Original Article

Prognostic Impact of Serum SCC Antigen in the 566 Upfront Surgery Group of Esophageal Squamous Cell Carcinoma: A Multi-Institutional Study of the Japan Esophageal Society

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Purpose: This study aimed to determine the clinicopathologic and prognostic significance of squamous cell carcinoma antigen (SCC-Ag) in patients with esophageal SCC who underwent radical surgery without neoadjuvant therapy.

Methods: This study included 566 patients with primary esophageal SCC who underwent radical resection without neoadjuvant therapy at 15 Japanese hospitals between 2008 and 2016. The cutoff value of SCC-Ag was 1.5 ng/mL based on the receiver operating characteristic curves. Preoperative SCC-Ag and postoperative SCC-Ag were analyzed to evaluate clinicopathological and prognostic significance. Survival curves were compared between the SCC-Ag-positive group and the SCC-Ag-negative group. The prognostic impact of SCC-Ag was evaluated using univariate and multivariate analyses.

Results: The preoperative SCC-Ag-positive rate was 23.5% (133/566). SCC-Ag-positive status was significantly associated with old age (p = 0.042), tumor depth (p <0.001), and tumor stages (p <0.001). The preoperative SCC-Ag-positive group had significantly poorer overall survival than the SCC-Ag-negative group (p = 0.030), but it was not an

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independent predictor of poor prognosis. Postoperative SCC-Ag-positive status was an independent risk factor for poor overall survival (p = 0.034).
Conclusion: Both pre- and postoperative SCC-Ag-positive statuses were significantly associated with poor prognosis. Postoperative SCC-Ag-positive status was an independent risk factor for predicting overall survival.

Keywords: squamous cell carcinoma antigen, esophageal squamous cell carcinoma, prognosis

Introduction

Esophageal cancer is the seventh most common cancer worldwide and the sixth most common cause of malignancy-related mortality in men. Its recurrence rate remains high despite the advancement of surgical techniques and multimodal treatment, resulting in poor prognosis. In Western countries, >50% of esophageal cancer is adenocarcinoma, whereas in Asian countries, including Japan, >90% are squamous cell carcinoma (SCC). The use of serum tumor markers is convenient for predicting tumor burden and monitoring recurrence.[1,2]

The most commonly used tumor marker for esophageal SCC is SCC antigen (SCC-Ag). SCC-Ag level has been reported to be a parameter of tumor progression and the monitoring marker for tumor recurrence.[3–5] To improve patient selection for perioperative adjuvant therapy, evaluation of SCC-Ag may help determine patients at a high risk for recurrence. The majority of the previous studies investigated adenocarcinoma and SCC and included patients who received neoadjuvant therapy. Only a few studies focused on surgery-alone group.[6,7] Currently, the standard treatment is preoperative chemotherapy and chemoradiotherapy, making analysis of Up Front Surgery more difficult.[8,9] Therefore, this nationwide multicenter retrospective study aimed to determine the clinicopathologic and prognostic significance of SCC-Ag in 566 patients who underwent surgery for esophageal SCC without neoadjuvant therapy.

Materials and Methods

Patients, adjuvant chemotherapy, and radiotherapy

The present study included 566 patients with primary esophageal SCC who underwent radical resection with lymph node dissection without neoadjuvant therapy between 2008 and 2016 at 15 Japanese hospitals. The study population consisted of 471 men (83.2%) and 95 women (16.8%) with a median age of 66 (range 37–89) years. Tumor stages were classified as stage I (n = 267), stage II (n = 114), stage III (n = 137), or stage IV (n = 48) according to the 8th edition of the International Union Against Cancer classification of esophageal cancer.[10] A total of 136 patients (24%) received chemotherapy and/or radiation therapy following surgery. Of the 566 patients analyzed, 281 had SCC-Ag measurements at 3 months after surgery. Of these, 66 (23.5%) were SCC-Ag positive. In addition, 74 (26.3%) patients received adjuvant chemotherapy.

Follow-up schedule and diagnosis of recurrence

The median follow-up period of the patients was 39 (range 0–114) months, and 316/566 (55.8%) were alive at 3 years following surgery. Postoperative recurrent metastases were screened according to the institution-specific criteria.

Blood sample analysis for SCC-Ag

Blood samples were collected before surgery, and SCC-Ag levels were assessed via enzyme-linked immunosorbent assay (Abbott Japan Co. Ltd., Tokyo, Japan & Roche Diagnostics K.K., Tokyo, Japan). A receiver operating characteristic curve was generated with death as the poor prognostic factor; a Youden index of 1.5 ng/mL was used as the cutoff value, and SCC-Ag ≥1.5 ng/mL was considered positive (**Fig. 1**). Univariate and multivariate analyses were conducted to evaluate the clinicopathologic and prognostic significance of preoperative SCC-Ag status.

Statistical analysis

The associations of SCC-Ag-positive status with clinicopathological factors were analyzed using Fisher's exact test. The Kaplan–Meier product-limit method was used to calculate survival probabilities from the time of surgery to the time of death. Survival differences between the two groups were determined using the log-rank test. Univariate analysis was conducted to evaluate

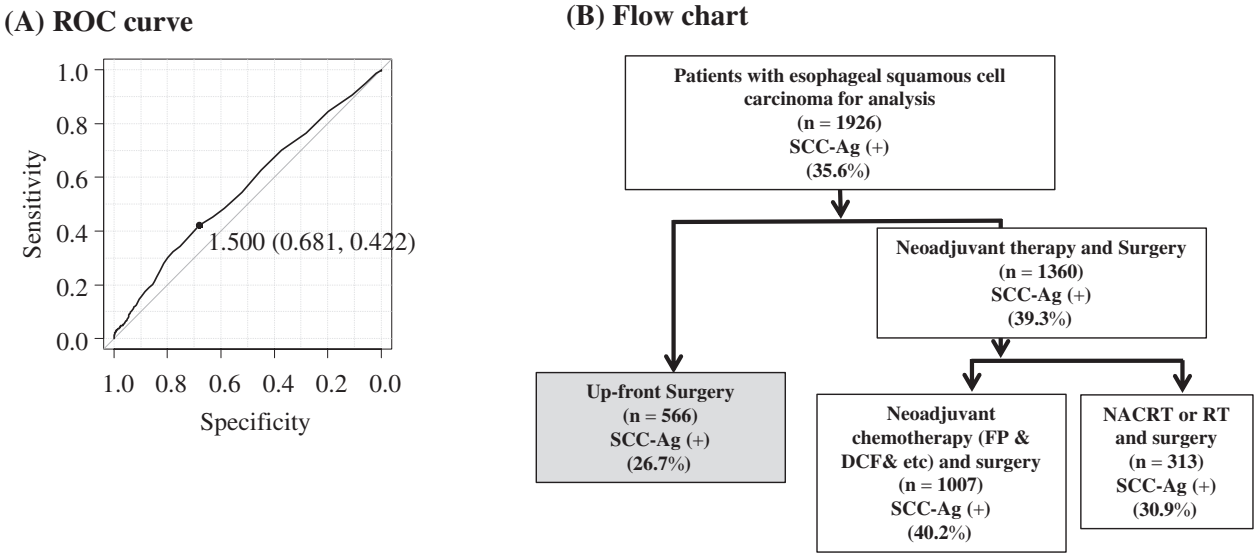

Fig. 1 (**A**) ROC curve to predict poor prognosis for SCC-Ag. Determination of cutoff value. (**B**) Flow chart of excluded items for this analysis. ROC: receiver operating characteristics; SCC-Ag: squamous cell carcinoma antigen; FP: fluorouracil and cyspiatin; DCF: docetaxel & fluorouracil and cyspiatin; NACRT: neoadjuvant chemoradiation therapy; RT: radiation therapy

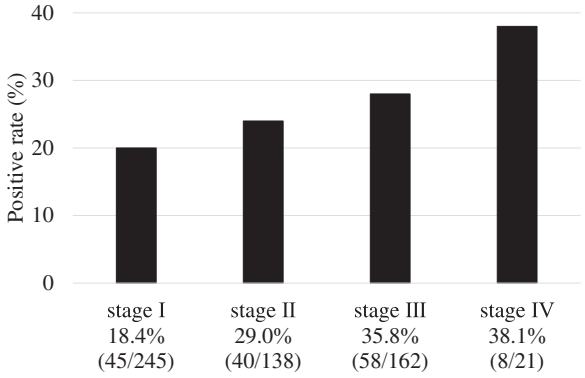

Fig. 2 Positive rates of SCC antigen according to tumor stages in 566 patients who underwent upfront surgery. SCC: squamous cell carcinoma

clinicopathological variables related to overall survival, and multivariate analysis was conducted using the Cox proportional-hazards model for pathological factors. p <0.05 was considered to indicate statistical significance. All statistical analyses were conducted using the EZR statistical software.[11)]

Results

Comparisons of SCC-Ag-positive rates according to each clinicopathological factor

A total of 151 patients (26.7%) were found to be positive for SCC-Ag, with a cutoff value of 1.5 ng/mL. The positive rates according to each stage were stage I: 18.4%, stage II: 29.0%, stage III: 35.8%, and stage IV: 38.1% (**Fig. 2**). SCC-Ag-positive rate was significantly associated with age (p = 0.042), tumor depth (p <0.001) and stage (p <0.001) (**Table 1**).

Table 1 Comparison of SCC antigen-positive rates according to various clinicopathological factors in the 566 upfront surgery group

Variables	Number of patients (Total = 566)	Number of patients with SCC-Ag ≥1.5 ng/mL	p value[a]
Gender			
Female	95	25 (26.3%)	1.000
Male	471	126 (26.8%)	
Age			
<65 years old	228	50 (21.9%)	0.042
≥65 years old	338	101 (29.9%)	
Tumor depth			
pT1–T2	371	66 (17.8%)	< 0.001
pT3–T4	195	85 (43.6%)	
Nodal status			
Negative	265	78 (29.4%)	0.183
Positive	301	66 (21.9%)	
Distant metastasis			
Negative	545	143 (26.2%)	0.220
Positive	21	8 (38.1%)	
pStage			
Stage I/II	383	85 (22.2%)	<0.001
Stage III/IV	183	66 (36.1%)	

(%) is the positivity rate per variable. *p <0.05 statistical significance. a: Fisher's exact probability test. SCC-Ag: squamous cell carcinoma antigen

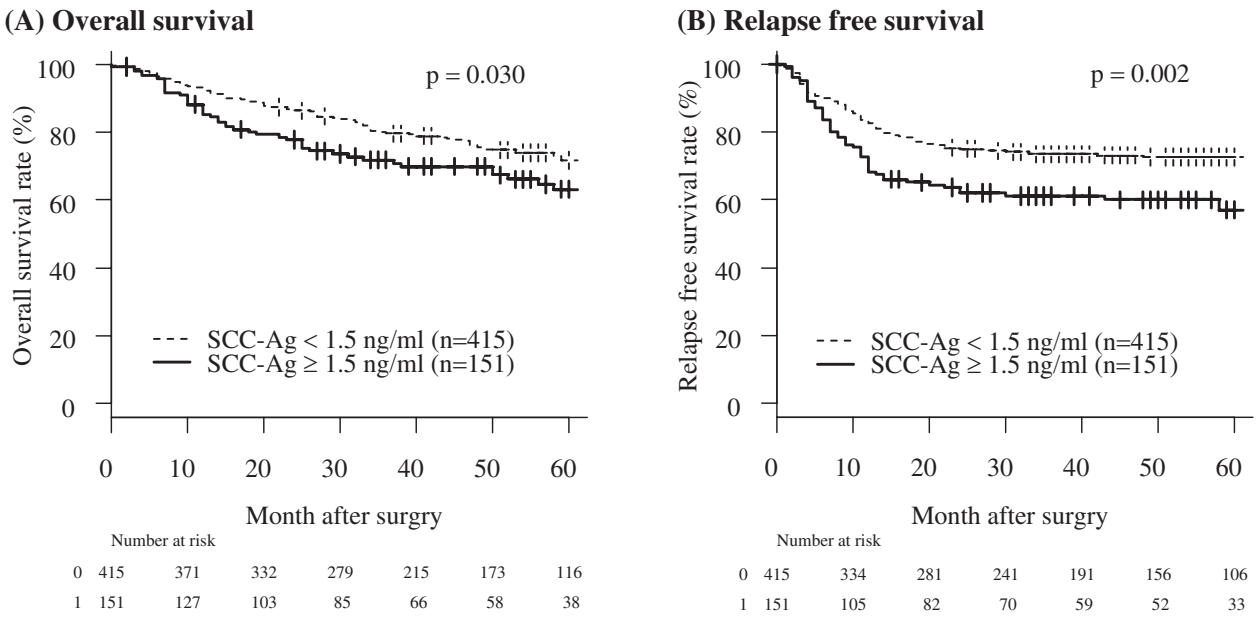

Fig. 3 Comparisons of survivals according to preoperative SCC-Ag status after surgery. (**A**) Overall survival and (**B**) relapse-free survival. *p <0.05 indicates statistical significance. SCC-Ag: squamous cell carcinoma antigen

Prognostic impacts of SCC-Ag on overall survival rate and relapse-free survival rate

The overall survival of the SCC-positive group was significantly poorer than that of the SCC-negative group (p = 0.003; **Fig. 3**). Furthermore, the relapse-free survival of the SCC-Ag-positive group was significantly poorer than that of the SCC-Ag-negative group (p = 0.002; **Fig. 3**). Tumor depth, lymph node metastasis, distant metastasis, and SCC-Ag-positive status were significant prognostic factors for overall survival. In the multivariate analysis, sex (p = 0.028), tumor depth (p <0.001), and nodal status (p = 0.001) were independent prognostic determinants, whereas SCC-Ag-positive status was not (**Table 2**).

Changes in the SCC-Ag levels after surgery and prognostic impact of postoperative SCC-Ag levels on overall survival

Changes in the SCC-Ag levels were re-assessed 3 months after surgery. The preoperative SCC-Ag-positive group had significantly decreased SCC-Ag levels following surgery (p <0.001). However, no significant decrease was observed in the preoperative SCC-Ag-negative group (**Fig. 4**).

The overall survival of the postoperative SCC-positive group was significantly poorer than that of the postoperative SCC-negative group (p = 0.014; **Fig. 5**). No significant difference was observed in the relapse-free survival between the postoperative SCC-Ag-positive group and postoperative SCC-Ag-negative group (p = 0.386; **Fig. 5**). Based on the multivariate analysis, deep tumor (p = 0.002), positive node (p = 0.035), and postoperative SCC-Ag-positive status (p = 0.034) were independent poor prognostic factors (**Table 3**).

Discussion

The present study is one of the largest series to evaluate pre- and postoperative SCC-Ag levels in patients with esophageal SCC surgically treated without neoadjuvant therapy. The positive rates were significantly associated with age, deep tumor, and tumor stages. Postoperative SCC-Ag-positive status was an independent risk factor for poor overall survival.

The cutoff value used in this study was determined using the receiver operating characteristic curve. This value was the same as that of SCC-Ag, according to the manufacturer's protocol. In previous studies, a cutoff value of 1.5 ng/mL for SCC-Ag was used, and positive cases were reported to have significantly higher tumor depth than negative ones. Our results are consistent with those of the previous studies (**Table 4**).[6,7,12–14)]

As can be seen from **Table 2**, preoperative SCC-Ag-positive status was associated with a trend toward poor prognosis in the univariate analysis but was not an independent poor prognostic factor. This

Table 2 Univariate and multivariate analyses of the prognostic impact of preoperative SCC antigen status

Variables	Univariate analysis	Multivariate analysis		
	p value[a]	Hazard ratio	95% CI[b]	p value[c]
Gender				
Female	0.187	1.783	1.065–2.985	0.028
Male				
Age				
≤65 years old	0.172	1.330	0.936–1.889	0.111
>65 years old				
Tumor depth				
pT1–T2	<0.001	2.704	1.863–3.926	<0.001
pT3–T4				
Nodal status				
Negative	<0.001	0.536	0.369–0.778	0.001
Positive				
Distant metastasis				
Negative	0.033	0.600	0.600–2.586	0.555
Positive				
SCC-Ag				
<1.5 ng/mL	0.030	1.054	0.725–1.532	0.783
≥1.5 ng/mL				

*p <0.05 statistical significance. a: Log-rank test. b: Confidence interval. c: Cox hazard model. SCC: squamous cell carcinoma; SCC-Ag: squamous cell carcinoma antigen

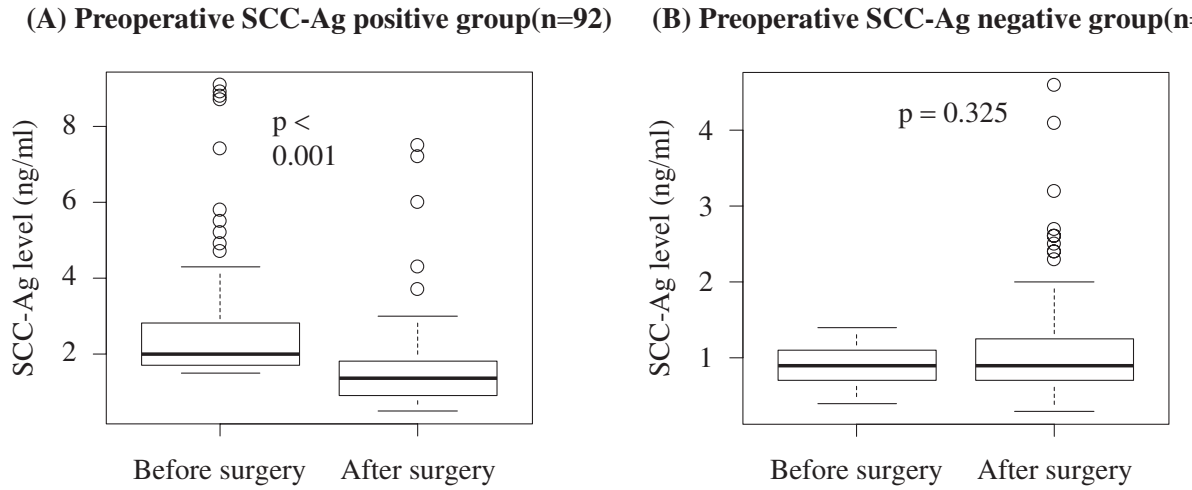

Fig. 4 Comparisons between preoperative SCC-Ag levels and postoperative SCC-Ag levels. (**A**) Preoperative SCC-Ag-positive group and (**B**) preoperative SCC-Ag-negative group. *p <0.05 indicates statistical significance. SCC-Ag: squamous cell carcinoma antigen

may be explained by the fact that SCC-Ag status is strongly confounded by tumor depth. The preoperative SCC-Ag-positive group exhibited significantly decreased SCC-Ag levels following surgery (**Fig. 4**). Contrarily, patients who had recurrence showed reelevated SCC-Ag levels. However, negative cases may remain essentially negative (**Fig. 4**). A similar study reported that SCC-Ag or SCC-Ag alone at initial diagnosis is likely insufficient to predict prognosis.[5] Two previous studies analyzed postoperative SCC-Ag values at 1 month postoperatively and at recurrence, suggesting that postoperative positive cases are associated with recurrence and poor or early prognosis.[6,13] In the present study, the cases in which SCC-Ag did not become negative even 3 months following surgery, and the cases in which SCC-Ag became positive in

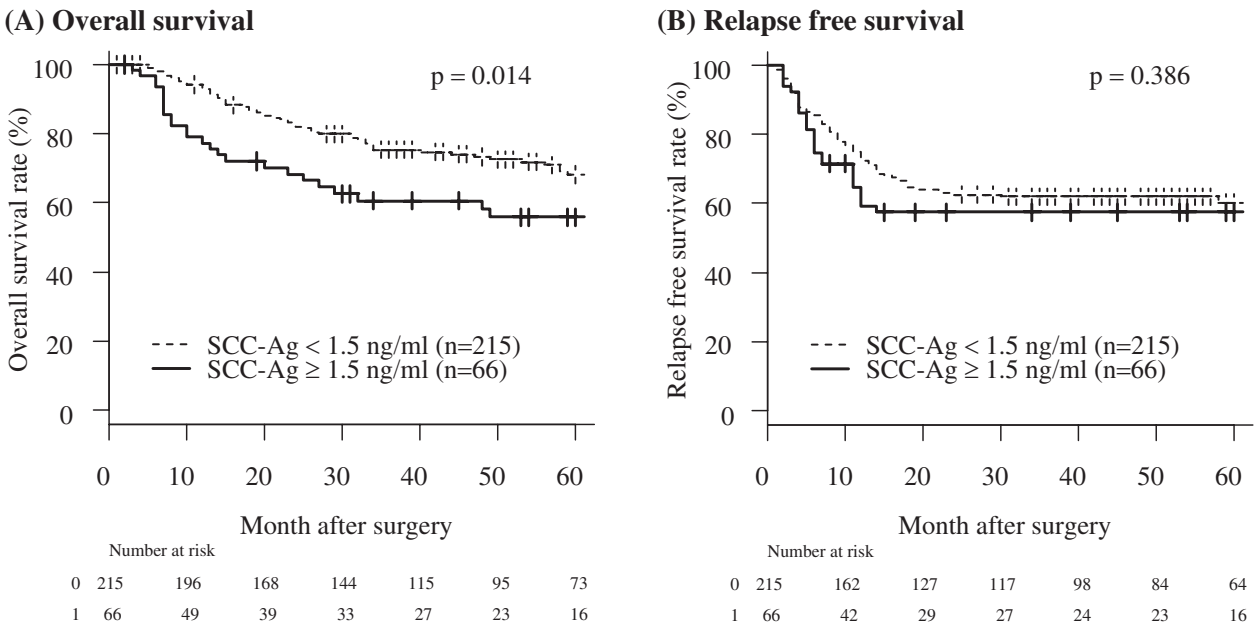

Fig. 5 Comparisons of survivals according to postoperative SCC-Ag status after surgery. (**A**) Overall survival and (**B**) relapse-free survival. *p <0.05 indicates statistical significance. SCC-Ag: squamous cell carcinoma antigen

Table 3 Univariate and multivariate analyses of the prognostic impact of postoperative SCC antigen status

Variables	Univariate analysis	Multivariate analysis		
	p value[a]	Hazard ratio	95% CI[b]	p value[c]
Gender				
Female	0.179	1.629	0.836–3.168	0.150
Male				
Age				
≤65 years old	0.731	0.990	0.637–1.540	0.965
>65 years old				
Tumor depth				
pT1–T2	< 0.001	2.111	1.321–3.374	0.002
pT3–T4				
Nodal status				
Negative	<0.001	1.740	1.039–2.913	0.035
Positive				
Distant metastasis				
Negative	0.068	1.535	0.690–3.415	0.294
Positive				
SCC-Ag				
<1.5 ng/mL	0.014	1.692	1.040–2.750	0.034
≥1.5 ng/mL				

a: Log-rank test. b: Confidence interval. c: Cox Hazard model. SCC: squamous cell carcinoma; SCC-Ag: squamous cell carcinoma antigen

preoperative SCC-Ag-negative cases had a poor prognosis. The postoperative SCC-Ag positive group was not significantly different from the negative group in RFS at 3 months after surgery. The discrepancy in OS with RFS might suggest that the SCC-Ag-positive group may have been resistant to treatment for recurrence. Previous reports have also reported the possibility of treatment resistance.[15,16] Some cases that were negative before surgery turned out to be positive after surgery, so we believe that postoperative monitoring of SCC-Ag will help us to predict recurrence. For such cases, more frequent CT imaging may detect early recurrence.

Table 4 Previous reports of SCC-Ag in patients with esophageal squamous cell carcinoma

Author (year)	No. of patients	Study design	Object of analysis and scc-Ag cut-off level	Poor prognosis in Univariate analysis	Multivariate analysis (predictors)
Shimada et al. (2003)[6]	309	Single institutional	Up front surgery and 1 month postoperatively 1.5 ng/mL	pT, N, M, scc-Ag	pT, N, scc-Ag (independent prognostic factor)
Cao et al. (2012)[7]	379	Single institutional	Stage II Up front surgery 1.5 ng/mL	pStage, scc-Ag, cyfra	pStage, scc-Ag, cyfra (independent prognostic factor)
Mei et al. (2019)[12]	108	Single institutional	Before neoadjuvant chemotherapy 1.5 ng/mL	pT, scc-Ag, cyfra	pT, cyfra (lymph node metastatic risk factor)
Kanie et al. (2021)[13]	208	Single institutional	Time of recurrence 1.3–2.2 ng/mL	pT, scc-Ag	pT, scc-Ag (risk factor of recurrence)
Kitasaki et al. (2022)[14]	84	Single institutional	Before neoadjuvant chemotherapy 1.5 ng/mL	pT, N, M, scc-Ag	pT, N, M, scc-Ag (independent prognostic factor)
Our study	566	Multi institutional	Up front surgery and 3 month postoperatively 1.5 ng/mL	pT, N, scc-Ag	pT, N, scc-Ag (independent prognostic factor)

SCC-Ag: squamous cell carcinoma antigen

This study had several limitations. First, no precise changes in the SCC-Ag levels have been assessed beyond 1 year after surgery. Therefore, no data about SCC-Ag levels were obtained at the time of recurrence. Our present multicenter study made it possible to analyze a sufficient number of cases to clarify the pathological significance of SCC-Ag levels. Second, SCC-AG may also be elevated in lung and skin inflammatory diseases, but this was not excluded in this study.[17] The limitation of this study was the difficulty in conducting a detailed analysis due to the wide variety of postoperative chemotherapy regimens. The new standard of neoadjuvant chemotherapy, including the docetaxel, cisplatin, and 5-fluorouracil regimen, and the introduction of immune checkpoint inhibitors may change the clinical significance of SCC-Ag. Further, a retrospective and/or prospective follow-up study is warranted to confirm the clinical significance of SCC-Ag under the new conditions.

Conclusion

Both pre- and postoperative SCC-Ag-positive statuses were significantly associated with poor overall survival. Postoperative SCC-Ag-positive status is an independent risk factor for predicting overall survival. It is important to consider close observation and postoperative adjuvant chemotherapy with recurrent metastases in mind.

Declarations

Compliance with ethical standards

The study protocol was approved by the Institutional Ethics Committee of Toho University (Tokyo, Japan) (#A18112_A17044_A16037). It has been guaranteed an opt-out opportunity after the disclosure of information.

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Disclosure statement

The authors declare no conflicts of interest.

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Author contributions

Hideaki Shimada was responsible for the study design. Satoshi Yajima, Takashi Suzuki, Akihiko Okamura, Naoya Yoshida, Yusuke Taniyama, Kentaro Murakami, Yu Ohkura, Yasuaki Nakajima, and Koichi Yagi, Takashi Fukuda, Ryo Ogawa, Isamu Hoshino, Chikara Kunisaki, Kosuke Narumiya, Yasuhiro Tsubosa, Kazuhiko Yamada were responsible for sample and data collection. Takashi

Suzuki performed the statistical data analysis. Hideaki Shimada and Takashi Suzuki drafted the initial version of the manuscript. All authors critically reviewed the manuscript and approved the final version for submission.

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