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ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH

Clinical Significance of Serum Squamous Cell Carcinoma Antigen for Patients with Recurrent Esophageal Squamous Cell Carcinoma

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ABSTRACT

Background. Squamous cell carcinoma antigen (SCC-Ag) is a widely used tumor marker of SCC. However, the clinical significance of serum SCC-Ag levels in recurrent esophageal SCC (ESCC) remains unclear. This study aimed to investigate the clinical relevance of serum SCC-Ag levels in patients with recurrent ESCC after surgery.

Methods. This study retrospectively analyzed 208 patients who experienced recurrence after curative resection for ESCC. Serum SCC-Ag levels at the time of recurrence were collected from the patients' records. The patients were classified into tertiles based on the serum SCC-Ag values (low, middle, and high), and the clinical characteristics and outcomes were compared among the groups.

Results. Significant differences in sex (p = 0.001), pathologic T (p = 0.034), and N stages of primary cancer (p = 0.015) were observed among the groups. Although the recurrence patterns did not differ significantly, a high SCC-Ag was significantly associated with multiple recurrences (p = 0.019). The high-SCC-Ag group patients demonstrated a shorter time to recurrence than the other groups (p = 0.044). The SCC-Ag levels were significantly associated with overall survival after recurrence (p = 0.036). Multivariate analysis showed that serum SCC-Ag value at recurrence was an independent poor prognosticator (p = 0.031).

Conclusion. Elevated serum SCC-Ag levels at recurrence were significantly associated with a reduced time to recurrence, multiple recurrences, and a poor prognosis after recurrence. An alternative to the current standard treatment is required to improve the outcome for patients with high serum SCC-Ag levels at recurrence.

Esophageal squamous cell carcinoma (ESCC) is the most common histologic subtype of esophageal cancer in Asian countries.[1–3] Despite the recent advances in multimodal treatment for esophageal cancer, recurrence after curative surgery often is observed.[2] Limited treatment methods exist for recurrent ESCC (rESCC), and survival after recurrence is unsatisfactory, with a reported survival time of 5 to 10 months.[4–7] Survival estimates are critical for both clinicians and patients when deciding the treatment strategy. However, to date, prognosticators for patients with rESCC remain unknown.

Serum squamous cell carcinoma antigen (SCC-Ag) has been primarily identified in patients with uterine cervical SCC, and increased serum SCC-Ag levels often are observed in patients with SCC regardless of cancer origin.[8] In the treatment of ESCC, serum SCC-Ag levels are used for various purposes, such as preoperative assessment, evaluation of therapeutic effect, and follow-up evaluation after esophagectomy. Previously, pretherapeutic serum SCC-Ag levels were reported to be useful for therapeutic

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response prediction in locally advanced ESCC.[9,10] Furthermore, preoperative serum SCC-Ag levels were found to be a useful predictive marker of recurrence after esophagectomy.[11] However, few reports have evaluated the significance of serum SCC-Ag levels in rESCC.[12]

We hypothesized that serum SCC-Ag levels at the time of recurrence can be predictive of prognosis after recurrence. This study aimed to investigate the relationship between serum SCC-Ag levels in rESCC and recurrent tumor status, as well as the prognosis after recurrence.

PATIENTS AND METHODS

Patients

We retrospectively reviewed 1067 patients who underwent esophagectomy for ESCC at Cancer Institute Hospital of Japanese Foundation for Cancer Research (JFCR) from 2005 to 2017. Among 948 patients who underwent curative resection, 271 (28.5 %) experienced recurrence during the follow-up period. Patients with concomitant SCC of other organs and those without sufficient data for analysis were excluded from the analysis. A total of 208 patients were eligible for the current study (Fig. S1). The study protocol was approved by the Institutional Review Board of the JFCR.

Treatment, Surgery, and Postoperative Follow-up Evaluation for ESCC

Principally, patients were treated according to the Japan Esophageal Society guidelines,[6,7] with surgery only for cT1N0, neoadjuvant chemotherapy followed by surgery for T1N1–3 or T2–4a any N, definitive chemoradiotherapy for T4b tumor or refusal of surgery irrespective of the cancer stage, and salvage surgery for the failure of chemoradiotherapy. Our standard curative surgical procedure was esophagectomy with en bloc lymph node dissection using a cervico-thoraco-abdominal approach. Thoracic and abdominal procedures were performed using either an open or a minimally invasive approach. Postoperative chemotherapy was considered for T1N1-3 or T2-4a any N if surgery was preceding. Neoadjuvant chemotherapy was introduced in 2009 based on the results of the randomized JCOG 9907 trial.[13]

After surgery, the patients were followed up every 4 months in the first year, then every 6 months after that. Physical examination, blood test including SCC-Ag, and computed tomography (CT) were performed at each visit. When any suspicious findings of recurrence were observed, 18F-fluorodeoxyglucose-positron emission tomography combined with CT (FDG-PET/CT) also was used for the diagnosis of rESCC. Upper gastrointestinal endoscopy was scheduled once a year.

Treatment for rESCC

Because the treatment strategy for rESCC has not been fully established to date, it was determined by the multidisciplinary tumor board based on the disease status and the patient's general condition, according to the guidelines.[6,7] The treatment for rESCC is summarized in Table S1. In general, patients with a diagnosis of multiregional, disseminated, or organ recurrences were treated with chemotherapy that included cisplatin, fluorouracil, docetaxel, and paclitaxel, whereas patients with recurrence in a single regional lymph node usually underwent definitive chemoradiotherapy for cure.

We performed surgery when the recurrent tumor was solitary, localized, and considered to be completely resectable, especially for patients with lymph node or lung recurrence and a relatively long disease-free interval. Also, diagnostic resection was sometimes performed when a solitary lung or liver tumor was detected. In this study, radical therapy was defined as a treatment aiming for a cure, such as surgery and definitive chemoradiotherapy, whereas palliative therapy was defined as treatment aiming for palliation, including chemotherapy, radiotherapy, and palliative chemoradiotherapy.

Definition

The pathologic tumor stage was classified based on the eighth edition the Union for International Cancer Control.[14] Tumor differentiation grade of ESCC in the resected specimens was assessed using the World Health Organization classification.[15] The performance status of the patients at the diagnosis of rESCC was defined by Eastern Cooperative Oncology Group performance status (ECOG-PS).[16] In this study, serum SCC-Ag levels were measured under a chemiluminescent microparticle immunoassay (Abbott Japan Co. Ltd, Tokyo, Japan), and serum SCC-Ag levels at the time of rESCC diagnosis were used for the analysis.

Statistical Analysis

All data are presented as median (range) or number (%). From the distribution of serum SCC-Ag levels, we classified patients into tertiles. Statistical differences in clinicopathologic factors between the groups were analyzed using Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables. Time to recurrence (TTR) was evaluated from surgery to recurrence or to the last follow-up visit, and overall survival after

recurrence (rOS) was evaluated from recurrence to death or the last follow-up visit.

Progression-free survival (PFS) also was evaluated from recurrence to any progression or death or to the last follow-up visit. The survival was estimated with the Kaplan-Meier method, and the statistical difference was evaluated using the log-rank test.

To assess the relationship between serum SCC-Ag levels and rOS, uni- and multivariate analyses were performed using Cox's proportional hazards model for the computation of hazard ratios (HRs) and 95 % confidence intervals (CIs). A p value lower than 0.05 was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), a graphic user interface for R software (R Foundation for Statistical Computing, Vienna, Austria) that incorporates frequently used biostatistical functions.[17]

RESULTS

Distribution of Serum SCC-Ag Levels and Patient Characteristics

The distribution of serum SCC-Ag levels in all eligible patients is described in Fig. S2. As mentioned, we classified patients into three groups according to the percentiles: first tertile (low group: 0.4–1.2 ng/mL; n = 69), second tertile (middle group: 1.3–2.2 ng/mL; n = 69), and third tertile (high group: 2.3–88.9 ng/mL; n = 70).

The pathologic findings of primary ESCC and clinical characteristics at recurrence among the three groups are shown in Table 1. Significant differences were observed in sex (p = 0.001), pathologic T stage (p = 0.034), N stages of primary cancer (p = 0.015), and number of recurrent lesions (p = 0.019). In contrast, no differences were observed in the tumor differentiation grade, treatment strategy for primary cancer, age at the diagnosis of rESCC, ECOG-PS at the diagnosis of rESCC, or recurrence pattern.

Time to Recurrence and Survival After Recurrence

The Kaplan-Meier curves comparing TTR after esophagectomy among the groups are shown in Fig. 1. The patients in the high-SCC-Ag group were observed to experience recurrences significantly earlier than the others, with pretherapeutic SCC-Ag levels found to be significantly associated with TTR (p = 0.044). The HR of the high-SCC-Ag group was 1.43 (95 % CI, 1.03–2.01) compared with the low group (data not shown) in the univariate analysis.

The Kaplan-Meier curves comparing rOS among the groups are shown in Fig. 2. The patients of the high-SCC-Ag group had worse rOS than the others (p = 0.036). The HR of the high-SCC-Ag group was 1.63 (95 % CI, 1.12–2.38) compared with the low SCC-Ag group (data not shown). Among the 66 patients with palliative chemotherapy or chemoradiotherapy, the patients in the high-SCC-Ag group experienced worse PFS after recurrence, although the difference did not reach statistical significance (Fig. S3; p = 0.069).

Factors Influencing Overall Survival After Recurrence and Clinical Significance of Serum SCC-Ag Levels

The univariate analysis for the factors influencing rOS is shown in Table 2. Furthermore, we performed multivariable analysis for rOS with adjustment for clinicopathologic variables at the diagnosis of rESCC. The independent variables influencing rOS were male sex (HR, 2.05; 95 % CI, 1.34–3.15), pathologic T3 or T4 (HR, 1.86; 95 % CI, 1.33–2.59), ECOG-PS of 1 or higher (HR, 2.89; 95 % CI, 2.06–4.05), serum SCC-Ag level (HR, 1.03; 95 % CI, 1.00–1.06), and multiple recurrence (HR, 1.89; 95 % CI, 1.28–2.81).

DISCUSSION

This study investigated the clinical significance of serum SCC-Ag levels at the time rESCC was diagnosed in terms of the recurrent tumor's status and the prognosis after recurrence. We showed that elevated serum SCC-Ag levels at recurrence were associated with advanced primary cancers, multiple recurrences, and a short TTR. Moreover, a high SCC-Ag level was found to be an independent factor of poor prognosis after the diagnosis of recurrence.

Although several serum tumor markers for patients with ESCC are available for clinical use, including carcinoembryonic antigen (CEA), SCC-Ag, cytokeratin fragment (CYFRA) 21-1, and anti-P53 antibody, little is known about the efficacy of these markers in treating rESCC. Kawaguchi et al.[18] reported that an increase in CYFRA 21-1 was found in 76.9 % of patients with rESCC, and that the increase was evident before clinical detection of the recurrence. However, the use of CYFRA 21-1 during the follow-up evaluation has not been approved by the health insurance system in Japan, and we do not have enough data on CYFRA 21-1 for patients with rESCC. Toh et al.[12] reported that an abnormal increase in tumor markers, including CEA and SCC-Ag, at the diagnosis of rESCC was an unfavorable prognostic factor.

TABLE 1 Patient characteristics

Variables	Low (n = 69) n (%)	Middle (n = 69) n (%)	High (n = 70) n (%)	p Value
Sex				0.001[a]
Male	47 (68.1)	64 (92.8)	56 (80.0)	
Female	22 (31.9)	5 (7.2)	14 (20.0)	
pT stage of primary cancer				0.034[a]
1	16 (22.2)	18 (26.1)	9 (12.9)	
2	16 (23.2)	22 (31.9)	13 (18.6)	
3–4	37 (53.6)	29 (42.0)	48 (68.6)	
pN stage of primary cancer				0.015[a]
0	11 (15.9)	21 (30.4)	10 (14.3)	
1	31 (44.9)	15 (21.7)	22 (31.4)	
2–3	27 (39.1)	33 (47.8)	38 (54.3)	
pM stage of primary cancer				0.17
0	59 (85.5)	63 (91.3)	56 (80.0)	
1	10 (14.5)	6 (8.7)	14 (20.0)	
Tumor differentiation grade				0.454
G1	10 (14.7)	10 (15.2)	17 (25.0)	
G2	45 (66.2)	46 (69.7)	39 (57.4)	
G3	13 (19.1)	10 (15.2)	12 (17.6)	
GX	1	3	2	
Treatment strategy for primary cancer				0.819
Preoperative therapy + surgery	44 (63.8)	41 (59.4)	43 (61.4)	
Surgery + adjuvant chemotherapy	10 (14.5)	8 (11.6)	7 (10.0)	
Surgery alone	15 (21.7)	20 (29.0)	20 (28.6)	
Median age at recurrence: years (range)	64.0 (45–84)	64.0 (44–79)	64.0 (48–84)	0.688
ECOG-PS at recurrence				0.689
0	45 (66.2)	43 (62.3)	42 (60.9)	
1	17 (25.0)	16 (23.2)	19 (27.5)	
$\geq$ 2	6 (8.8)	10 (14.4)	8 (11.5)	
Recurrence pattern				0.771
Locoregional	22 (31.9)	22 (31.9)	19 (27.1)	
Distant	47 (68.1)	47 (68.1)	51 (72.9)	
No. of recurrent lesions				0.019[a]
Solitary	30 (43.5)	20 (29.0)	15 (21.4)	
Multiple	39 (56.5)	49 (71.0)	55 (78.6)	
Treatment for recurrence				0.219
Radical treatment	34 (49.3)	26 (37.7)	21 (30.0)	
Surgery	12 (17.4)	9 (13.0)	6 (8.6)	
Chemoradiotherapy	22 (31.9)	17 (24.6)	15 (21.4)	
Palliative treatment	25 (36.2)	32 (46.4)	34 (48.6)	
Chemoradiotherapy	5 (7.2)	0 (0)	2 (2.9)	
Chemotherapy	16 (23.3)	22 (31.9)	24 (34.3)	
Radiotherapy	4 (5.8)	10 (14.4)	8 (11.5)	
Best supportive care	10 (14.5)	11 (15.9)	15 (21.4)	

[a] $p < 0.05$

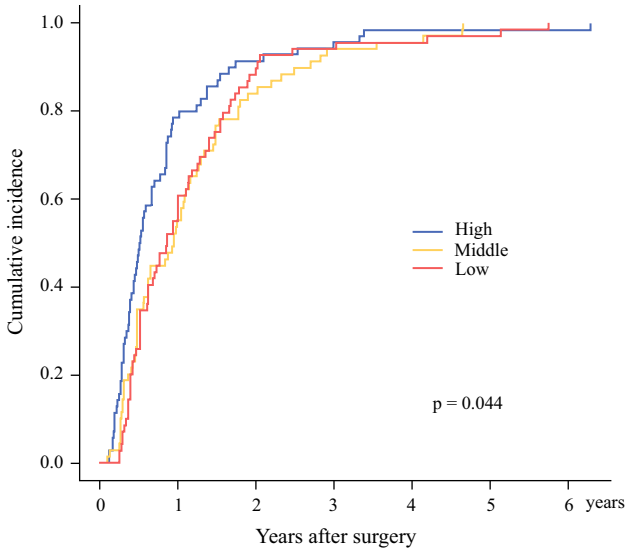

FIG. 1 Time to recurrence and serum squamous cell carcinoma antigen (SCC-Ag) levels at recurrence.

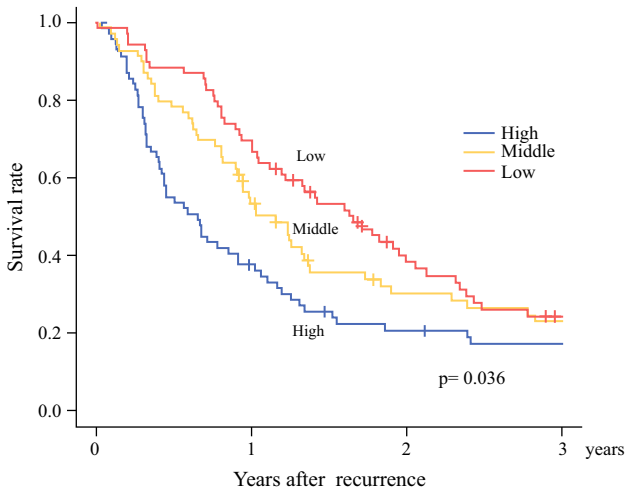

FIG. 2 Overall survival after recurrence and serum squamous cell carcinoma antigen (SCC-Ag) levels at recurrence.

The standard upper limit of SCC-Ag is 1.5 ng/ml, whereas the cutoff value for unfavorable prognosis in the aforementioned study was 2 ng/mL.[12] In the current study, the third tertile, which demonstrated significantly poor survival after recurrence, had an SCC-Ag of 2.3 ng/ml or higher. The optimal cutoff value for predicting a patients' prognosis with rESCC should be determined using a multi-institutional, large-scale cohort. Nevertheless, this study showed that the serum SCC-Ag level is one of the independent prognosticators when analyzed as a continuous variable.

Previously, it was suggested that SCC-Ag messenger ribonucleic acid (mRNA) detection is a useful predictive factor for hematogenous or local recurrence in ESCC patients who undergo curative resection.[19] Also, the high serum SCC-Ag group was associated with advanced primary cancers and multiple recurrences in this study, and thus the SCC-Ag values may relate to tumor burden. Meanwhile, as shown in the multivariate analysis, a higher serum SCC-Ag level was one of the prognostic factors independent of the number of recurrent lesions. Previous studies have suggested that SCC-Ag 1, one of the two SCC-Ag isoforms, can protect cancer cells from apoptosis induced by irradiation, medicine, cytokine, and effector cells.[20–22] Also, it was reported that high serum SCC-Ag levels were associated with high expression of epidermal growth factor and high cell proliferation in uterine SCC.[23] Although the mechanisms remain unclear, high serum SCC-Ag levels may reflect the aggressive biologic behavior.

Previous studies have suggested that multimodal therapy for rESCC could prolong survival.[4,5,24,25] However, whether the curative-intent treatment may be administered depends on the recurrence pattern and the patient's general condition. The majority of rESCC patients in the high-SCC-Ag group could not undergo radical treatment in this study.

Currently, chemotherapy with cisplatin plus fluorouracil is the standard treatment for rESCC as palliative therapy,[6,7] and the survival remains unsatisfactory. Alternative regimens with more powerful antitumor activity such as docetaxel, cisplatin, and fluorouracil, or a regimen containing immune checkpoint inhibitors are expected to improve the outcomes.[26–29]

This study had some limitations. First, this study was a retrospective observational investigation conducted in a single institution with a limited number of patients. Second, the study period was relatively long, and the change in treatment strategy may have affected the results. Therefore, a larger-scale, prospective study is necessary to validate the clinical significance of SCC-Ag in rESCC. However, the measurement of SCC-Ag is a simple test and reproducible that can provide useful information about the risk stratification of prognosis.

CONCLUSIONS

The patients with high serum SCC-Ag levels at recurrence had multiple recurrences, a short TTR, and a poor prognosis after diagnosis of recurrence. An alternative to the current standard treatment is required to improve the outcome for patients with high serum SCC-Ag levels at recurrence.

DISCLOSURE There are no conflicts of interest.

TABLE 2 Cox's proportional hazard regression analysis of prognosis after recurrence

Variables	Reference	Univariate			Multivariate		
		HR	95 % CI	*p* Value	HR	95 % CI	*p* Value
Sex							
Male	Female	1.43	0.96–2.14	0.081	2.05	1.34–3.15	< 0.001[a]
pT of primary cancer							
pT ≥3	pT < 3	1.64	1.20–2.24	0.002[a]	1.86	1.33–2.59	< 0.001[a]
pN of primary cancer							
pN1	pN0	0.97	0.62–1.52	0.905	0.99	0.62–1.58	0.958
pN2-3	pN0	1.24	0.81–1.88	0.323	0.89	0.57–1.38	0.599
pM of primary cancer							
pM1	pM0	1.30	0.87–1.96	0.202	1.20	0.78–1.86	0.409
Treatment strategy for primary cancer							
Surgery + adjuvant chemotherapy	Surgery alone	1.14	0.68–1.92	0.619	0.79	0.44–1.44	0.442
Preoperative therapy + surgery	Surgery alone	1.00	0.70–1.42	0.992	0.81	0.56–1.18	0.276
Age at recurrence	Per 1 year	1.01	0.99–1.03	0.31	1.00	0.98–1.02	0.863
ECOG-PS at recurrence							
≥1	0	2.56	1.87–3.50	< 0.001[a]	2.89	2.06–4.05	< 0.001[a]
SCC-Ag at recurrence	Per 1 ng/mL	1.05	1.02–1.07	< 0.001[a]	1.03	1.00–1.06	0.031[a]
No. of recurrent lesions							
Multiple	Solitary	1.95	1.39–2.73	< 0.001[a]	1.89	1.28–2.81	0.001[a]
Recurrent pattern							
Distant	Locoregional	1.87	1.32–2.63	< 0.001[a]	1.34	0.91–1.98	0.144

[a] $p < 0.05$

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