

Prognostic Significance of Serum Squamous Cell Carcinoma Antigen in Surgically Treated Lung Cancer

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The serum concentrations of squamous cell carcinoma antigen (SCC-Ag) obtained from 124 surgically treated primary non-small cell lung cancer patients, including 75 adenocarcinomas (AD) and 49 squamous cell carcinomas (SQ), were studied. The changes in the SCC-Ag concentration, which were obtained before and one month after surgery, were analyzed. The 5-year survival rate of the patients with AD who were positive for SCC-Ag preoperatively (32%) was lower than that for those who were negative for SCC-Ag preoperatively (57%, $p < 0.05$). Meanwhile, in those with SQ, the 5-year survival rate of those who were positive for SCC-Ag preoperatively (59%) was not different when compared with those who were negative for SCC-Ag preoperatively (73%). The 5-year survival rate of patients with AD who were positive for SCC-Ag preoperatively and negative postoperatively was 53% versus 17% for those who remained positive postoperatively ($p < 0.05$). In those with SQ, the 5-year survival rate of those who were positive for SCC-Ag preoperatively and negative postoperatively was 76% while it was 0% for those who remained positive postoperatively ($p < 0.01$). In patients with negative SCC-Ag postoperatively, 5-year survival rates were not different between the patients who had positive antigen preoperatively and the patients who had negative antigen preoperatively both in AD (53% and 57%, respectively) and SQ (76% and 75%, respectively). In conclusion, though SCC-Ag is widely used for SQ, preoperative SCC-Ag did not reflect the prognosis. In AD, the survival rate was lower in antigen-positive than antigen-negative patients. Survival rate was higher in antigen-positive patients who became antigen-negative following resection than in patients who remained antigen-positive for both AD and SQ. In the patients who were negative for SCC-Ag postoperatively, survival was the same regardless of the preoperative SCC-Ag positivity in both AD and SQ. (*Ann Thorac Cardiovasc Surg* 2003; 9: 98–104)

Key words: lung cancer, tumor marker, squamous cell carcinoma antigen, adenocarcinoma, prognosis

Introduction

Squamous cell carcinoma antigen (SCC-Ag) is a tumor antigen that was originally purified from squamous cell carcinoma (SQ) of the uterine cervix.¹ It is a glycoprotein secreted by various cancers and has been used as a

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guide for the management of SQ.¹ Studies conducted to investigate the usefulness of SCC-Ag in the diagnosis and prognosis of cancer has produced contradictory results.^{2,3}

The prognostic significance of the preoperative serum SCC-Ag concentration in patients with lung cancer is limited.⁴ However, in some patients, SCC-Ag concentration decreases after surgery.⁵ The prognostic significance of this decrease in the serum SCC-Ag concentration after surgery has not been adequately tested.

SCC-Ag is produced not only by SQ but also some adenocarcinomas (AD).^{1,5} The significance of SCC-Ag in AD, especially in lung cancer, has not been studied extensively.

Table 1. Preoperative positive rate of the squamous cell carcinoma antigen and pathologic TNM factor

	Adenocarcinoma			Squamous cell carcinoma		
	Positive	Negative	(Positive rate)	Positive	Negative	(Positive rate)
T1,2	10	46	(18%)	12	21	(37%)
T3,4	9	10	(47%)	8	8	(50%)
			p<0.01			n.s.
N0	9	31	(23%)	15	21	(42%)
N1,2,3	10	25	(29%)	5	8	(38%)
			n.s.			n.s.
Stage I,II	8	38	(17%)	17	25	(40%)
Stage III,IV	11	18	(38%)	3	4	(43%)
			p<0.05			n.s.
W/D	6	24	(20%)	5	8	(38%)
M/D	4	12	(25%)	12	12	(50%)
P/D	9	20	(31%)	3	9	(25%)
			n.s.			n.s.

W/D, well differentiated; M/D, moderately differentiated; P/D, poorly differentiated.

We therefore studied the prognostic significance of the preoperative serum SCC-Ag concentration and whether or not it decreased after surgery in lung cancer patients with either AD or SQ.

Patients and Methods

Serum samples for the measurement of the SCC-Ag concentration were collected from patients with surgically treated primary non-small cell lung cancer. Samples were taken from the patients before and one month after surgery. The serum concentrations of SCC-Ag were assayed using a solid phase immunoradiometric method and a monoclonal antibody (Dainabot Ltd., Tokyo, Japan).⁶⁾ A concentration of 1.5 ng/mL was used as the upper limit of normal, representing the 95th percentile in a control group.^{6,7)} Tumor staging was performed based upon the pathologic examination of the surgical specimens according to the TNM staging classification. The TNM classification was based upon General Rule for Clinical and Pathological Record of Lung Cancer.⁸⁾ Patients who had distant metastasis or a contralateral lung metastasis identified preoperatively were not included in this study because these patients were excluded from the surgical indication in our hospital. All stage IV cases had an ipsilateral extra-lobar metastasis. Patients who had double synchronous or metachronous primary cancer were excluded. Patients undergoing chemotherapy or radiotherapy before surgery were also excluded. Patients with either AD (n=75) or SQ (n=49) were included in this study. The data are expressed by the mean \pm standard deviation and

were compared by the chi-square test or unpaired or paired t test. Survival was measured from the time of surgery until death or the date of last follow-up. The survival rates, including non-cancer-related deaths, were calculated by the Kaplan-Meier method, and comparison between curves was made by the log-rank test. Prognostic factors were analyzed using the Cox proportional hazards model. A value of $p < 0.05$ was considered significant.

Results

Forty-eight of the AD patients were male and 27 were female; on the other hand, 43 of the SQ patients were male and 6 were female ($p < 0.01$). The mean age of the AD and SQ groups were 64 ± 10 years old and 65 ± 9 years old, respectively (n.s.). The preoperative positive rate of SCC-Ag was 25% (19/75) in AD and 41% (20/49) in SQ and the difference was not of significance.

The preoperative positive rate for SCC-Ag and pathologic TNM staging are summarized in Table 1. In the AD group, patients with T3 and T4 disease had a higher positive rate than did patients with T1 and T2 disease ($p < 0.01$) and patients with stages III and IV disease had a higher positive rate than did patients with stages I and II disease ($p < 0.05$). Lymph node metastasis and histologic differentiation were not associated with the preoperative positive rate for SCC-Ag. In SQ, the preoperative positive rate for SCC-Ag was not affected by T factor, N factor, stage, or histologic differentiation (n.s.).

In AD, the 5-year survival rate of the patients who had a positive serum SCC-Ag concentration preoperatively

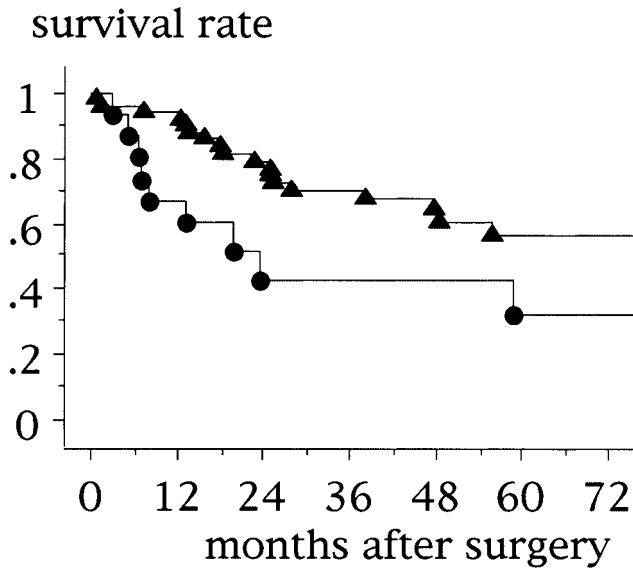


Fig. 1. Survival curves of the patients with adenocarcinoma (AD). The 5-year survival rate of the patients with AD who were positive for squamous cell carcinoma antigen (SCC-Ag) preoperatively (32%) was lower than that for those who were negative for SCC-Ag preoperatively (57%, $p < 0.05$). Circle, positive SCC-Ag preoperatively; triangle, negative SCC-Ag preoperatively.

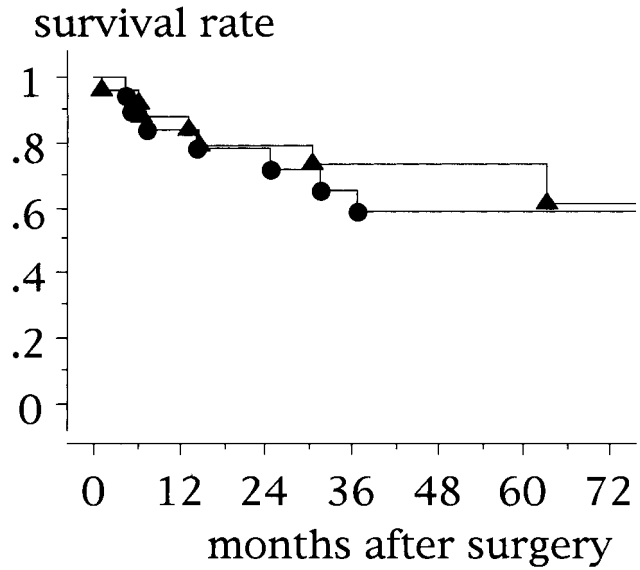


Fig. 2. Survival curves of the patients with squamous cell carcinoma (SQ). In those with SQ, the 5-year survival rate of those who were positive for squamous cell carcinoma antigen (SCC-Ag) preoperatively (59%) was not different when compared with those who were negative for SCC-Ag preoperatively (73%, n.s.). Circle, positive SCC-Ag preoperatively; triangle, negative SCC-Ag preoperatively.

Table 2. Patient distribution according to the pre- and post-operative pattern of the squamous cell carcinoma antigen (SCC-Ag)

Group	Preoperative SCC-Ag	Postoperative SCC-Ag	Adenocarcinoma	Squamous cell carcinoma
A	Positive	Positive	11 cases	6 cases
B	Positive	Negative	8 cases	14 cases
C	Negative	Positive	0 case	4 cases
D	Negative	Negative	56 cases	25 cases
Total			75 cases	49 cases

was 32% while it was 57% for those who had a negative value (Fig. 1, $p < 0.05$). In SQ, the 5-year survival rate of the patients who had a positive serum SCC-Ag concentration preoperatively was 59% while it was 73% for those who had a negative value (Fig. 2, n.s.).

The pattern of the preoperative and postoperative SCC-Ag concentrations and the 5-year survival rates are summarized in Tables 2 and 3. In the AD group, the 5-year survival rate of patients who were positive for SCC-Ag preoperatively and remained positive postoperatively (group A) was 17% while the rate for patients who were positive for SCC-Ag preoperatively and became negative postoperatively (group B) was 53% (Fig. 3, Table 3, $p < 0.05$). In the SQ group, the 5-year survival rate of the

Table 3. Five-year survival rates associated with the groups

Group	Adenocarcinoma	Squamous cell carcinoma
A	17%	0%
B	53%	76%
C	(-)	50%
D	57%	75%
Total	51%	67%

patients who were positive for SCC-Ag preoperatively and remained positive postoperatively (group A) was 0% while the rate for the patients who were positive for SCC-Ag preoperatively and became negative postoperatively (group B) was 76% (Fig. 4, Table 3, $p < 0.01$).

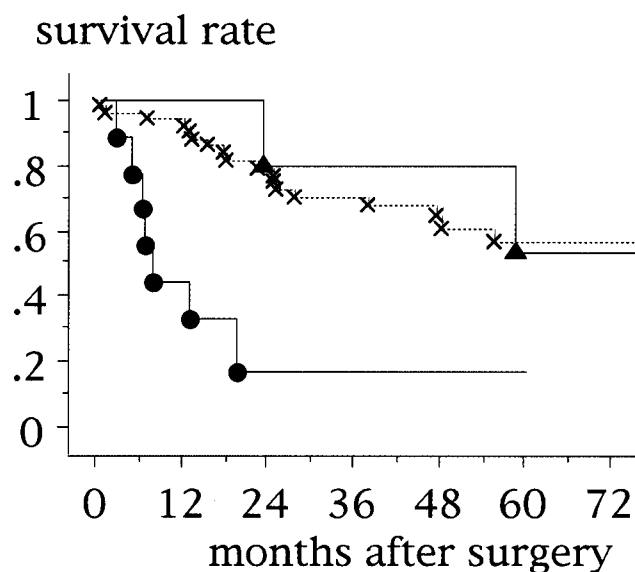


Fig. 3. Survival curves of the patients with adenocarcinoma (AD). The 5-year survival rate of patients with AD who were positive for squamous cell carcinoma antigen (SCC-Ag) preoperatively and negative postoperatively was 53% versus 17% for those who remained positive postoperatively ($p < 0.05$). In patients with negative SCC-Ag postoperatively, 5-year survival rates were not different between the patients who had positive antigen preoperatively and the patients who had negative antigen preoperatively in AD (53% and 57%, respectively, n.s.). Circle, positive SCC-Ag pre- and post-operatively; triangle, positive SCC-Ag preoperatively and negative postoperatively; cross, negative SCC-Ag pre- and post-operatively.

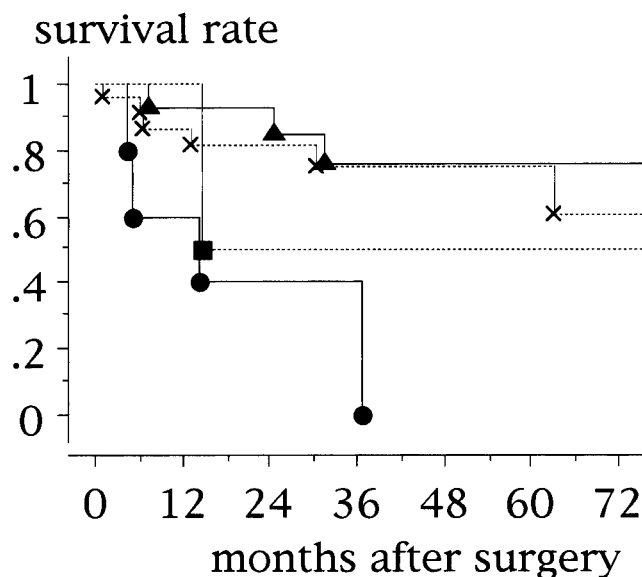


Fig. 4. Survival curves of the patients with squamous cell carcinoma (SQ). The 5-year survival rate of patients with SQ who were positive for squamous cell carcinoma antigen (SCC-Ag) preoperatively and negative postoperatively was 76% while it was 0% for those who remained positive postoperatively ($p < 0.01$). In patients with negative SCC-Ag postoperatively, 5-year survival rates were not different between the patients who had positive antigen preoperatively and the patients who had negative antigen preoperatively in SQ (76% and 75%, respectively, n.s.). Circle, positive SCC-Ag pre- and post-operatively; triangle, positive SCC-Ag preoperatively and negative postoperatively; square, negative SCC-Ag preoperatively and positive postoperatively; cross, negative SCC-Ag pre- and post-operatively.

Four patients with SQ were negative for SCC-Ag preoperatively and became positive postoperatively (group C). Two patients had an intrapulmonary metastasis in the same lobe and were categorized as T4N0M0 and the remaining 2 patients were T2N0M0. One patient with T2N0M0 disease died 14 months after surgery because of metastases but the remaining 3 patients are disease free. The five-year survival rate of these 4 patients was 50% (Fig. 4, Table 3). No patients with AD were in group C.

Five-year survival rates of the patients who were negative for SCC-Ag pre- and post-operatively (group D) were 57% for those with AD and 75% for those with SQ (Figs. 3, 4). The survival rate of the patients in group D was not different from that of patients in group B for those with either AD or SQ (Figs. 3, 4; Table 3).

Multivariate analyses of prognostic factors using the Cox proportional hazards model were performed on preoperative positivity, postoperative positivity, T factor, N

factor, histological type, differentiation, and gender. Only postoperative positivity appeared to have independent prognostic significance ($p < 0.01$).

Discussion

SCC-Ag was first isolated biochemically from SQ tissue of the uterine cervix.¹⁾ The serum concentrations of this antigen, a serine protease inhibitor, in some patients with gynecologic, head, neck, lung, and esophageal SQ are elevated, and SCC-Ag has been used for the management of SQ arising from various sites.^{9,10)} However, the mechanism responsible for the elevation of this protein in the serum of patients with SQ is still unclear.¹¹⁾ Moreover, SCC-Ag has not been studied extensively in AD because of the low positive rate of SCC-Ag in AD.⁷⁾

SCC-Ag is present in the cytoplasm of SQ.¹²⁻¹⁶⁾ SCC-Ag is produced by the peripheral portions of a tumor.¹²⁾

In our study, the T factor was not associated with the positive rate of SCC-Ag in the serum of patients with SQ. This may be due to the fact that SCC-Ag is produced by the peripheral regions of the tumor and not by all the cancer cells in a tumor. Additionally, there have been several studies that have found the expression of SCC-Ag in tumor tissue does not always correlate with the serum SCC-Ag concentration.^{17,18)} This might explain why the incidence of an elevated serum SCC-Ag concentration is not related with T factor in SQ.

In our study, the positive rate of the serum SCC-Ag was not correlated with the N factor in both AD and SQ. Kato et al. found that the tumor tissues obtained from metastatic lesions are not always rich in SCC-Ag, which indicates that SCC-Ag is not directly related to the malignant potential of tumor cells.¹²⁾ This might be the reason why the N factor did not correlate with the positive rate of the preoperative serum SCC-Ag.

SCC-Ag is closely related to squamous epithelium and appears in the more differentiated types of carcinoma.^{16,19)} However, the clinical data revealed that there was no significant difference in the incidence of a positive serum SCC-Ag concentration between the undifferentiated type and more differentiated types of carcinoma¹²⁾ as in our study.

SCC-Ag was positive in 25% (19/75 patients) of the patients with AD in this study. It is not known how AD produces SCC-Ag.^{12-16,20)} Although it is not clear that SCC-Ag is present in the cytoplasm of AD, lung AD may produce SCC-Ag because the serum SCC-Ag concentration is elevated in some lung cancer patients and because the cytosolic SCC-Ag concentration is raised in lung AD.²¹⁾ However, AD in other organs, such as uterine, ovary, stomach, or colon, rarely raise SCC-Ag.^{1,3,5,10,19)} The positive rate of SCC-Ag in lung AD is reported from 20% to 40% and the rates are higher than that in other organs.⁷⁾ Accordingly, the mechanisms involved in the increase in SCC-Ag in lung AD may be different when compared with AD in other organs. The first explanation is that the lung AD cell itself produces more SCC-Ag than AD cells of other organs. The second possible explanation is that SCC-Ag is produced by the squamous cells elements in AD tumor.⁵⁾ Although no patients with adenosquamous cell carcinoma were included in our study, some squamous cell element was present in the lung AD. The incidence of an elevated SCC-Ag concentration in patients with adenosquamous cell carcinoma is higher than that in patients with AD.⁵⁾ It is well known that the postoperative survival of patients with adenosquamous cell carcinoma

is poorer than that of patients with lung AD.²²⁾ In AD, since the prognosis of the patients with a positive serum SCC-Ag was statistically lower than the patients with a negative SCC-Ag in our study, the squamous cell elements that produced the SCC-Ag may be one of the prognostic factors. The third explanation for the production of SCC-Ag by lung AD is that the AD invades and destroys the bronchus and lung. Picardo et al. have shown that the cytosolic SCC-Ag concentration obtained from normal lung specimens is not 0 mg/ml.²¹⁾ In benign bronchial and lung diseases or even under normal conditions, SCC-Ag producer cells may be present in bronchial lung tissue. When lung cancer cells invade and destroy the bronchus and lung, SCC-Ag may be released directly from the bronchi into the circulation and the serum concentration of SCC-Ag could increase, even if the tumor itself does not produce the antigen. One or more of these mechanisms may be responsible for the high positive rate of serum SCC-Ag in lung AD.

After surgery, the serum SCC-Ag concentration normalized in some patients but not in others. Normalization of the antigen correlated with a better survival in patients with both AD and SQ in this study. If the serum SCC-Ag concentration does not normalize after surgery, this may indicate residual disease such as micrometastasis.

The preoperative serum SCC-Ag concentration was negative but became positive in 4 of the 124 patients in our study. This unusual phenomenon was observed in patients with SQ. One explanation is that vascular and lymphatic dissemination occurred during surgery. This hypothesis is based on the fact that 2 of these 4 patients had intrapulmonary metastases and that the prognosis of these 4 patients was lower than that of the patients who were negative for SCC-Ag pre- and post-operatively. However, because 3 of the 4 patients have remained disease free postoperatively and since the recurrence was observed in an early stage in one patient (pT2N0M0), this mechanism may not always be applicable. Another explanation is that the postoperative SCC-Ag was released from the non-cancerous lung tissue and not released from any residual lung cancer. The serum concentrations of SCC-Ag have been reported to be elevated in patients with non-malignant disease in many organs.^{6,10)} Pneumonia, acute respiratory distress syndrome, and asthma can increase the serum SCC-Ag concentration,^{2,7,23)} though our 4 patients did not have any detectable postoperative pneumonia or acute respiratory distress syndrome clinically. The cytosolic SCC-Ag concentration obtained from normal lung specimens is not 0 mg/ml and, in benign bron-

chial and lung processes or even under normal conditions, SCC-Ag producer cells may be present in bronchial lung tissue.²¹⁾ There may be multiple mechanisms responsible for the elevation of the serum SCC-Ag in benign lung disease or in normal bronchial epithelium and lung tissue.

When a tumor marker in the serum is negative preoperatively, many physicians believe that the marker is not a useful tool. In our study, a preoperative negative SCC-Ag was observed in 69% (85/124 patients) of the patients and the majority (83%) were negative postoperatively (103/124 patients). Though SCC-Ag is widely used for SQ, preoperative SCC-Ag did not reflect the prognosis in SQ patients. However, the prognosis of the patients whose serum SCC-Ag concentrations were negative pre- and post-operatively was the same as that of the patients whose SCC-Ags were positive preoperatively and became negative postoperatively. From this result, it is clear that the preoperative positivity is not associated with the prognosis if the postoperative serum SCC-Ag concentration is negative. Especially for SQ, the postoperative serum SCC-Ag concentration has prognostic value when compared with the preoperative SCC-Ag.

In conclusion, the survival of patients with AD who were positive for SCC-Ag preoperatively was lower than that of the patients who were negative preoperatively; however, the incidence of an elevated serum SCC-Ag concentration preoperatively was not correlated with survival in patients with SQ. The survival of the patients who had a positive serum SCC-Ag concentration preoperatively but became negative after surgery was higher than that of the patients who remained positive postoperatively in both AD and SQ. The survival of both AD and SQ patients with a negative serum SCC-Ag postoperatively was the same regardless of whether the preoperative concentration was elevated or not.

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