Original Article

Postrecurrence Prognostic Impact of Squamous Cell Carcinoma Antigen and Serum p53 Antibody at the Time of Recurrence on the Patients with Esophageal Squamous Cell Carcinoma

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ABSTRACT

Introduction: Only a few papers have evaluated the postrecurrence prognostic impact of serum squamous cell carcinoma antigen (SCC-Ag) and serum p53 antibody (s-p53-Abs) on esophageal squamous cell carcinoma (ESCC) recurrence.

Methods: A total of 218 patients with ESCC who underwent subtotal esophagectomy between 2009 and 2020 were enrolled. Among them, 67 patients developed recurrence by the end of 2020. The postrecurrence prognostic impact of SCC-Ag and s-p53-Abs on recurrence was evaluated.

Results: SCC-Ag, but not s-p53-Abs, positivity increased significantly at recurrence. After combining both tumor markers, 52 of the 67 patients (78%) showed positivity at recurrence. The positivity of s-p53-Abs was not associated with postrecurrence prognosis. SCC-Ag positivity was slightly associated with poor postrecurrence prognosis, although the difference was not significant. Among the subgroups according to the SCC-Ag and the s-p53-Abs status at recurrence, the double-positive group showed the worst prognosis after recurrence.

Conclusions: A combination of serum SCC-Ag and s-p53-Abs showed a high positivity rate of 78% at recurrence, and concurrent use of both the tumor markers may guide postoperative follow-up.

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KEYWORDS: serum SCC antigen, serum p53 antibodies, esophageal squamous cell carcinoma, recurrence, prognosis

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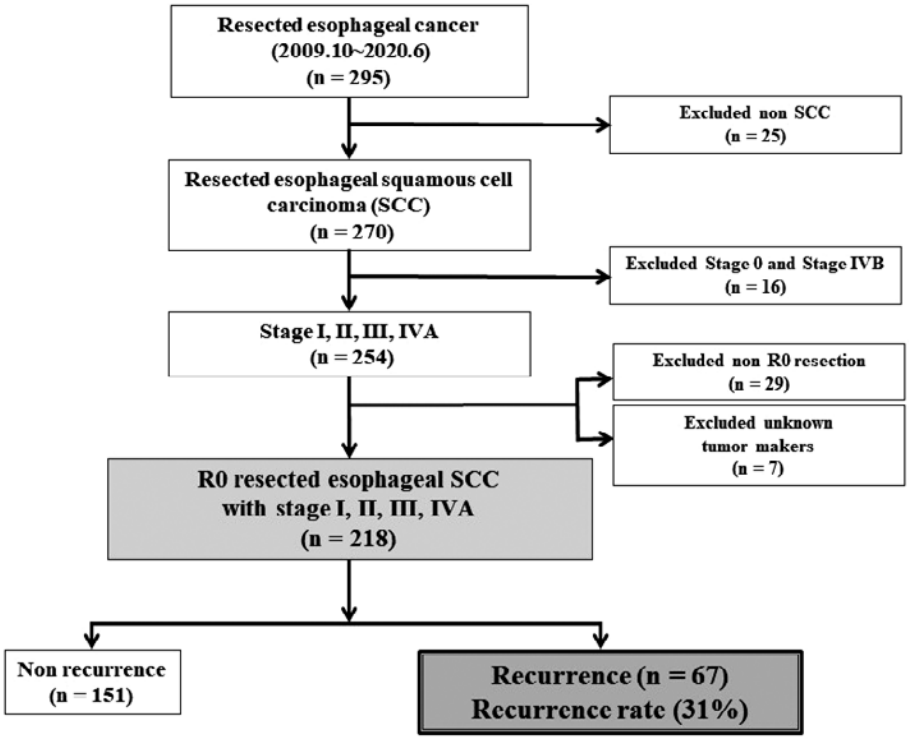

Fig. 1 Flowchart of patient selection.

Introduction

While recent advancements in diagnostic modalities,[1] surgical techniques,[2,3] perioperative management,[4] and multidisciplinary treatment[5,6] have improved the prognosis of esophageal cancer, prognosis after recurrence remains abysmal.[7,8] Studies have identified several prognostic factors for recurrent esophageal cancer, including recurrence patterns, number of metastases, and recurrence-free-survival time.[9–11] Moreover, preoperative tumor markers have been evaluated for their prognostic significance.[12–14] In line with this, reports have shown that serum p53 antibody (s-p53-Abs) was associated with the outcomes of patients with recurrent esophageal squamous cell carcinoma (ESCC).[8]

Although the postrecurrence prognostic impact of serum tumor markers has been evaluated in patients with recurrent gastric cancer[15] and recurrent colorectal cancer,[16] only two reports have investigated the prognostic impact of tumor markers in patients with recurrent ESCC.[8,17] Nonetheless, given that both studies evaluated the postrecurrence prognostic impact of only squamous cell carcinoma antigen (SCC-Ag) or only s-p53-Abs at recurrence, no study has determined the postrecurrence prognostic impact of both tumor markers at recurrence.

Therefore, the current study sought to evaluate the postrecurrence prognostic impact of combining both SCC-Ag and s-p53-Abs at recurrence of ESCC.

Methods

Patients

Fig. 1 presents a flowchart for patient selection. A total of 295 patients with primary esophageal cancer underwent surgery at Toho University Hospital from October 2009 to June 2020. Among these patients, 25 with malignancies other than squamous cell carcinoma, 8 with stage 0 disease, 8 with stage IVB disease and distant metastasis (according to the TNM Classification of Malignant Tumors, UICC 8th edition), 29 with unresectable disease, and 7 who had no tumor marker measurements were excluded, ultimately leaving 218 patients. Among the 218 patients, 67 (31%) developed recurrence by the end of 2020.

Among the 67 patients who developed recurrence, 38 (57%) received neoadjuvant therapy, with 28 receiving neoadjuvant chemotherapy (5-fluorouracil and cisplatin) and 10 receiving neoadjuvant chemoradiotherapy. All patients underwent standard radical esophagectomy with lymph node dissection according to the treatment guideline for esophageal cancer.[7]

Table 1 Comparison of recurrence rates in clinicopathological variables of R0 resected esophageal squamous cell carcinoma

Variables (n = 218)	Recurrence (n = 67)	Non recurrence (n = 151)	p value[a]
Age			
≧65 years (n = 131)	37 (28%)	94 (72%)	0.37
＜65 years (n = 87)	30 (34%)	57 (66%)	
Gender			
Female (n = 48)	13 (27%)	35 (73%)	0.59
Male (n = 170)	54 (32%)	116 (68%)	
Tumor location			
Upper (n = 47)	13 (28%)	34 (72%)	0.72
Lower (n = 171)	54 (32%)	117 (68%)	
Tumor depth			
pT1/2 (n = 121)	23 (19%)	98 (81%)	＜0.01 * *
pT3/4 (n = 97)	44 (45%)	53 (55%)	
Lymph node status			
Negative (n = 101)	12 (12%)	89 (88%)	＜0.01 * *
Positive (n = 117)	55 (47%)	62 (53%)	
Stage			
pStage I/II (n = 121)	15 (12%)	106 (88%)	＜0.01 * *
pStage III/IVA (n = 97)	52 (54%)	45 (46%)	
SCC-Ag before treatment (cut-off value = 1.5 ng/ml)			
Negative (n = 114)	33 (29%)	81 (71%)	0.56
Positive (n = 104)	34 (33%)	70 (67%)	
s-p53-Abs before treatment (cut-off value = 1.3 U/ml)			
Negative (n = 171)	51 (30%)	120 (70%)	0.59
Positive (n = 47)	16 (34%)	31 (66%)	

[a] Fisher's exact probability test

Serum tumor markers and follow-up

After surgery, physical examinations, computed tomography, and laboratory tests were performed as follow-up. These tumor markers were measured every 1-3 months after surgery until recurrence. The cutoff values for s-p53-Abs and SCC-Ag were 1.3 U/mL and 1.5 ng/mL, respectively.[18] Recurrence was determined based on computed tomography findings. Other tests such as positron emission tomography were also performed to determine recurrence, if necessary. All patients were followed up until the end of 2020 or death. The median follow-up duration for survivors was 22 months.

Statistical analysis

Differences between groups were analyzed using Fisher's exact probability test for the categorical variables. Overall survival curves were generated using the Kaplan-Meier method, with differences being assessed using the log-rank test. The overall survival was assessed using univariate analyses with the log-rank test. A p value <0.05 was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface of R (R Foundation for Statistical Computing, Vienna, Austria). This software is a modified version of the R Commander designed to add statistical functions frequently used in biostatistics more precisely.[19]

Results

Comparison of recurrence rates in clinicopathological variables of R0-resected esophageal squamous cell carcinoma

Table 1 compares the recurrence rates among the various clinicopathological characteristics of R0-resected ESCC. Recurrence rates were significantly higher in T3T4 tumors (45%, $p < 0.01$), lymph node-positive patients (47%, $p < 0.01$), and stage III/IVA patients (54%, $p < 0.01$) com-

Table 2 Comparison of tumor marker positivity rates at recurrence in clinico-pathological variables

(A) Variables (n = 67)	SCC-Ag Positive at recurrence (n = 47)	SCC-Ag Negative at recurrence (n = 20)	p value[a]
Age			
≧65 years (n = 37)	26 (70%)	11 (30%)	1
＜65 years (n = 30)	21 (70%)	9 (30%)	
Gender			
Female (n = 13)	9 (69%)	4 (31%)	1
Male (n = 54)	38 (70%)	16 (30%)	
Tumor location			
Upper (n = 13)	7 (54%)	6 (46%)	0.18
Lower (n = 54)	40 (74%)	14 (26%)	
Tumor depth			
pT1/2 (n = 23)	13 (57%)	10 (43%)	0.09
pT3/4 (n = 44)	34 (77%)	10 (23%)	
Lymph node status			
Negative (n = 12)	8 (67%)	4 (33%)	0.74
Positive (n = 55)	39 (71%)	16 (29%)	
Stage			
pStage I/II (n = 15)	9 (60%)	6 (40%)	0.35
pStage III/IVA (n = 52)	38 (81%)	14 (70%)	
SCC-Ag before treatment (cut-off value = 1.5 ng/ml)			
Negative (n = 33)	17 (52%)	16 (48%)	＜0.01 **
Positive (n = 34)	30 (88%)	4 (12%)	
s-p53-Abs before treatment (cut-off value = 1.3 U/ml)			
Negative (n = 51)	36 (71%)	15 (29%)	1
Positive (n = 16)	11 (69%)	5 (31%)	

(B) Variables (n = 67)	s-p53-Abs Positive at recurrence (n = 20)	s-p53-Abs Negative at recurrence (n = 47)	p value[a]
Age			
≧65 years (n = 37)	9 (24%)	28 (76%)	0.29
＜65 years (n = 30)	11 (37%)	19 (63%)	
Gender			
Female (n = 13)	3 (23%)	10 (77%)	0.74
Male (n = 54)	17 (31%)	37 (69%)	
Tumor location			
Upper (n = 13)	4 (31%)	9 (69%)	0.72
Lower (n = 54)	16 (30%)	38 (70%)	
Tumor depth			
pT1/2 (n = 23)	8 (35%)	15 (65%)	0.58
pT3/4 (n = 44)	12 (27%)	32 (73%)	
Lymph node status			
Negative (n = 12)	6 (50%)	6 (50%)	0.16
Positive (n = 55)	14 (25%)	41 (75%)	
Stage			
pStage I/II (n = 15)	7 (47%)	8 (53%)	0.12
pStage III/IVA (n = 52)	13 (25%)	39 (75%)	

Table 2 continued

(B) Variables (n = 67)	s-p53-Abs Positive at recurrence (n = 20)	s-p53-Abs Negative at recurrence (n = 47)	p value[a]
SCC-Ag before treatment (cut-off value = 1.5 ng/ml)			
Negative (n = 33)	12 (36%)	21 (64%)	0.29
Positive (n = 34)	8 (24%)	26 (76%)	
s-p53-Abs before treatment (cut-off value = 1.3 U/ml)			
Negative (n = 51)	6 (12%)	45 (88%)	< 0.01 **
Positive (n = 16)	14 (88%)	2 (12%)	

[a] Fisher's exact probability test

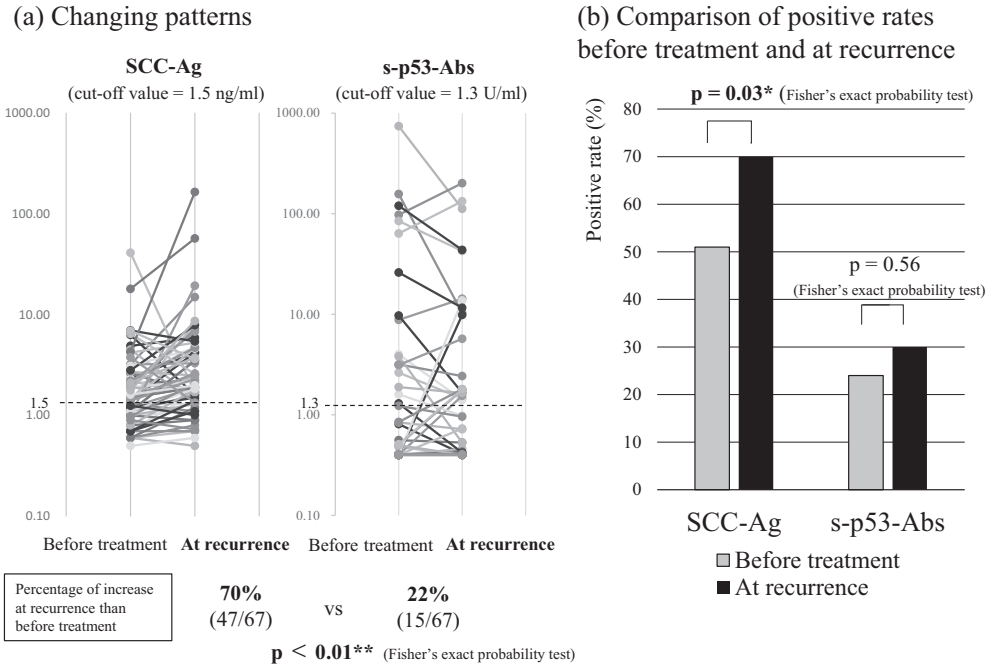

Fig. 2 Comparison of pretreatment tumor markers and postrecurrent tumor markers: (a) changing patterns and (b) comparison of positive rates before treatment and at recurrence. The *p*-values were analyzed by Fisher's exact probability test.

pared to other patients. Moreover, the recurrence rates were higher in the SCC-Ag-positive group (33%, $p = 0.56$) and also in the s-p53-Abs-positive group (34%, $p = 0.59$); however, the difference was not significant.

Comparison of tumor marker positivity rates at recurrence in clinicopathological variables

Table 2A shows the positive rates of SCC-Ag at recurrence. SCC-Ag positivity before treatment was significantly associated with that at recurrence ($p < 0.01$). Table 2B shows the s-p53-Abs positivity rates at recurrence. s-p 53-Abs positivity before treatment was significantly associated with that at recurrence ($p < 0.01$). The other variables showed no significant differences in positivity rates at recurrence.

Comparison of pretreatment tumor markers and postrecurrence tumor markers

Changes in tumor markers at recurrence relative to that before treatment are shown in Fig. 2a. Accordingly, 70% (47/67) of the patients with recurrence showed increased SCC-Ag values, whereas only 22% (15/67) of the patients showed increased s-p53-Abs values. The frequency of patients with increased SCC-Ag values was sig-

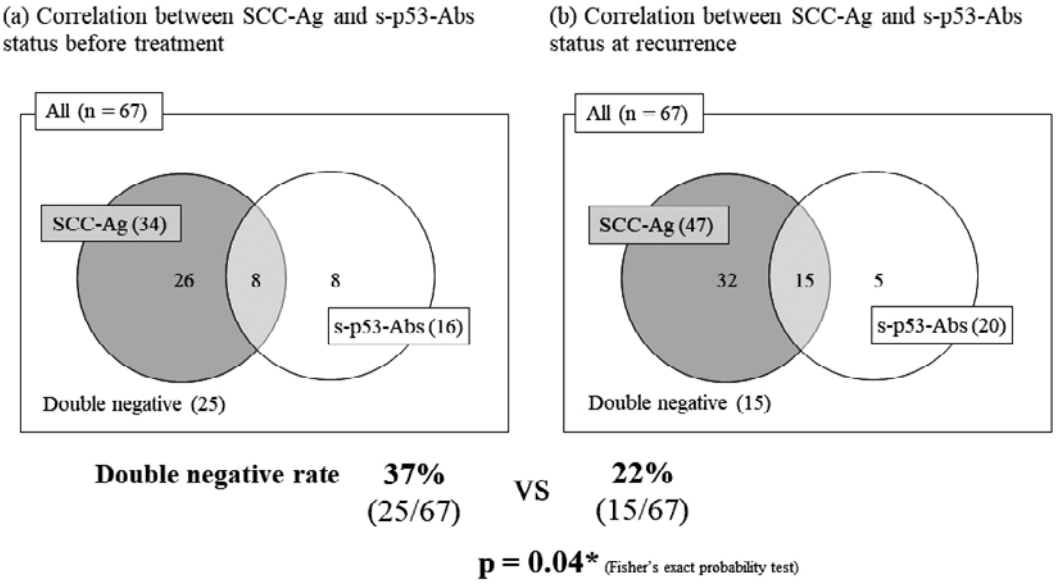

Fig. 3 Correlation between the SCC-Ag and the s-p53-Abs status before treatment and at recurrence: (a) before treatment and (b) at recurrence. The *p*-values were analyzed by Fisher's exact probability test.

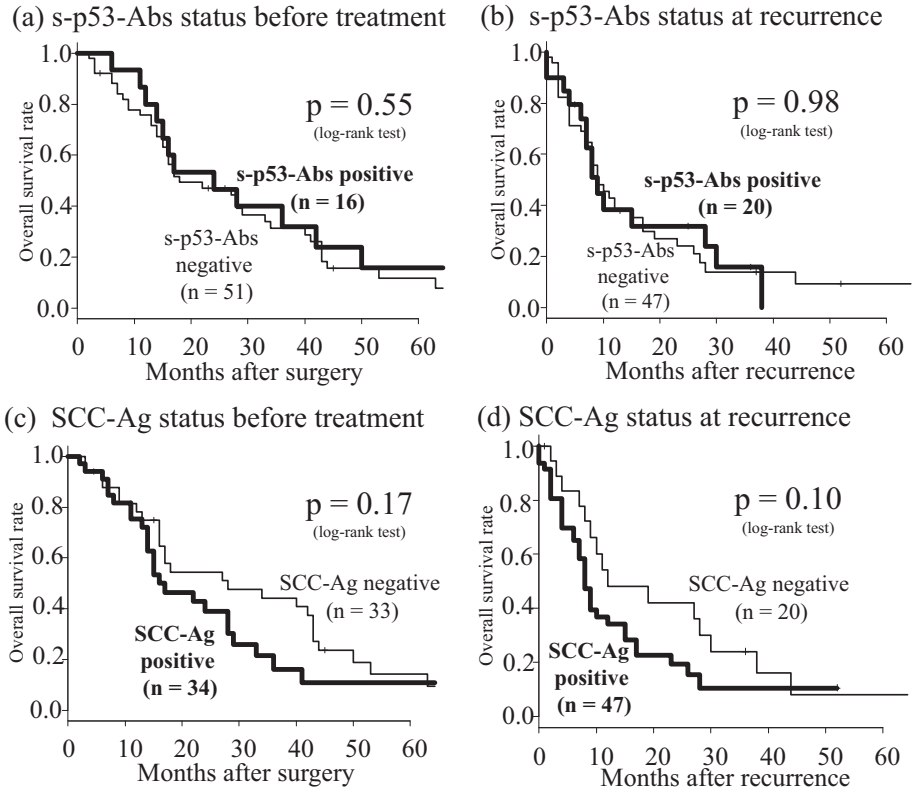

Fig. 4 Comparison of the overall survival according to the SCC-Ag/s-p53-Abs status before treatment and at recurrence: (a) the s-p53-Abs status before treatment and months after surgery, (b) the s-p53-Abs status at recurrence and months after recurrence, (c) the SCC-Ag status before treatment and months after surgery, and (d) the SCC-Ag status at recurrence and months after recurrence. The *p*-values were analyzed by the log-rank test.

nificantly higher than those with increased s-p53-Abs values ($p < 0.01$).

The SCC-Ag positivity rates increased significantly from 51% (34/67) before treatment to 70% (47/67) at recurrence ($p = 0.03$), whereas the s-p53-Abs positivity rates increased from 24% (16/67) before treatment to 30% (20/67) at recurrence, although the difference was not significant ($p = 0.56$) (Fig. 2b).

Table 3 Univariate analyses of prognostic variables for overall survival after recurrence in the patients with recurrent esophageal squamous cell carcinoma

Variables	Univariate p value[a]
Age (year) (before treatment) ≧65/＜65	0.11
Gender Male/Female	0.24
Tumor depth pT3T4/pT1T2	0.76
Nodal status positive/negative	0.11
Tumor marker status (at recurrence)	
s-p53-Abs Positive/Negative	0.98
SCC-Ag Positive/Negative	0.10

[a] log-rank test

Correlation between the SCC-Ag and the s-p53-Abs status before treatment and at recurrence

The correlation between the SCC-Ag and the s-p53-Abs status before treatment and at recurrence is shown in Fig. 3. After combining both tumor markers, the double positivity group increased from 8 to 15 cases, whereas the double negativity group decreased from 25 (37%) to 15 (22%) cases ($p = 0.04$). Thus, the positivity rate of the tumor markers at recurrence reached as high as 78% after combining both markers.

Comparison of the overall survival according to the SCC-Ag/s-p53-Abs status before treatment and at recurrence

No significant difference in prognosis was observed between s-p53-Abs-positive and -negative groups before treatment and at recurrence ($p = 0.55$, $p = 0.98$) (Fig. 4a, b). However, the SCC-Ag-positive group tended to have poorer prognosis ($p = 0.17$, $p = 0.10$) (Fig. 4c, d).

Comparison of the postrecurrence overall survival according to the SCC-Ag/s-p53-Abs status at recurrence

None of the clinicopathological variables were identified

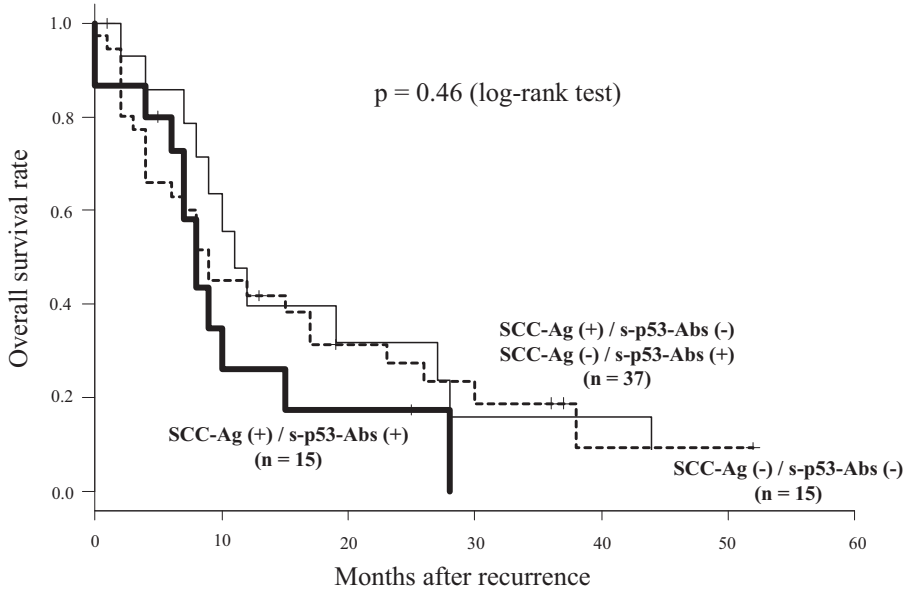

Fig. 5 Comparison of the postrecurrence overall survival according to the SCC-Ag/s-p53-Abs status at recurrence.
SCC-Ag (+) /s-p53-Abs (+) and SCC-Ag (−) /p-53-Abs (−) are shown as solid lines, and SCC-Ag (+) /s-p53-Abs (−) and SCC-Ag (−) /s-p53-Abs (+) are shown as dashed lines.

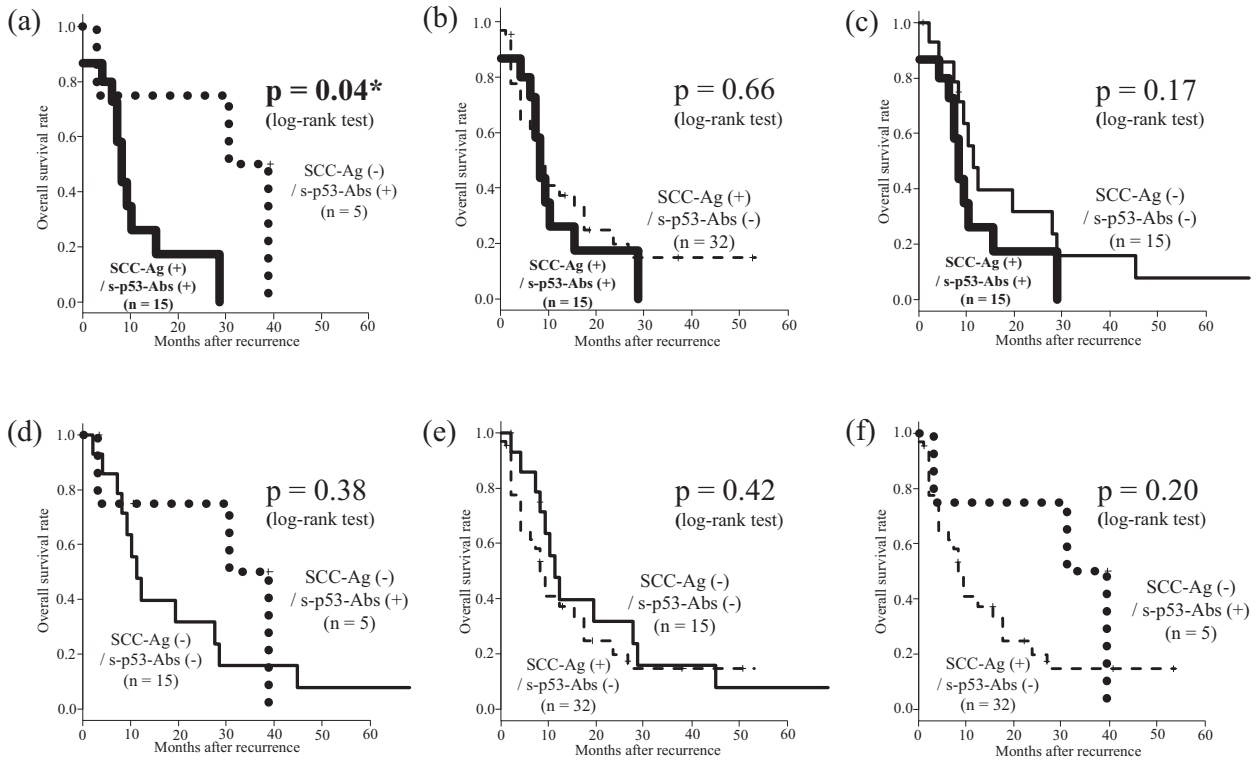

Fig. 6 Comparison of the postrecurrence overall survival according to the SCC-Ag/s-p53-Abs status at recurrence: (a) SCC-Ag positive and s-p53-Abs positive vs. SCC-Ag negative and s-p53-Abs positive, (b) SCC-Ag positive and s-p53-Abs positive vs. SCC-Ag positive and s-p53-Abs negative, (c) SCC-Ag positive and s-p53-Abs positive vs. SCC-Ag negative and s-p53-Abs negative, (d) SCC-Ag negative and s-p53-Abs negative vs. SCC-Ag negative and s-p53-Abs positive, (e) SCC-Ag negative and s-p53-Abs negative vs. SCC-Ag positive and s-p53-Abs negative, and (f) SCC-Ag positive and s-p53-Abs negative vs. SCC-Ag negative and s-p53-Abs positive. The *p*-values were analyzed by the log-rank test.

as significant prognostic factors after recurrence (Table 3).

The postrecurrence overall survival was compared among the following three patterns of the SCC-Ag/s-p53-Abs status: double positive, single positive, and double negative (Fig. 5). The double-positive group showed relatively worse survival than the other groups, although the difference was not significant ($p = 0.46$).

The double-positive group, SCC-Ag (+)/s-p53-Abs (+), tended to have a poor prognosis (Fig. 6a-c). Among the single positive groups, the SCC-Ag (+)/s-p53-Abs (−) group tended to have a poor prognosis (Fig. 6e, f), whereas the SCC-Ag (−)/s-p53-Abs (+) group tended to have a slightly better prognosis (Fig. 6d, f). Moreover, the SCC-Ag (−)/s-p 53-Abs (+) group had a significantly better prognosis than the double-positive group (Fig. 6a, $p = 0.04$).

Discussion

The current study evaluated the postrecurrence prognostic impact of SCC-Ag and s-p53-Abs at ESCC recurrence. Our findings showed that patients showing double positivity, SCC-Ag (+)/s-p53-Abs (+), at recurrence showed a slightly poor prognosis, although the difference was not significant.

Both markers increased at recurrence in some patients. Notably, the increase in SCC-Ag was significantly more frequent than that in s-p53-Abs (70% vs. 22%, $p = 0.04$). Thus, SCC-Ag may be more useful for detecting recurrence compared to s-p53-Abs. The pretreatment positive group had a higher recurrence rate than the pretreatment negative group for both SCC-Ag and s-p53-Abs, although the difference was not significant. Previous reports have shown that upon pretreatment and/or immediately after surgery, the positive group had a poor overall survival.[14, 20] Given the lack of a significant difference in the recurrence rate according to the pretreatment tumor marker status, our findings showed that a pretreatment positive status does not affect the recurrence rate itself, although it might be associated with poor prognosis after recurrence. After combining both tumor markers, our findings showed significantly fewer double-negative patients at recurrence

than before treatment. Thus, the combined assessment of both markers may be useful for detecting recurrence.

We precisely evaluated the impact of the positive tumor marker status at recurrence on postrecurrence prognosis. Notably, our findings showed that s-p53-Abs did not affect the overall survival. However, although no significant difference was observed in SCC-Ag, the postrecurrence prognosis of the positive group tended to be worse than that of the negative group. Tumor volume, which is associated with the SCC-Ag levels, at recurrence has been considered a cause of poor prognosis after recurrence.[13] These results suggest that SCC-Ag may be a prognostic factor after recurrence. Moreover, patients with a double-positive status at recurrence, SCC-Ag (+)/s-p53-Abs (+), tended to have a worse prognosis than those with other statuses. However, the s-p53-Abs single positive group tended to have a better prognosis. Reports have shown that DCF chemotherapy (docetaxel, cisplatin, and 5-fluorouracil) was effective in patients with s-p53-Abs-positive ESCC,[21] which may be attributed to its influence on chemotherapy response after recurrence. Although there were only five patients in the p53 (+)/SCC (−) group, two of them used DOC after recurrence.

This study has several limitations that are worth noting. First, this retrospective analysis included a small number of cases from a single institute. Therefore, a multivariate analysis could not be performed, only univariate analysis was performed. Second, the postoperative observation period was insufficient, and some of the patients who did not develop recurrence may do so after this study.

In conclusion, the current study suggested that simultaneous measurement of serum SCC-Ag and s-p53-Abs at recurrence may be useful for predicting the overall survival after recurrence in patients with ESCC. A positive status for both tumor markers may have an effect on prognosis after recurrence, although the difference was not statistically significant.

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Authors' contributions: J. Moriyama, H. Shimada, and T. Suzuki designed the study; J. Moriyama, T. Suzuki, Y. Oshima, T. Nanami, S. Yajima, and F. Shiratori analyzed the data; K. Funahashi and H. Shimada supervised the experiments; and J. Moriyama and H. Shimada wrote the manuscript.

Ethics statement: The ethical statement of this retrospective study was approved by the Ethics Committee of Toho University Omori Medical Center (Tokyo, Japan). The approval numbers were M20196 19056 18002. An opt-out method was used to allow it to decline from the subject of analysis.

Conflicts of interest: None decleared.

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