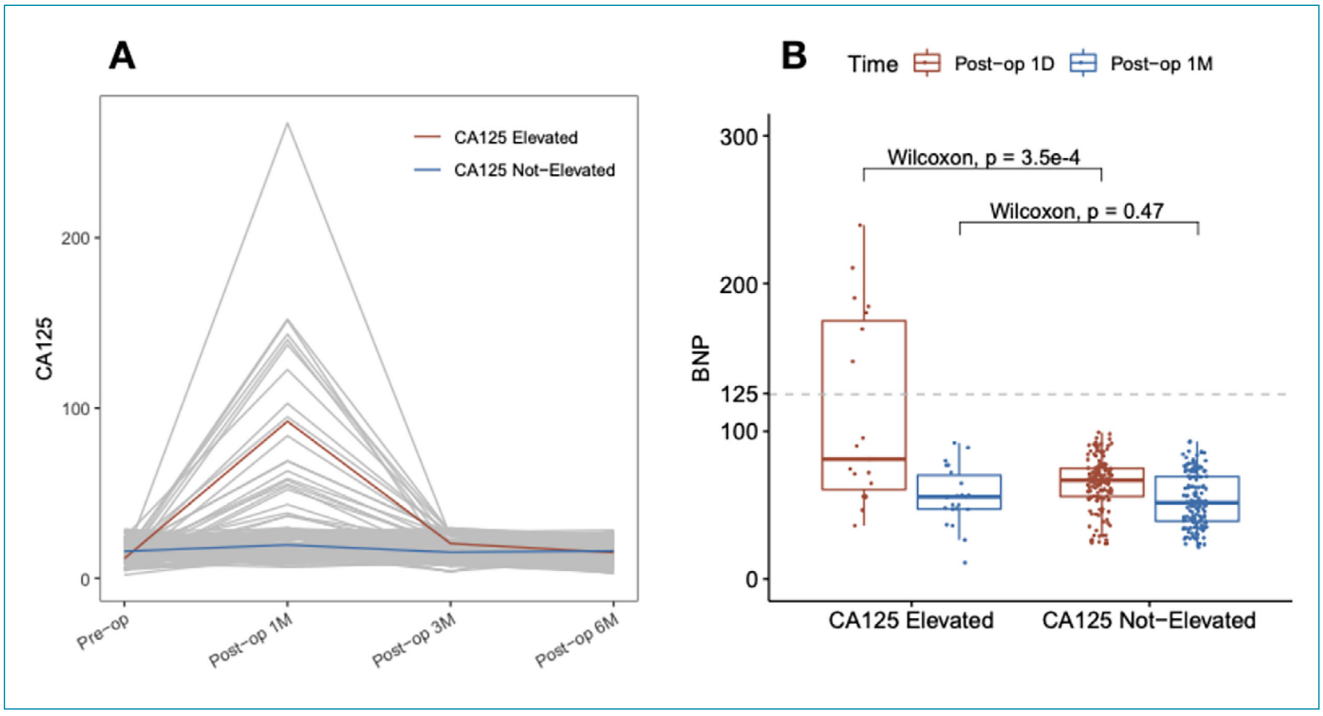

Figure 1. (A) Serum CA125 levels from pre-operation to 6 months post-operation in all 181 NSCLC patients; (B) boxplot showing the comparison of pro-BNP between CA125 elevated and normal group.

Several studies have shown that high levels of preoperative serum CA-125 were significantly correlated with poor prognosis in NSCLC[17]. However, the correlation of postoperative CA-125 level and prognosis in lung cancer patients remains elusive. But some other studies found that the prognostic values of CA-125 for NSCLC are limited[11]. Therefore, the prognostic effect of CA-125 remains to be further studied.

In this study, we noticed a group of NSCLC patients presented transient elevation of serum CA-125 after surgery, and evaluated the potential of using this phenomenon as a prognostic biomarker. It was also found that serum CA-125 was decreased to normal level three months after surgery. By univariate analysis, transient elevation of serum CA-125 has not reached statistically significant DFS compared with no transient elevation of serum CA-125 (MST:

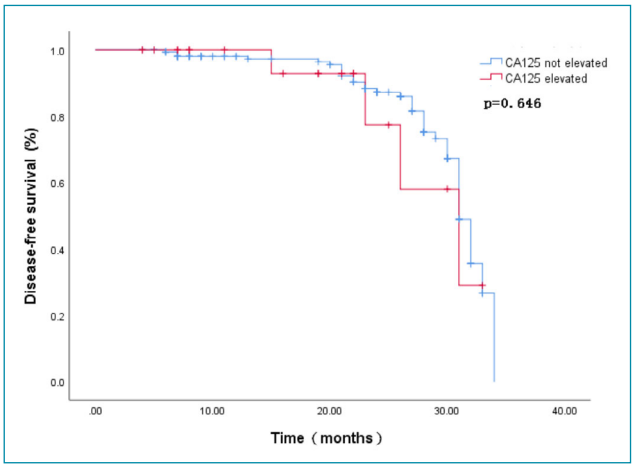

Figure 2. Kaplan-Meier estimates of disease-free survival in the patients with transiently elevated CA125 (n=22, red) and in patients without CA125 elevation (n=159, blue)

Table 2. Correlation between cancer antigen 125 elevation/nonelevation and clinicopathological characteristics.

		Cancer antigen 125 elevated	Not	p
Age (years)	<70	19	12	0.400
	≥70	3	147	
Gender	Male	13	84	0.652
	Female	9	75	
Smoking	Yes	3	48	0.132
	No	19	111	
Operation time (hours)	<3	19	129	0.770
	≥3	3	30	
Surgical approach	Thoracotomy	1	13	1.000
	Video-assisted thoracoscopic surgery	21	146	
Type of resection	Lobectomy/pneumonectomy	16	140	0.090
	Segmentectomy/wedge resection	6	19	
Tumor location	Upper lobe	14	93	0.818
	Middle lobe/low lobe	8	65	
Hypertension	Yes	2	35	0.257
	No	20	124	
Postoperative pleural effusion	Yes	3	24	1.000
	No	19	135	
Stage	I	16	96	0.351
	II/III	6	63	
Histology	Adenocarcinoma	16	104	0.632
	Squamous cell carcinoma/ Other type	6	55	
Pro-brain natriuretic peptide elevated postoperatively	Yes	10	28	0.00035*
	No	12	131	

Cancer antigen 125 elevation: serum cancer antigen 125 was transiently elevated in one month after surgery.

Table 3. Univariate analysis for disease-free survival (DFS) of clinical variables in relation to DFS for non-small cell lung cancer patients

	Univariate analysis	
	Hazard ratio (95%CI)	p
Age (<70y vs. ≥70y)	0.650 (0.271–1.561)	0.335
Gender, (F/M)	0.912 (0.492–1.693)	0.771
Smoking (yes vs. no)	0.814 (0.386–1.714)	0.587
Operation time (<3h vs. ≥3h)	1.384 (0.559–3.426)	0.482
Surgical approach Thoracotomy vs. video-assisted thoracoscopic surgery	1.248 (0.522–2.984)	0.619
Type of resection (Lobectomy/pneumonectomy vs. segmentectomy/wedge resection)	0.042 (0.000–5.498)	0.202
Tumor location (upper vs. middle/low lobe)	0.860 (0.452–1.637)	0.646
Hypertension (yes vs. no)	1.619 (0.759–3.453)	0.213
Postoperative pleural effusion (yes vs. no)	0.905 (0.379–2.159)	0.821
Stage (I vs. II/III)	2.944 (1.539–5.632)	0.001
Histology (adenocarcinoma vs. squamous cell carcinoma/other)	0.828 (0.421–1.628)	0.584
Cancer antigen 125 elevated (yes vs. no)	1.263 (0.448–3.563)	0.659
Pro-brain natriuretic peptide elevated postoperatively (yes vs. no)	0.988(0.437–2.232)	0.976

31.0 vs. 31.0 months, p=0.646) (Figure 2). Therefore, the condition of transient elevation of serum CA-125 in postoperated patients may not be a prognostic factor for NSCLC after surgery.

The transient elevation of CA-125 levels after surgery is an interesting clinical phenomenon and worth thorough investigation. One explanation is possible tumor cell shedding from tumor tissues during surgery. This notion is supported by studies showing that post-operative circulating tumor DNA (ctDNA) levels in some patients were higher than preoperative levels during the lung cancer surgery[19,20]. However, in our study, transiently elevated CA-125 levels in postoperated patients are not relevant to operation time, surgery type of resection, or worse DFS. Therefore, this hypothesis needs further investigation.

High serum levels of CA-125 have also been reported in other nonmalignant diseases, including heart failure, nephrotic syndrome, liver cirrhosis, tuberculosis, and pelvic inflammatory disease[4-10]. All five patients with tuberculosis had normal levels of CA-125 postoperatively. We cannot confirm the relationship between these nonmalignant diseases and elevation of serum CA-125 postoperatively according to our limited data.

By careful examination of all clinical features with transient CA-125 elevation, we found that pro-BNP levels after surgery were strongly correlated with transient elevation of serum CA-125 in NSCLC patients (Figure 1B) p=0.00035 (Table 2). Several previous studies have shown that both CA-125 and pro-BNP was significantly related with heart function in heart disease patients, and the CA-125 levels were positively correlated with pro-BNP in heart disease patients[21-23]. Pro-BNP is a quantitative biomarker of myocardial function. Postoperative elevation of pro-BNP was correlated with the pulmonary vascular resistance increased in pulmonary resection patients[24]. We speculated that postoperative transient elevation of serum CA-125 is not specifically related to NSCLC, but is more likely to be associated with enhancement of pulmonary vascular resistance after pulmonary surgery.

CONCLUSIONS

It can be concluded from the above findings that postoperative transient elevation serum CA-125 had no correlation to recommend their use for diagnosis of tumor prognosis and recurrence in NSCLC patients. Transient elevation of CA-125 was found to be associated with pro-BNP level, and further investigation on these features and their clinical relevance is needed.

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