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Impact of Preoperative Serum Tumor Markers in Patients with Lung Squamous Cell Carcinoma

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Abstract

Background: Several previous researchers have investigated the prognostic value of serum tumor markers, especially carcinoembryonic antigen (CEA). Only a limited number of studies reported the usefulness of serum tumor markers for lung squamous cell carcinoma (SQ). We aimed to examine the significance of serum tumor markers for lung SQ. **Methods:** Eighty-five lung SQ patients who underwent surgery and followed more than 5-year were included. The ratios of 5-year survivors to all patients in groups with several clinicopathologic factors, including tumor markers, were compared. We also compared the clinicopathologic factors between central type and peripheral type SQ. **Results:** The majority of patients were male gender and current/former smokers. Age, pN status, cytokeratin-19 fragment (CYFRA 21-1), squamous cell carcinoma antigen (SCC), and comorbid interstitial pneumonia (IP) were associated with the ratio of 5-year survivors significantly. When patients were compared based on tumor location, high p-stage and CYFRA 21-1 were related to central type SQ. **Conclusion:** Both SCC and CYFRA 21-1 appeared to be useful prognostic markers for patients with lung SQ. Furthermore, CYFRA 21-1 was related to central type SQ.

Keywords

Lung Squamous Cell Carcinoma, Cytokeratin-19 Fragment, Squamous Cell Carcinoma Antigen

1. Introduction

Serum tumor markers have been investigated as prognostic factors for non-small cell lung cancer (NSCLC). Preoperative carcinoembryonic antigen (CEA) has emerged as an independent prognostic factor for patients with NSCLC, especially adenocarcinoma (AD) [1] [2] [3]. Although several studies reported the

prognostic role of CEA [1] [2] [3], only a limited number of recent previous studies reported the prognostic role of squamous cell carcinoma antigen (SCC) in NSCLC [2] [4] [5] [6]. Emerging evidence suggests that preoperative cytokeratin-19 fragment (CYFRA 21-1) is now known as a useful tumor marker for NSCLC [2] [3] [7] [8]. Both SCC and CYFRA 21-1 are generally known to be sensitive to squamous cell carcinoma (SQ) as compared to AD [2] [4] [5] [7] [8]. However, the majority of previous studies examined all NSCLC patients, including AD and SQ. The number of previous studies which focused on lung SQ is small, although SQ is one of the major NSCLC [2] [7] [8]. Therefore, in the present study, the prognostic usefulness of preoperative tumor markers for lung SQ was investigated.

Furthermore, lung SQ can be classified into a central type (c-SQ) and a peripheral type (p-SQ) based on the tumor location [9] [10]. Recently, it has been well accepted that c-SQ and p-SQ have different clinicopathologic characteristics and should be classified into different categories [9] [10]. Therefore, we also compared the clinical factors, including tumor markers, between c-SQ and p-SQ.

2. Patients and Methods

The Medical Ethics Committee of our hospital approved the study protocol (O-0997) and waiver of the written informed consents from each patient, considering the retrospective design and anonymous clinical data. A total of 684 patients with newly diagnosed NSCLC who received curative resections at our hospital over a 10-year period up to June 2016, were retrospectively analyzed. Patients with loss to follow-up within 5 years were excluded from this study. All patients were followed for more than 5 years. Among these patients, there are 85 patients with primary lung SQ.

Preoperative complete blood count and routine biochemistry test, including serum CEA, SCC, and CYFRA 21-1, of each patient, was applied within 1 month before surgery. Upper cutoff levels of serum CEA, SCC, and CYFRA 21-1 were 5.0 ng/ml, 1.5 ng/ml, and 2.3 ng/ml, respectively. Preoperative data were retrospectively extracted from the patients' medical records. All patients in this study were staged according to the 8th edition Cancer Staging [11].

For survival analysis, Sagawa *et al*. [12] reported that the calculated cumulative survival rate occasionally can be confounded by those patients with a short follow-up period. Therefore, they presented the clinicopathologic characteristics of long-term survivors using a follow-up period of more than 5 years and an actual number of survivors [12]. According to this manuscript, in the present study, we omitted the patients with a follow-up period of fewer than 5 years and analyzed the actual number of survivors rather than the cumulative survival rate. Pearson's chi-square analysis with Yate's correction was used to compare the various rates. A *p*-values < 0.05 was considered statistically significant. All statistical analyses were performed using JMP Pro software, version 15 (SAS Institute, Cary, NC, USA).

3. Results

The majority of our lung SQ patients were male gender (76/85) and current/ former smokers (78/85). There were 40 patients with c-SQ and 45 with p-SQ. Forty-one patients (48.24%) survived more than 5 years.

As shown in Table 1, we compared the 5-year survivors and others based on the various clinicopathologic factors. Our result showed that age, pN status, and comorbid interstitial pneumonia (IP) were associated with the ratio of 5-year survivors, whereas, gender, smoking status, pT status, and tumor location were not. The p-stage was marginally significantly associated with 5-year survivors *(p = 0.054)*.

Concerning serum tumor markers, we failed to find the difference in CEA

Table 1. Comparison between 5-year survivors and others.

|		5-year survivors	Non-survivors	*p* Value
Age	<65	15	7	0.028
	≥65	26	37	
Gender	Male	35	41	0.239
	Female	6	3	
Smoking status	Current/former	39	39	0.269
	Never	2	5	
p-stage	I	28	21	0.054
	II-III	13	23	
pT status	pT1	22	16	0.108
	pT2-3	19	28	
pN status	pN0	35	27	0.011
	pN1-2	6	17	
Tumor location	Central	19	21	0.898
	Peripheral	22	23	
IP	IP+	3	10	0.043
	IP−	38	34	
CEA	Normal	30	31	0.781
	High	11	13	
SCC	Normal	28	16	0.003
	High	13	28	
CYFRA 21-1	Normal	29	18	0.005
	High	12	26	
SCC & CYFRA 21-1	Both normal	23	9	0.001
	Others	18	35	

IP: Interstitial pneumonia; CEA: Carcinoembryonic antigen; SCC: Squamous cell carcinoma antigen; CYFRA 21-1: Cytokeratin-19 fragment.

between 5-year survivors and others. However, 28/44 (63.6%) patients with normal SCC were 5-year survivors, whereas 13/41 (31.7%) with high SCC survived more than 5 years (p = 0.003). Similarly, 29/47 patients (61.7%) with normal CYFRA 21-1 were 5-year survivors, whereas 12/38 (31.6%) with high CYFRA 21-1 survived (p = 0.005). The relationship between 5-year survivors and serum tumor markers had been also shown as a box plot with a scatter diagram (Figure 1). To examine the combined use of tumor markers, SQ patients were subdivided into 2 groups based on SCC and CYFRA 21-1; both normal group and others. Twenty-three of 32 (71.9%) patients with both normal were 5-year survivors, whereas 18/53 (34.0%) with others survived more than 5 years (p = 0.001).

Although the ratio of 5-year survivors was not different between c-SQ and p-SQ, the clinical characteristics were compared between c-SQ and p-SQ (Table 2). Age, gender, smoking status, pT status, pN status, CEA, and SCC were not related to tumor location. There was a trend towards an association between p-SQ and comorbid IP, but this did not reach statistical significance *(p* = 0.053). On the other hand, high p-stage was significantly related to c-SQ (p = 0.026). Furthermore, 16/47 (34.0%) patients with normal CYFRA 21-1 were c-SQ, whereas 24/38 (63.2%) with high CYFRA 21-1 were c-SQ (p = 0.007). Figure 2 also showed a box plot with a scatter diagram comparing the c-SQ and p-SQ based on tumor markers.
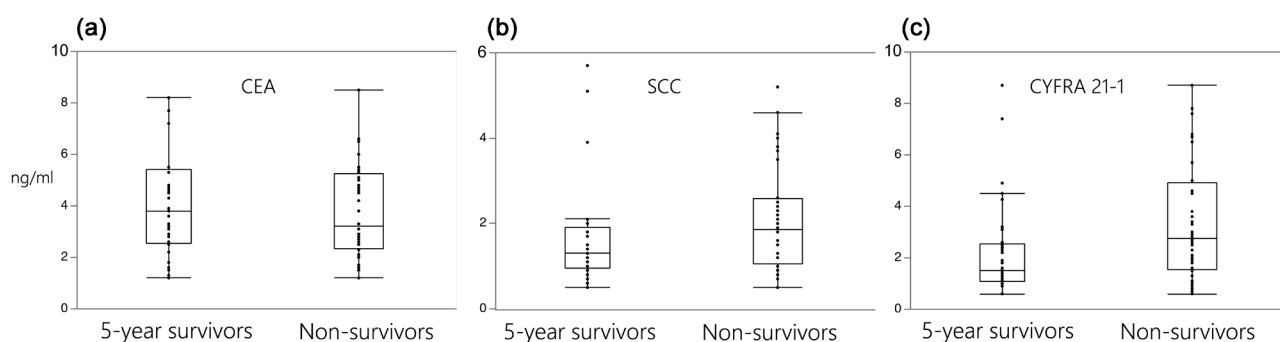
Figure 1. A box plot with a scatter diagram comparing the 5-year survivors and others based on CEA (a), SCC (b), and CYFRA 21-1 (c).
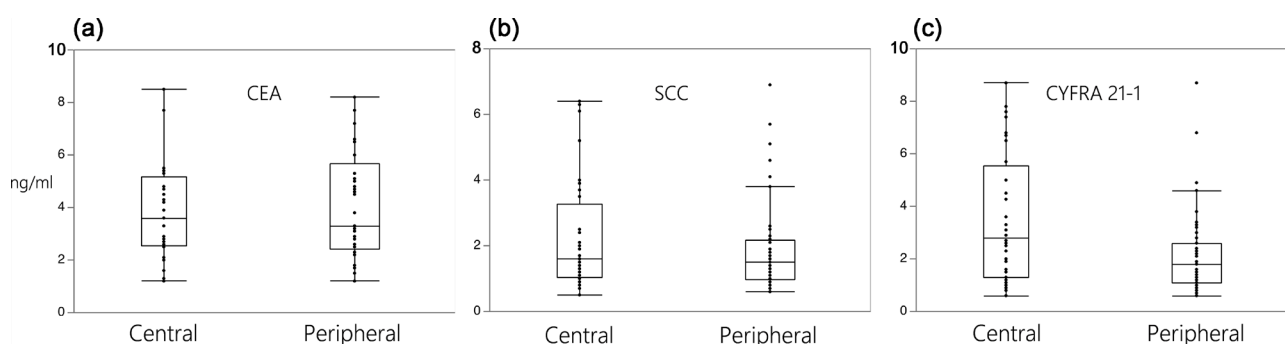
Figure 2. A box plot with a scatter diagram comparing the central and peripheral type based on CEA (a), SCC (b), and CYFRA 21-1 (c).

Table 2. Comparison between c-SQ and p-SQ.

		c-SQ	p-SQ	*p* Value
Age	<65	10	12	0.861
	≥65	30	33	
Gender	Male	37	39	0.378
	Female	3	6	
Smoking status	Current/former	36	42	0.577
	Never	4	3	
p-stage	I	18	31	0.026
	II-III	22	14	
pT status	pT1	15	23	0.207
	pT2-3	25	22	
pN status	pN0	26	36	0.120
	pN1-2	14	9	
IP	IP+	3	10	0.053
	IP−	37	35	
CEA	Normal	30	31	0.531
	High	10	14	
SCC	Normal	19	25	0.458
	High	21	20	
CYFRA 21-1	Normal	16	31	0.007
	High	24	14	

c-SQ: Central type squamous cell carcinoma; p-SQ: Peripheral type squamous cell carcinoma; IP: Interstitial pneumonia; CEA: Carcinoembryonic Antigen; SCC: Squamous Cell Carcinoma antigen; CYFRA 21-1: Cytokeratin-19 fragment.

4. Discussion

The SCC is a widely used tumor marker for NSCLC, especially for SQ. The prognosis of patients with squamous cell carcinomas originating from the head and neck, and esophagus had been shown to be associated with SCC [13] [14]. However, in manuscripts published in the 21st century, only a limited number of manuscripts report the prognostic significance of SCC in NSCLC [2] [4] [5] [6] [7] and the results were conflicting. Kinoshita *et al.* [2] showed that high SCC or vascular invasion were independent prognostic factors in lung SQ, and they proposed that the current stage IA SQ with high SCC or vascular invasion should be upgraded to stage IB. Yu *et al.* [4] found that the overall survival was significantly shorter in lung SQ patients with high SCC. On the other hand, Takeuchi *et al.* [5] concluded that preoperative SCC did not reflect the prognosis in lung SQ, although they found that the survival rate was higher in high SCC patients who became normal SCC following resection than in patients who remained high SCC. Vassilakopoulos *et al.* [6] failed to find the prognostic roles of

preoperative SCC, although they included not only SQ, but also other NSCLCs. Kulpa *et al.* [7] also revealed that SCC was not an independent prognostic factor in lung SQ patients. Our result showed preoperative SCC was related to 5-year survivors in lung SQ. These conflicting findings might be due to a small number of patients, and differences in cut-off values of each study. Further, there might be a possibility that the prognostic power of SCC is limited in lung SQ.

In contrast to SCC, several studies reported the prognostic value of CYFRA 21-1 in NSCLC [2] [3] [7] [8]. Although CYFRA 21-1 is generally known to be sensitive to SQ, there are only a limited number of previous studies that focused on SQ [7] [8]. Kulpa *et al.* [7] revealed that CYFRA 21-1 was an independent prognostic factor in the operable patients with lung SQ. Niklinski *et al.* [8] also obtained a relationship between CYFRA 21-1 and prognosis in patients with lung SQ. The present study also showed that preoperative CYFRA 21-1 was also related to 5-year survivors. Although the number of previous studies for CYFRA 21-1 focused on lung SQ is small, to our knowledge, there are no studies that failed to find the prognostic value of CYFRA 21-1. Our result also showed the possible utility of tumor marker combination with SCC and CYFRA 21-1. Kashiwabara *et al.* [15] also examined the utility of tumor marker combination and showed that the prognosis of the high levels of both SCC and CYFRA 21-1 group was significantly lower. However, they also found no prognostic differences between the high SCC/normal CYFRA 21-1 group and both normal group and between the normal SCC/high CYFRA group and both high groups [15]. They concluded that CYFRA 21-1, not SCC, relates to the prognosis [15]. Unfortunately, they did not show a prognostic significance of either SCC or CYFRA 21-1 alone. Furthermore, 63/120 their patients were non-surgery patients, and the prognosis was examined using the 2-year survival rates [15].

Based on tumor location, lung SQ can be classified into c-SQ and p-SQ [9] [15]. Not only tumor location, but also the clinicopathologic characteristics of these have been known to be different [9] [15]. Lin *et al.* [9] summarized the previous studies that investigated the clinicopathologic differences between c-SQ and p-SQ. They concluded that the patients with p-SQ were characterized by older age, less frequent lymph node metastasis, an earlier pathologic stage, good differentiation, less lymphovascular invasion, and less pleural invasion [9]. However, the differences in tumor markers between c-SQ and p-SQ have not been reported. Saijo *et al.* [15] compared the tumor markers between c-SQ and p-SQ and found that CEA, SCC, and neuron-specific enolase were not significantly different. Unfortunately, the differences in CYFRA 21-1 between c-SQ and p-SQ have not been investigated. Our result showed that high p-stage and CYFRA 21-1 were related to c-SQ. To our knowledge, this is the first report that showed differences in CYFRA 21-1 based on different tumor locations of lung SQ. The biological significance of this difference in CYFRA 21-1 between c-SQ and p-SQ is not clear and merits further investigation.

Our study had several limitations. It was a single-center, retrospective study

with relatively small sample size. Thus, conclusions from the present study may have a bias, indicating that studies using a larger population are needed.

5. Conclusion

We demonstrate that preoperative SCC and CYFRA 21-1 were related to 5-year survivors in patients with lung SQ. Therefore, both SCC and CYFRA 21-1 appeared to be useful prognostic markers for patients with lung SQ. Furthermore, CYFRA 21-1 was related to central type SQ.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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