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Carcinoembryonic antigen as prognostic factor for metastatic non-small cell lung cancer by percutaneous cryosurgery

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Abstract. Carcinoembryonic antigen (CEA) is a prognostic marker for early-stage non-small cell lung cancer (NSCLC), and cryoablation is a new therapeutic alternative for lung cancer. We determined whether cryoablation-induced changes in serum CEA levels correlated with tumor type (adenocarcinoma or squamous carcinoma) and treatment type (comprehensive therapy [cryoablation of all intra- and extrapulmonary tumors] or palliative therapy [cryoablation of only extrapulmonary tumors]) in patients with metastatic NSCLC, and assessed whether pre-treatment CEA levels predicted overall survival (OS). We retrospectively reviewed the clinical data of 88 patients with metastatic NSCLC who underwent comprehensive (62 patients) or palliative (26 patients) therapy. Pre- and post-cryoablation serum CEA levels and overall survival were determined for all patients. Cryoablation significantly reduced CEA levels in adenocarcinoma, but not squamous carcinoma, patients. Among adenocarcinoma patients, the cryoablation-induced reduction in CEA levels was significantly greater after comprehensive treatment than after palliative treatment; the OS of patients under comprehensive cryoablation was longer than those under palliative treatment. Among adenocarcinoma patients receiving comprehensive cryoablation, OS was significantly longer in those with normal pre-treatment serum CEA levels than in those with abnormal pre-treatment serum CEA levels. Pretreatment level and change of serum CEA can be a good indicator for therapeutic effects and OS in metastatic NSCLC patients under percutaneous cryosurgery.

Keywords: Cryosurgery, carcinoembryonic antigen, metastatic non-small cell lung cancer

1. Introduction

Lung cancer is the leading cause of cancer death in most countries. Surgical resection with radical lymphadenectomy has been advocated as the treatment of choice for early-stage lung cancer [1]. Primary tumors of the lung are conventionally classified according to their histological appearance into non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLC is further classified into adenocarcinoma, squamous carcinoma and carcinoid carcinoma. In patients with NSCLC, serum tumor markers, such as carcinoembryonic antigen (CEA), squamous carcinoma antigen and carbohydrate antigen 125, as well as serum growth factors have long been used to evaluate tumor stages and predict tumor recurrence and metastasis [2–4], and tumor CEA levels in stage IV NSCLC patients might correlate with metastatic tumor extent and development of brain metastasis [5]. According to a 2012 review by Grunnet and Sorensen, elevated serum CEA levels were a significant prognostic marker of overall survival, recurrence after surgery and/or progression-free survival in 18 NSCLC trials, including 12 trials involving early-stage cancer (stage I–II) mainly treated using surgery. The prognostic value of CEA serum levels in late stage (stages IIIb–IV) and non-adenocarcinoma NSCLC remains controversial [6].

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Cryosurgery, a widely accepted, minimally invasive, curative technique for solid tumors such as prostate cancer, renal carcinoma, hepatocellular carcinoma, and metastatic liver deposits [7,8]. In 2007, Asimakopoulos et al. reported that cryosurgery was a safe method for the treatment of endobronchial malignancies with airway obstruction [9]. In 2011, Yamauchi et al. reported the successful use of percutaneous cryoablation for pulmonary metastases from colorectal cancer [10]. In 2012, we also confirmed the safety and efficiency for cryosurgery of lung cancer [11,12]. However, the effects of palliative cryosurgery on serum CEA levels in metastatic NSCLC patients and how to predict the therapeutic effects using CEA remain unknown. In this study, we collected data pertaining to metastatic NSCLC patients who underwent cryoablation in our hospital and investigated the relationship of serum CEA levels before and after cryoablation with different pathologic types of cancer and type of therapy. We also assessed the relationship serum CEA level before cryoablation with overall patient survival.

2. Materials and methods

2.1. Ethics

The study protocol was approved by the regional ethics committee at Guangzhou Fuda Hospital. Written, informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

2.2. Patient selection

This retrospective study involved 88 patients treated for metastatic lung tumors (stage IV lung cancer) in our hospital between October 2005 and April 2011. Diagnoses of metastatic NSCLC were principally based on positron emission tornography-computed tomography (PET-CT) imaging, and confirmed by CT-guided fine-needle biopsy. An 18-gauge Tru-Cut biopsy needle (Baxter; Deerfield, IL, United States) was inserted percutaneously to obtain one or two cores of tissue from the solid lung tumor. Some patients had a history of surgical resection; all patients received their final treatments in our hospital, and follow-up assessments continued for a total of 6.5 years.

The following were exclusion criteria for cryosurgery: (a) diffuse lung cancer, (b) diffuse systemic metastasis, (c) severe complications (e.g., hypertension, hydrothorax and ascites), (d) brain or adrenal gland metastases and (e) advanced age. The inclusion criteria were as follows: (a) Karnofsky performance status (KPS) score $\geqslant 70$; (b) platelet count $\geqslant 80 \times 10^9$/l, white blood cell count $\geqslant 3 \times 10^9$/l, neutrophil count $\geqslant 2 \times 10^9$/l and hemoglobin $\geqslant 90$ g/l; (c) prothrombin time, international normalized ratio $\geqslant 1.5$; (d) diameter of largest primary or metastatic tumor $\leqslant 8$ cm on preoperative CT; (e) absence of level 3 hypertension, severe coronary disease, myelosuppression, respiratory disease and acute or chronic infection; (f) compensation stage of pulmonary functional and (g) failure of or refusal to undergo chemotherapy.

2.3. Percutaneous cryoablation and iodine-125 seed implantation

Complete information was available for all these patients who received cryoablation plus brachytherapy treatment [11,12]: 62 of these patients received comprehensive treatment, including treatments of intra- and extrapulmonary tumors; 26 patients refused comprehensive treatment for reasons that included cost and pain and received palliative treatment for extrapulmonary tumors. Cryoablation was performed using double-row helical CT guidance (Somatom Emotion Duo; Siemens, Germany) under general anesthesia. Mainly three experienced doctors performed all cryosurgeries. Depending on the tumor location, cryoprobes (Cryo-42; Endocare, Irvine, CA) were inserted percutaneously into the scapular line, posterior axillary line or rib margin. For tumors greater than 3 cm in diameter, more than two 1.7-mm cryoprobes were used. We performed 1–3 freeze/thaw cycles using an argon gas-based cryosurgical unit (Cryocare, Endocare). Before cryoablation, we preferentially implanted iodine-125 seeds (Syncor Pharmaceuticals, Shanghai, China) in these regions (using a percutaneous transhepatic cholangiography [PTC] needle and a 3D treatment-planning system; usually < 20 seeds) for patients who had a central lung cancer that was not entirely covered by the effective freezing area. Metastases, for example, to the liver and bone, were also treated using cryoablation (and iodine-125 seed implantation), when feasible.

2.4. Serum CEA level detection

Serum CEA level was measured 1 week before and 1 month after cryosurgery by using an automatic elec-

trochemiluminescence system (Cobas e 411; Roche, Basel, Switzerland) and a quantitative CEA determination kit (100T, REF 11731629322; Roche). CEA levels $\geqslant$ 4.7 ng/ml were considered possibly abnormal according to the operational manual; this cut-off value was used because it yielded a 95% specificity level in our data of healthy people as well.

2.5. Statistical analysis

Cryoablation-induced differences in serum CEA levels associated with different pathologic cancer types or different therapies were detected using the chi square test ($n \geqslant 40$ and $T \geqslant 5$) or Fisher's exact test ($n < 40$ or $T < 1$). Overall survival of the patients was calculated from the month in which metastatic NSCLC was first diagnosed and compared using Newman-Keuls multiple comparision test. A significant difference was indicated by a P value < 0.05. Statistical analyses were conducted with the GraphPad Prism 5 (GraphPad software, San Diego, CA, USA).

3. Results

3.1. Clinical data

The study involved 88 participants: 56 patients had an adenocarcinoma, 23 had a squamous carcinoma, and 9 had a carcinoid carcinoma; bone metastases (29 lesions) were present in 20 patients, liver metastases (33 lesions) in 23 patients, contralateral lung metastases (49 lesions) in 32 patients, and localregional metastasis of multiple organs (31 lesions) in 13 patients.

3.2. Perioperative outcome

All percutaneous cryoablations were successfully performed under CT monitoring. No severe side effects such as cardiac arrest, asthmatic attack and respiratory failure occurred postoperatively. In the comprehensive treatment group, both primary and metastatic tumors were treated, and slight adverse effects occurred as follows. Transient hemoptysis and pneumothorax occurred in 21 (33.9%) and 18 (29%) patients, respectively, usually immediately after the completion of the procedure. Bradycardia, hypotension and fever occurred in three (4.8%), five (8%) and six (9.7%) patients, respectively, and resolved following appropriate treatment in 1 week. In all cases, perioperative pain was controlled by a 1-week treatment with loxoprofen. Some patients complained of a dull pain in the anterior chest soon after treatment, which was most likely due to damage to the intercostal nerves; the pain usually resolved within a few months. No treatment-related deaths or conversions to surgical intervention occurred in the comprehensive treatment group. A mild decrease in platelet count occurred after seven sessions in four patients (6.5%); the count returned to normal within 10–15 days without treatment. Nine patients (14.5%) complained of a cough and blood-streaked sputum, which improved within 3–5 days without any treatment. Similar adverse effects (e.g., fever, pain and decreased platelet count) occurred in the palliative treatment group, and these resolved within 2 weeks of symptomatic treatment. No treatment-related deaths or conversions to chemo- or radiotherapy occurred in the palliative treatment group.

Within 2 weeks of comprehensive treatment, 43 patients (69.4%) experienced a $\geqslant$ 50% reduction in pain score, 32 patients (51.6%) experienced a 50% decrease in analgesic consumption and 29 patients (46.8%) had a $\geqslant$ 20% increase in their KPS score. Within 2 weeks of palliative treatment, 10 patients (58.8%) experienced a $\geqslant$ 50% reduction in pain score, nine patients (52.9%) experienced a 50% decrease in analgesic consumption and eight patients (47.1%) had a $\geqslant$ 20% increase in their KPS score.

3.3. Pathological cancer type and serum CEA levels before and after cryoablation

Of the 88 patients with complete information, nine patients with carcinoid carcinoma had a normal serum CEA level both before and after cryosurgery; therefore, we only considered the data of the adenocarcinoma ($n = 56$) and squamous carcinoma ($n = 23$) patients for analysis of the correlation between serum CEA level and pathologic cancer type (Fig. 1). In adenocarcinoma patients, only 48 patients had complete data, 23 or 25 persons were with normal or abnormal serum CEA level before cryoablation, and CEA level of 12 persons returned to normal after cryoablation; in squamous carcinoma patients, 14 or 9 persons were with normal or abnormal serum CEA level before cryoablation, and CEA level of 5 persons returned to normal after cryoablation. The chi-square test showed a significant reduction in serum CEA level after cryoablation in adenocarcinoma patients ($P = 0.0123$) but not in squamous carcinoma patients ($P = 0.1016$). We, therefore, assessed the relationship of serum CEA levels before and after cryoablation with type of treatment in patients with adenocarcinoma or squamous carcinoma.

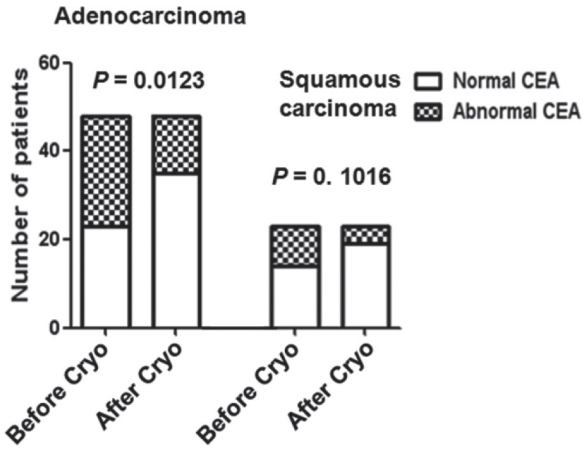

Fig. 1. Correlation of serum CEA levels before and after cryoablation with pathologic type of NSCLC in all patients. The chi square tests were used in both detections. Serum CEA level of no less than 4.7 ng/mL was determined as abnormal. Cryo represents cryoablation.

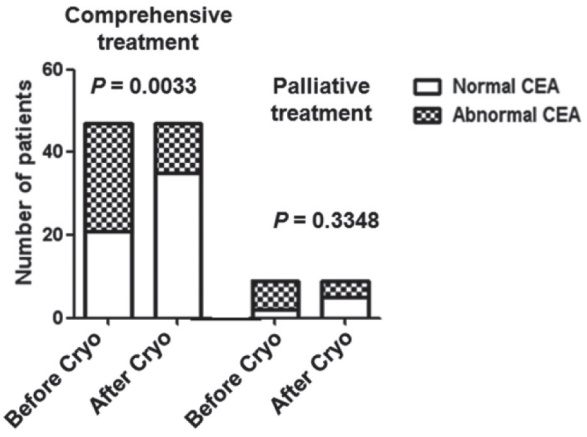

Fig. 2. Correlation of CEA levels before and after cryoablation with type of therapy in 56 patients with adenocarcinoma. The chi square test was used inr comprehensive treatment group; Fisher's exact test was used in palliative treatment group. Serum CEA level of no less than 4.7 ng/mL was determined as abnormal. Cryo represents cryoablation.

3.4. Type of therapy and serum CEA levels before and after cryoablation

Of the 56 adenocarcinoma patients, 47 received comprehensive treatment and nine received palliative treatment. The correlation of pre- and post-cryoablation CEA levels and type of therapy are shown in Fig. 2. For patients who received comprehensive treatment, 21 or 26 persons were with normal or abnormal serum CEA level before cryoablation, and CEA level of 14 persons returned to normal after cryoablation; for patients who received palliative treatment, 2 or 7 persons were with normal or abnormal serum CEA level before cryoablation, and CEA level of 3 persons returned to normal after cryoablation. The chi square test showed a significant reduction in serum CEA level after cyroablation compared to the level before cryoablation in the comprehensive treatment group ($P = 0.0033$). The Fisher exact test showed no such reduction in the palliative treatment group ($P = 0.3348$). No correlation between serum CEA levels and type of treatment was found in patients with squamous carcinoma (Fisher exact test; comprehensive treatment group, 11 patients, $P = 0.183$; palliative treatment group, 12 patients, $P = 0.68$; Supplementary Fig. 1).

3.5. Serum CEA levels before cryoablation and short overall survival

In the comprehensive treatment group, 21 adenocarcinoma patients had a normal serum CEA level before cryoablation, and 26 had an abnormal serum CEA level. In the palliative treatment group, only two adenocarcinoma patients had a normal pre-treatment serum CEA level; the remaining seven had abnormal serum CEA levels. Variance analysis of factorial design was used to assess the correlation between pre-cryoablation CEA levels and overall survival (Table 1). Patients with a normal serum CEA level before cryoablation had a considerably longer overall survival than those with abnormal CEA levels ($P = 0.0063$). For different treatment methods, the OS of comprehensive group was longer than that of palliative treatment groups ($P = 0.0153$).

In the comprehensive treatment group, five patients with squamous carcinoma had normal serum CEA levels before cryoablation; the remaining six patients had abnormal serum CEA levels. In the palliative treatment groups, six squamous carcinoma patients had normal serum CEA levels, and six had abnormal serum CEA levels. Variance analysis of factorial design showed that overall survival was similar in patients with normal or abnormal CEA levels before cryoablation ($P = 0.762$; supplementary Table 1), and it was similar in the comprehensive and palliative treatment groups ($P = 0.997$).

4. Discussion

Most patients with metastatic lung cancer have unresectable tumors. Radiofrequency ablation, chemother-

Table 1
Correlation of CEA level before cryoablation with overall survival in 56 patients with adenocarcinoma

CEA level (no. of patients)	Overall survival (months)		
	Comprehensive treatment	Palliative treatment	P value
Normal (23)	13, 14, 14, 14, 14, 15, 16, 21, 24, 25, 25, 26, 34, 36, 36, 37, 57, 58, 58, 58, 60	5, 6	0.0063
Abnormal (33)	7, 8, 8, 8, 9, 9, 10, 10, 10, 10, 12, 16, 17, 17, 17, 18, 21, 22, 22, 22, 24, 34, 36, 36, 38, 39	4, 5, 5, 8, 9, 11, 32	
P value	**0.0153**		

apy and other palliative therapies are possible options in such patients [13,14]. With advances in cryosurgery and imaging techniques, percutaneous cryoablation has increasingly been used to successfully treat lung cancer [9,15–17]. This approach avoids the risks of thoracic surgery, decreases the likelihood of complications, and improves patients' quality of life. Large tumors, those with adhesions to other organs and tissues and invasive tumors may not be completely treated with percutaneous cryoablation, and a combination of this treatment with brachytherapy may be a better option [18–21]. In this study, the comprehensive and palliative therapy both achieved satisfactory results, with fewer slight side effects, obviously relieved tumor pain and increased KPS scores in most patients. However, whether cryosurgery affects tumor marker levels and whether these markers are prognostic predictors of metastatic lung cancer remain unclear.

CEA is a glycoprotein involved in cell adhesion and is normally produced during fetal development. CEA is critical to the metastatic dissemination of colon carcinoma, and is used as a marker for colorectal cancer. Many researchers have reported that CEA can also be used as a prognostic marker for NSCLC [6]. Serum CEA levels before treatment are usually considered a good prognostic sign, but data on CEA levels in different pathologic cancer types are contradictory [1,22–24]. This was the first study to assess the correlation between serum CEA levels and cryoablation in metastatic NSCLC patients. Our findings show that the cryoablation-induced reduction in serum CEA levels was significantly greater in adenocarcinoma patients than in squamous carcinoma patients (Fig. 1). This finding may attributable to tumor characteristics, patient prognosis and therapy type. Like our results, increase of serum CEA level after cryosurgeries was often found in different histological subtypes [25–27], the exact mechanisms still needs further investigation.

Further analysis showed that the cyroablation-induced decrease in CEA levels in adenocarcinoma patients was significant only in the comprehensive treatment group (Fig. 2). This finding may be attributed to more thorough ablation of the tumors in this group; serum CEA level of 12 patients remained abnormal after treatment, may be relevant to the following factors: imcomplete tumor ablation, fast growth of substantial micrometastases, liver disease [28] and metabolic syndrome [29]. These factors may directly or indirectly related to the bad prognosis of these patients. In contrast, the patients who received palliative therapy had considerable residual tumor tissue. Although palliative treatment can produce remarkable symptomatic improvement, it does not alter the levels of tumor markers. In the patients with squamous carcinoma, however, even comprehensive therapy failed to reduce serum CEA levels (Supplementary Fig. 1), confirming our speculation that the effect of cyroablation on serum CEA levels is related to tumor characteristics. The reason for this finding requires further investigation.

Among patients with adenocarcinoma, a normal CEA level before cryoablation, as well as comprehensive treatment, was positively correlated with longer survival time (Table 1). The median OS time usually range from 7–36 months according to the histology, performance status and other treatment factors [30]. But in our study, the long survival of 57–60 months for 5 patients maybe due to other unkonwn factors (e.g. immunotherapy, Chinese herb), and further study on these patient may be helpful for treatment. Above all, a normal pre-treatment CEA level and comprehensive treatment method may indicate good prognosis in adenocarcinoma patients, but not in squamous carcinoma patients (Supplementary Table 1). More suitable prognostic markers for squamous carcinoma should be sought. Our results indicated that the reduction of serum CEA levels to within the normal range after cryoablation indicates good prognosis in adenocarcinoma patients. In adenocarcinoma patients, multiple comprehensive treatments should aim to maintain the serum CEA level within the normal range.

We found that serum CEA level is a good indicator for therapeutic effects and prognostic in patients with metastatic NSCLC that is histologically classified as an adenocarcinoma. Clinically, a normal CEA level before cryoablation and/or after comprehensive therapy will indicate good prognosis and overall survival.

The results of this preliminary study and the effects of cryosurgery on other types of NSCLCs and tumor markers should be further investigated.

Acknowledgments

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Conflict of interest

No author has any conflict of interest.

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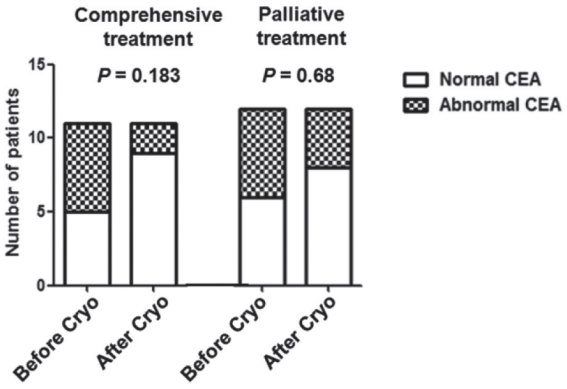
Supplemental material

Supplementary Table 1.
Correlation of CEA level before cryoablation with short OS in 23 patients with squamous carcinoma

CEA level (no. of patients)	Overall survival (months)		
	Comprehensive treatment	Palliative treatment	*P* value
Normal (11)	14, 17, 18, 20, 22	2, 3, 10, 11, 18, 20	0.997
Abnormal (12)	5, 6, 9, 15, 17, 23	2, 4, 6, 9, 10, 15	
P value		0.762	



Supplement Fig. 1. Correlation of CEA levels before and after cryoablation with type of therapy in 23 patients with squamous carcinoma. Fisher's exact tests were used in both detections. Serum CEA level of no less than 4.7 ng/mL was determined as abnormal. Cryo represents cryoablation.