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ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH AND BIOMARKERS

Clinical Significance of Pretherapeutic Serum Squamous Cell Carcinoma Antigen Level in Patients with Neoadjuvant Chemotherapy for Esophageal Squamous Cell Carcinoma

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ABSTRACT

Background. Although squamous cell carcinoma antigen (SCC-Ag) is a tumor marker widely used to estimate the progression of esophageal SCC (ESCC), only a few studies have focused on the relationship between serum SCC-Ag levels and the therapeutic effect of neoadjuvant chemotherapy (NAC).

Objective. This study aimed to elucidate the clinical significance of pretherapeutic serum SCC-Ag levels in patients who underwent NAC followed by esophagectomy.

Methods. Data of 453 patients who underwent NAC followed by esophagectomy were collected from the esophageal cancer database of two high-volume Japanese centers. Serum SCC-Ag levels were measured prior to NAC, and the pathological therapeutic effect of NAC and patient survival were evaluated. Patients were classified according to the tertiles of the serum SCC-Ag value (low, middle, and high groups), and the outcomes among the groups were compared.

Results. The levels of serum SCC-Ag were significantly associated with tumor stage ($p < 0.01$). With regard to the pathological therapeutic effect, the levels of serum SCC-Ag were negatively correlated with the therapeutic effect ($p = 0.02$). Moreover, increased levels of serum SCC-Ag negatively influenced relapse-free survival ($p < 0.01$). Multivariate analyses revealed the 'high' group as the independent factor for both the unfavorable therapeutic effect ($p = 0.01$) and the increased risk of disease recurrence ($p < 0.01$) when compared with the 'low' group.

Conclusion. Elevated levels of pretherapeutic serum SCC-Ag are significantly associated with advanced tumor stage, poor response to NAC, and increased risk of disease recurrence.

Esophageal squamous cell carcinoma (ESCC) is a globally predominant histological subtype of esophageal cancer, particularly in Asian and African countries.[1,2] Despite the gradual improvement of its prognosis with recent advances in multidisciplinary treatment,[2] it remains unsatisfactory. Currently, neoadjuvant therapy with chemotherapy or chemoradiotherapy has supplemented surgery as the standard treatment of locally advanced esophageal cancer. In Japan, the standard treatment for locally advanced resectable ESCC is neoadjuvant chemotherapy (NAC) followed by esophagectomy, based on the results of the JCOG9907 study.[3–5] Although NAC is

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expected to improve curative resection rates and eliminate micrometastases, not a few patients experience a poor response to NAC and disease recurrence is often observed.

Serum SCC antigen (SCC-Ag) was primarily identified in patients with uterine cervical SCC, and increased serum SCC antigen levels are often observed in patients with SCC, regardless of cancer origin.[6] In clinical practice, measurement of serum SCC-Ag levels is widely practiced, and some studies have suggested its clinical advantages in predicting the prognosis of patients with ESCC.[7–9] However, in the era of neoadjuvant treatment, only a few studies have focused on the relationship between pretherapeutic serum SCC-Ag and the response to NAC.[9]

This study aimed to elucidate the significance of pretherapeutic serum SCC-Ag levels in predicting the therapeutic effect of NAC, as well as disease recurrence, utilizing the database of two high-volume Japanese centers. The data were integrated into the project to evaluate the residual disease distribution and recurrence patterns in patients with ESCC receiving NAC.

PATIENTS AND METHODS

Data Collection

This study retrospectively examined 453 patients with ESCC who underwent transthoracic esophagectomy following NAC at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (JFCR) and Keio University Hospital, Japan, between 2005 and 2016. ESCC patients with clinical stage I, II, III (excluding cT1N0 and cT4b), and IV disease due to supraclavicular lymph node metastasis who underwent NAC followed by esophagectomy were included in this analysis, while patients with R2 resection and those with missing data were excluded. Serum SCC-Ag levels were assessed at the time of the initial visit to outpatient clinics before NAC and then the visit after NAC. In both centers, serum SCC-Ag levels were measured independently, in the same manner, under a chemiluminescent microparticle immunoassay (Abbott Japan Co. Ltd, Tokyo, Japan). The study protocol was approved by the Institutional Review Board of the JFCR and the Keio University School of Medicine.

Definition

Tumor stage classification was based on the 8th edition of the Union for International Cancer Control.[10] Prior to treatment, the clinical stage was determined by each Multidisciplinary Tumor Board in accordance with the findings of the esophagogastroduodenoscopy, computed tomography (CT), and/or positron emission tomography. After surgery, the resected specimens were examined and the pathological stage was determined. The pathological therapeutic effect of NAC was classified into five categories according to the Japanese Classification of Esophageal Cancer:[11,12] grade 0, no recognizable cytological or histological therapeutic effect; grade 1a, viable cancer cells accounting for two-thirds or more of tumor tissue; grade 1b, viable cancer cells accounting for one-third or more, but less than two-thirds, of tumor tissue; grade 2, viable cancer cells accounting for less than one-third of tumor tissue; and grade 3, no viable cancer cells.

Neoadjuvant Treatment

Patients in both institutions were treated according to the Japan Esophageal Society guidelines.[3,4] NAC was performed for patients with T1N1-3 or T2-4a (any N) disease. The standard NAC regimen was cisplatin and 5-fluorouracil (CF) twice every 3 weeks, as similarly used in the JCOG9907 study.[3] A cisplatin 80 mg/m^2 dose was administered by intravenous drip infusion for 2 h on day 1, and 5-fluorouracil was administered at a dose of 800 mg/m^2/day by continuous intravenous drip infusion from days 1 to 5. Meanwhile, for patients with either borderline resectable disease or multiple lymph node metastases, an alternative regimen of docetaxel, cisplatin, and 5-fluorouracil (DCF) with strong antitumor activity was considered. In this regimen, which was the same as used in the COSMOS trial,[13,14] chemotherapy consisted of a 1-h intravenous drip infusion of docetaxel 70 mg/m^2 and a 2-h infusion of cisplatin 70 mg/m^2 on day 1, and a continuous infusion of 5-fluorouracil 750 mg/m^2/day from days 1 to 5. This regimen was repeated every 3 weeks. The appropriate regimen was deliberated by the Multidisciplinary Tumor Board of each institute.

Surgery and Postoperative Follow-Up

Our standard, curative surgical procedure involved esophagectomy along with *en bloc* lymph node dissection using a cervico-thoraco-abdominal approach. Thoracic and abdominal procedures were performed using an open or minimally invasive approach. A gastric conduit was conveyed through the retrosternal or posterior mediastinal route, and esophagogastric anastomosis was performed at the neck. Reconstruction using a pedicled ileocolic graft was performed in the absence of gastric conduit due to synchronous gastric cancer or a history of gastrectomy. With regard to postoperative follow-up, patients were followed up at least every 6 months, for 5 years postoperatively. Physical examination and CT were performed every visit. Moreover, upper endoscopy was

performed at least annually. Postoperative adjuvant chemotherapy after NAC plus esophagectomy was not conducted.

Statistical Analysis

All data are presented as median (range) or number (%). From the distribution of pretherapeutic serum SCC-Ag levels, we classified patients into tertiles, and further analyses followed. Statistical comparisons among the groups were executed using the Kruskal–Wallis test or Fisher's exact test as appropriate. The survival analysis for recurrence was carried out using the Kaplan–Meier method and the log-rank test. Relapse-free survival (RFS) was evaluated from either surgery to recurrence or last follow-up. To assess the relationship between serum SCC-Ag levels and the pathological therapeutic effect, as well as disease recurrence, univariate and multivariate analyses were performed. The former was evaluated by logistic regression analysis, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The latter was analyzed using a Cox proportional hazards regression model for the computation of hazard ratios (HRs) and 95% CIs. In multivariate models, we adjusted for pretherapeutic confounders. To evaluate the difference in serum SCC-Ag levels between the period before and after NAC, the Wilcoxon signed rank test was used. A p value < 0.05 was considered statistically significant. All statistical analyses were performed utilizing the SPSS software package version 25.0 (IBM SPSS, Inc., Armonk, NY, USA).

RESULTS

Distribution of Pretherapeutic Serum Squamous Cell Carcinoma Antigen (SCC-Ag) LevelS and Clinicopathological Factors

The distribution of pretherapeutic serum SCC-Ag levels in all patients is described in Electronic Supplementary Fig. 1. As mentioned, we classified patients into three groups according to the percentiles: first tertile (low group, 0.2–0.9 ng/mL; n = 176); second tertile (middle group, 1.0–1.5 ng/mL; n = 149); and third tertile (high group, 1.6–8.3 ng/mL; n = 128). Upon comparing the clinicopathological factors among groups (Table 1), significant differences in sex and pretherapeutic clinical T stage were observed ($p = 0.01$ and 0.04, respectively). Moreover, significant differences were noted in pathological T stage and the curative resection rate among the groups ($p < 0.01$ and = 0.03, respectively). Together, patients with higher serum SCC-Ag levels had more advanced cancers before and after NAC, despite not having substantial differences in other factors.

Pretherapeutic Serum SCC-Ag Levels and Pathological Therapeutic Effect

When the pathological therapeutic effect was compared among the groups, a significant difference was observed, as shown in Fig. 1 ($p = 0.02$); the good responders with grade 2 or higher were significantly less frequent in the high group than in the low group. The ORs for achieving an effect of grade 2 or higher in univariate analyses were 0.71 ($p = 0.24$; 95% CI 0.40–1.26) in the middle group and 0.40 ($p = 0.01$; 95% CI 0.20–0.81) in the high group when compared with the low group. In a multivariate analysis to adjust for pretherapeutic confounders (Table 2), the high group was independently associated with a decreased incidence of grade 2 or higher effect ($p = 0.01$; OR 0.41, 95% CI 0.20–0.83).

Pretherapeutic Serum SCC-Ag Levels and Relapse-Free Survival

The Kaplan–Meier curves comparing RFS among the groups are shown in Fig. 2. The levels of pretherapeutic SCC-Ag were significantly associated with RFS ($p < 0.01$). The HRs calculated in univariate analyses were 1.31 ($p = 0.15$; 95% CI 0.91–1.88) in the middle group and 2.01 ($p < 0.01$; 95% CI 1.41–2.85) in the high group when compared with the low group. Multivariate analysis indicated that the high group was independently associated with disease recurrence ($p < 0.01$; HR 1.79, 95% CI 1.25–2.56) (Table 3); however, no significant differences were observed in the recurrence pattern among the groups, especially in the incidence of distant metastasis ($p = 0.64$) (Fig. 3).

Change in Serum SCC-Ag Levels and Pathological Therapeutic Effect

We examined the relationships between the change in serum SCC-Ag levels before and after NAC and pathological therapeutic effect; however, there was no significant decrease in serum SCC-Ag levels after NAC, even in patients with a good response of grade 2 or higher (Electronic Supplementary Fig. 2; $p = 0.62$).

DISCUSSION

In this study, we explored the relationship between pretherapeutic serum SCC-Ag levels and the therapeutic effect of NAC, as well as disease recurrence, in 453 ESCC

TABLE 1 Patient clinicopathological factors

Variables	Low [$n = 176$]	Middle [$n = 149$]	High [$n = 128$]	p value
Sex				
Male	131 (74.4)	128 (85.9)	109 (85.2)	0.01*
Female	45 (25.6)	21 (14.1)	19 (14.8)	
Age, years	62 (32–78)	64 (40–79)	64 (34–78)	0.20
Location				0.71
Upper	24 (13.6)	22 (14.8	16 (12.5)	
Middle	90 (51.1)	79 (53.0)	60 (46.9)	
Lower	62 (35.2)	48 (32.2)	52 (40.6)	
cT (UICC)				0.04*
T1	26 (14.8)	17 (11.4)	8 (6.3)	
T2	57 (32.4)	48 (32.2)	29 (22.7)	
T3	91 (51.7)	81 (54.4)	89 (69.5)	
T4	2 (1.1)	3 (2.0)	2 (1.6)	
cN (UICC)				0.25
N0	57 (32.4)	43 (28.9)	31 (24.2)	
N1	94 (53.4)	79 (53.0)	69 (53.9)	
N2	23 (13.1)	25 (16.8)	28 (21.9)	
N3	2 (1.1)	2 (1.3)	(0.0)	
cM (UICC)				0.44
M0	161 (91.5)	130 (87.2)	116 (90.6)	
M1	15 (8.5)	19 (12.8)	12 (9.4)	
NAC regimen				0.13
CF	170 (96.6)	137 (91.9)	118 (92.2)	
DCF	6 (3.4)	12 (8.1)	10 (7.8)	
pT (UICC)				< 0.01*
T0	11 (6.3	6 (4.0)	2 (1.6)	
T1	66 (37.5)	49 (32.9)	24 (18.8)	
T2	38 (21.6)	24 (16.1)	17 (13.3)	
T3	60 (34.1)	68 (45.6)	77 (60.2)	
T4	1 (0.6)	2 (1.3)	8 (6.3)	
pN (UICC)				0.11
N0	69 (39.2)	54 (36.2)	45 (35.2)	
N1	65 (36.9)	52 (34.9)	32 (25.0)	
N2	29 (16.5)	31 (20.8)	35 (27.3)	
N3	13 (7.4)	12 (8.1)	16 (12.5)	
pM (UICC)				0.44
M0	161 (91.5)	130 (87.2)	116 (90.6)	
M1	15 (8.5)	19 (12.8)	12 (9.4)	
Resection margin				0.03*
R0	170 (96.6)	145 (97.3)	116 (90.6)	
R1	6 (3.4)	4 (2.7)	12 (9.4)	

Data are expressed as median (range) or n (%)

UICC Union for International Cancer Control, *NAC* neoadjuvant chemotherapy, *CF* cisplatin and 5-fluorouracil, *DCF* docetaxel, cisplatin, and 5-fluorouracil

*$p < 0.05$

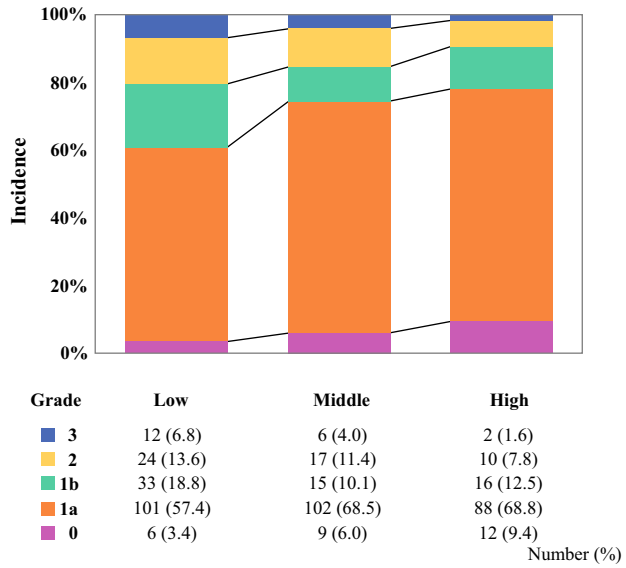

FIG. 1 Pretherapeutic serum squamous cell carcinoma antigen levels and pathological therapeutic effect

patients from two high-volume Japanese centers. The results of this study revealed that patients with higher pretherapeutic serum SCC-Ag levels had more advanced cancers before and after NAC. Furthermore, high SCC-Ag was associated with poor response to NAC as well as poor RFS. However, there was no significant decrease in serum SCC-Ag levels after NAC, even in patients with a good response. These findings suggest that high pretherapeutic serum SCC-Ag levels may reflect aggressive biological behavior of ESCC.

SCC-Ag was discovered primarily as a tumor marker of uterine cervical SCC. The increased serum SCC antigen levels were observed not only in benign diseases, including pulmonary and skin diseases, but also in SCC of the head and neck, esophagus, skin, lung, urothelium, anal canal, and vulva.[6] Despite the fact that SCC-Ag is produced in normal epithelium and epithelial tissues, there is a quantitative abnormality of this antigen in patients with SCC.[15] Thus far, several studies have suggested that serum SCC-Ag levels were predictive for advanced tumor stage, recurrence, and survival of patients with ESCC.[7–9] We also demonstrated that serum levels of SCC-Ag were associated with tumor stage and recurrence. Furthermore, we demonstrated that the pretherapeutic serum SCC-Ag levels were predictive of the sensitivity to NAC.

Since higher serum SCC-Ag levels were significantly associated with advanced T stage and disease recurrence, the tumor burden might affect treatment response and recurrence. However, among patients with T stage 3–4 disease, the higher serum SCC-Ag levels were significantly associated with a decreased incidence of grade 2 or higher

TABLE 2 Multivariate analysis of pretherapeutic factors for achieving good therapeutic effect

Variables	OR (95% CI)	*p* value
Sex		
Male	Reference	–
Female	1.87 (1.0–3.46)	0.04*
Age	1.01 (0.97–1.04)	0.78
SCC		
Low	Reference	–
Middle	0.71 (0.39–1.30)	0.27
High	0.41 (0.20–0.83)	0.01*
Location		
Upper	Reference	–
Middle	0.84 (0.38–1.85)	0.66
Lower	0.81 (0.35–1.87)	0.61
cT (UICC)		
T1-2	Reference	–
T3-4	0.77 (0.45–1.32)	0.34
cN (UICC)		
N0	Reference	–
N1-3	1.53 (0.83–2.82)	0.18
cM (UICC)		
M0	Reference	–
M1	0.29 (0.04–2.29)	0.24
NAC regimen		
CF	Reference	–
DCF	2.60 (1.04–6.50)	0.04*

OR odds ratio, *CI* confidence interval, *SCC* squamous cell carcinoma, *UICC* Union for International Cancer Control, *NAC* neoadjuvant chemotherapy, *CF* cisplatin and 5-fluorouracil, *DCF* docetaxel, cisplatin, and 5-fluorouracil

*$p < 0.05$

effect ($p = 0.01$) as well as disease recurrence ($p = 0.02$). In addition, as shown in multivariate analysis, a higher serum SCC-Ag level was an independent prognostic factor to clinical T stage.

With regard to the biological function of SCC-Ag, literature reported that SCC-Ag 1, one of the two isoforms of SCC-Ag (SCC-Ag 1 and SCC-Ag 2), prevented stress-induced cell death in SCC.[16–18] Although the mechanisms remain uncertain, these results suggest that SCC-Ag 1 may protect cancer cells from apoptosis that was induced by noxious stimuli such as radiation, drug, cytokine, and effector cell.[16–19] Such an activity of SCC-Ag 1 may influence the resistance to NAC in ESCC.

Some authors reported the relationships between tumor markers and the therapeutic effect of NAC in ESCC. It was reported that cytokeratin 19 fragment antigen 21–1 (CYFRA21-1) and carcinoembryonic antigen (CEA) are

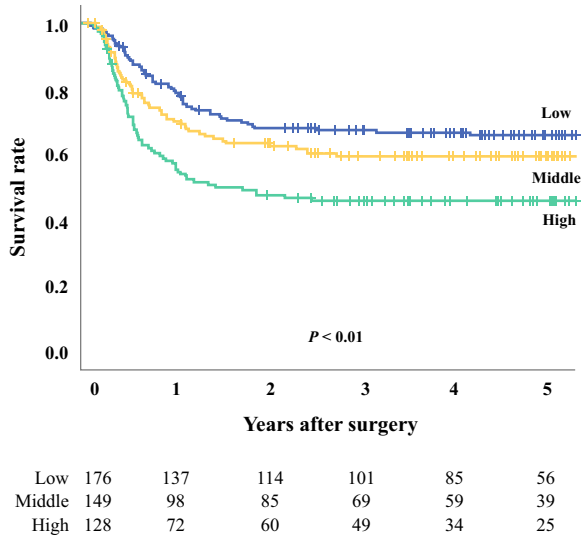

FIG. 2 Pretherapeutic serum squamous cell carcinoma antigen levels and relapse-free survival

useful in predicting the sensitivity to chemoradiotherapy in patients with ESCC.[20,21] In addition, Yang et al. indicated that patients with higher pretherapeutic serum SCC-Ag levels did not benefit from postoperative chemotherapy compared with those with lower levels.[22] However, no study has been conducted regarding the predictive value of pretherapeutic tumor markers for pathologic response to NAC. To the best of our knowledge, this is the first study to elucidate the implication of pretherapeutic serum SCC-Ag levels in predicting the pathologic therapeutic effect of NAC in ESCC patients.

In this study, the majority of eligible patients received the CF regimen as NAC. Our data demonstrate that the sensitivity to CF was not high enough in patients with high pretherapeutic SCC-Ag. Therefore, alternative regimens with strong antitumor activity are required to improve the outcomes. DCF, perioperative fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT), as well as a neoadjuvant regimen containing immune checkpoint inhibitor, is expected to provide enough efficacy.[23–26]

Our study has several limitations that should be addressed. First, despite the inclusion of a relatively higher number of patients with NAC from two high-volume Japanese centers, the retrospective observational study design resulted in bias. Second, patients who did not undergo esophagectomy due to distant metastasis or local failure during NAC were not included in our study. To grasp the entire aspect, these patients should be included and evaluated using other modalities because the pathological therapeutic effect in resected specimens could not be evaluated. Third, due to the lack of re-review of pathology in this study, there could be diagnostic discordance among pathologists and institutions. Fourth, the

TABLE 3 Multivariate analysis of pretherapeutic factors for disease recurrence

Variables	HR (95% CI)	*p* value
Sex		
Male	Reference	–
Female	0.72 (0.47–1.11)	0.13
Age	1.00 (0.98–1.02)	0.92
SCC		
Low	Reference	–
Middle	1.20 (0.83–1.74)	0.34
High	1.79 (1.25–2.56)	<0.01*
Location		
Upper	Reference	–
Middle	1.35 (0.84–2.17)	0.22
Lower	1.12 (0.68–1.85)	0.67
cT (UICC)		
T1-2	Reference	–
T3-4	1.40 (1.02–1.92)	0.03*
cN (UICC)		
N0	Reference	–
N1-3	1.34 (0.95–1.90)	0.10
cM (UICC)		
M0	Reference	–
M1	1.46 (0.74–2.91)	0.28
NAC regimen		
CF	Reference	–
DCF	1.32 (0.76–2.28)	0.33

HR hazard ratio, *CI* confidence interval, *SCC* squamous cell carcinoma, *UICC* Union for International Cancer Control, *NAC* neoadjuvant chemotherapy, *CF* cisplatin and 5-fluorouracil, *DCF* docetaxel, cisplatin, and 5-fluorouracil

*$p < 0.05$

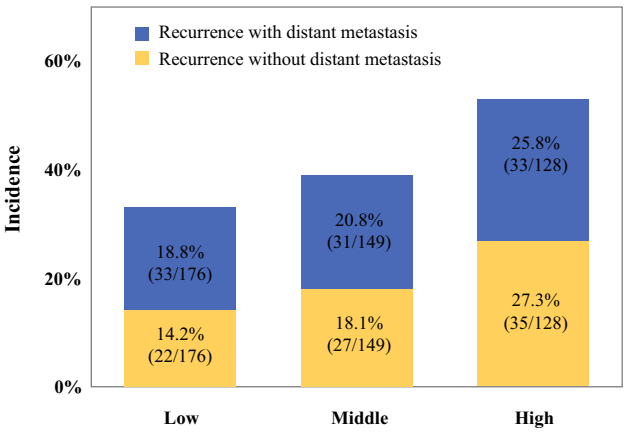

FIG. 3 Pretherapeutic serum squamous cell carcinoma antigen levels and recurrence pattern

factors influencing serum SCC-Ag levels, even in healthy populations, were not evaluated in this study and therefore could affect the results. Nevertheless, measurement of serum SCC-Ag levels is widely applied in clinical practice and is noninvasive and reproducible. Moreover, serum SCC-Ag can be measured prior to treatment and could provide useful information to improve the decision-making process in neoadjuvant treatment.

CONCLUSIONS

The present study suggested that higher pretherapeutic serum SCC-Ag levels are associated with more advanced cancer, poor sensitivity to NAC, and increased risk of disease recurrence. To improve the outcomes of patients with high pretherapeutic levels of serum SCC-Ag, alternative strategies consisting of multimodality treatment should be investigated.

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REFERENCES

1. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med*. 2003;349:2241–52.
2. Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. *Lancet*. 2017;390:2383–96.
3. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5–fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol*. 2012;19:68–74.
4. Kitagawa Y, Uno T, Oyama T, et al. Esophageal cancer practice guidelines 2017 edited by the Japan Esophageal Society: part 1. *Esophagus*. 2019;16:1–24.
5. Kitagawa Y, Uno T, Oyama T, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 2. *Esophagus*. 2019;16:25–43.
6. Torre GC. SCC antigen in malignant and nonmalignant squamous lesions. *Tumour Biol*. 1998;19:517–26.
7. Shimada H, Nabeya Y, Okazumi S, et al. Prediction of survival with squamous cell carcinoma antigen in patients with resectable esophageal squamous cell carcinoma. *Surgery*. 2003;133:486–94.
8. Kosugi S, Nishimaki T, Kanda T, Nakagawa S, Ohashi M, Hatakeyama K. Clinical significance of serum carcinoembryonic antigen, carbohydrate antigen 19–9, and squamous cell carcinoma antigen levels in esophageal cancer patients. *World J Surg*. 2004;28:680–5.
9. Kanda M, Koike M, Shimizu D, et al. Optimized cutoff value of serum squamous cell carcinoma antigen concentration accurately predicts recurrence after curative resection of squamous cell carcinoma of the esophagus. *Ann Surg Oncol*. 2020;27:1233–1240.
10. Brierley JD, Gospodarowicz MK, Wittekind C (eds). TNM classification of malignant tumors. International Union Against Cancer. 8th ed. Oxford: Wiley; 2017.
11. Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part I. *Esophagus*. 2017;14:1–36.
12. Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part II and III. *Esophagus*. 2017;14:37–65.
13. Yokota T, Kato K, Hamamoto Y, et al. Phase II study of chemoselection with docetaxel plus cisplatin and 5–fluorouracil induction chemotherapy and subsequent conversion surgery for locally advanced unresectable oesophageal cancer. *Br J Cancer*. 2016;115:1328–34.
14. Yokota T, Kato K, Hamamoto Y, et al. A 3–year overall survival update from a phase 2 study of chemoselection with DCF and subsequent conversion surgery for locally advanced unresectable esophageal cancer. *Ann Surg Oncol*. 2020;27:460–7.
15. Kato H, Torigoe T. Radioimmunoassay for tumor antigen of human cervical squamous cell carcinoma. *Cancer*. 1977;40:1621–8.
16. Suminami Y, Nagashima S, Vujanovic NL, Hirabayashi K, Kato H, Whiteside TL. Inhibition of apoptosis in human tumour cells by the tumour-associated serpin, SCC antigen-1. *Br J Cancer*. 2000;82:981–9.
17. Murakami A, Suminami Y, Hirakawa H, Nawata S, Numa F, Kato H. Squamous cell carcinoma antigen suppresses radiation-induced cell death. *Br J Cancer*. 2001;84:851–8.
18. Markovina S, Wang S, Henke LE, et al. Serum squamous cell carcinoma antigen as an early indicator of response during therapy of cervical cancer. *Br J Cancer*. 2018;118:72–8.
19. Luke CJ, Pak SC, Askew YS, et al. An intracellular serpin regulates necrosis by inhibiting the induction and sequelae of lysosomal injury. *Cell*. 2007;130:1108–19.
20. Yi Y, Li B, Wang Z, Sun H, Gong H, Zhang Z. CYFRA21–1 and CEA are useful markers for predicting the sensitivity to chemoradiotherapy of esophageal squamous cell carcinoma. *Biomarkers*. 2009;14:480–5.
21. Yi Y, Li B, Sun H, et al. Predictors of sensitivity to chemoradiotherapy of esophageal squamous cell carcinoma. *Tumour Biol*. 2010;31:333–40.
22. Yang Y, Huang X, Zhou L, et al. Clinical use of tumor biomarkers in prediction for prognosis and chemotherapeutic effect in esophageal squamous cell carcinoma. *BMC Cancer*. 2019;19:526.
23. Watanabe M, Baba Y, Yoshida N, et al. Outcomes of preoperative chemotherapy with docetaxel, cisplatin, and 5–fluorouracil followed by esophagectomy in patients with resectable node-positive esophageal cancer. *Ann Surg Oncol*. 2014;21:2838–44.
24. Takeuchi M, Kawakubo H, Mayanagi S, et al. The benefits of docetaxel plus cisplatin and 5–fluorouracil induction therapy in conversion to curative treatment for locally advanced esophageal squamous cell carcinoma. *World J Surg*. 2019;43:2006–15.

25. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393:1948–57.
26. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:1506–17.