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Risk Factors of Severe Benign Cicatricial Stricture After Definitive Chemoradiation for Localized T3 Esophageal Carcinoma

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Abstract. *Background/Aim: Severe benign cicatricial stricture (SBCS) is a major complication after definitive chemoradiation therapy (dCRT) for esophageal squamous cell carcinoma (ESCC). This study was conducted to investigate risk factors of SBCS in patients with localized ESCC. Patients and Methods: This study included 197 patients with clinical stage (cSt) II/III ESCC with T3 primary tumor, treated with dCRT between 2000 and 2011. SBCS was defined as the inability to pass a 9-mm diameter endoscope or the presence of symptoms requiring treatment. Results: Complete response was obtained in 87 patients (44%). Multivariate analysis revealed that hypoalbuminemia (hazard ratio=5.65; 95% confidence interval=1.50-21.28; p=0.010) and the inability to pass an endoscope (hazard ratio=5.90; 95% confidence interval=1.52-22.85; p=0.010) were risk factors of SBCS. Conclusion: The inability to pass an endoscope and hypoalbuminemia were identified as risk factors of SBCS in patients with cSt II/III ESCC with T3 primary tumor.*

Esophageal cancer is the eighth leading cause of cancer-related death among Japanese males, with a mortality rate of 15.8 per 100,000 population per year (1). Pathologically, >90% of the patients in Japan are diagnosed with squamous cell carcinoma (SCC).

As described in the National Comprehensive Cancer Network guidelines, definitive chemoradiation therapy (dCRT) is one of the treatment options for patients with cT1b-T4b, N0-N+ esophageal SCC (ESCC) who decline surgery (2). In Japan, the combination of 5-fluorouracil and cisplatin (FP) is the most frequently used chemotherapeutic regimen, as part of dCRT.

Severe benign cicatricial stricture (SBCS) is one of the major complications after dCRT for ESCC. SBCS causes impairment of oral intake leading to deterioration of the quality of life even after cure. Therefore, in this retrospective study, we investigated the incidence and risk factors (RFs) of SBCS in patients with clinical Stage (cSt) II/III ESCC with T3 primary tumor (PT).

Patients and Methods

Patient selection. The medical records of patients with cSt II/III ESCC with T3 PT who were treated with dCRT between January 2000 and December 2011 at the National Cancer Center Hospital were retrospectively reviewed. The dCRT comprised chemotherapy with FP (5-fluorouracil (5FU): 700-1,000 mg/m^2/day, continuous intravenous infusion, days 1-4 plus cisplatin (CDDP): 70-75 mg/m^2, drip infusion, day 1, 28 day-cycle) plus radiotherapy (RT) with 50.4-60 Gy (3-5). Patients who achieved complete response (CR) were included in this analysis. This study was approved by the institutional review board of the National Cancer Center Hospital (2012-268).

Evaluation. CR to dCRT was defined as disappearance of all measurable and non-measurable lesions on contrast-enhanced computed tomography (CT), based on the response evaluation criteria in solid tumours (RECIST) version 1.1 (6). Moreover, endoscopic findings had to satisfy all of the following conditions: i) disappearance of endoscopic findings suggesting the presence of a tumor even if it was not possible for the endoscope to pass the primary lesion due to severe stricture; ii) absence of cancer cells in a biopsy from the area of the PT; and iii) absence of active esophagitis. Confirmation of CR was required *via* repeated CT and endoscopy with a ≥4-week interval. After confirmation of CR, patients were

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Key Words: Esophageal cancer, esophageal stricture, chemotherapy, radiotherapy, risk factor.

Table I. *Patient characteristics and treatment*.

Characteristic	SBCS (–) (n=74)	SBCS (+) (n=13)	*p*-Value
Age – No. (%)			1.000
<63	36 (48.6)	6 (46.2)	
≥63	38 (51.4)	7 (53.8)	
Gender – No. (%)			0.043
Male	64 (86.5)	8 (61.5)	
Female	10 (13.5)	5 (38.5)	
PS – No. (%)			0.553
0	37 (50.0)	8 (61.5)	
1-2	37 (50.0)	5 (38.5)	
Albumin – No. (%)			0.114
<4.0	22 (29.7)	7 (53.8)	
≥4.0	52 (70.3)	6 (46.2)	
CRP – No. (%)			0.392
<0.1	2 (2.7)	1 (7.7)	
≥0.1	71 (97.3)	12 (92.3)	
WBC – No. (%)			0.505
<9000	57 (77.0)	9 (69.2)	
≥9000	17 (23.0)	4 (30.8)	
Hb – No. (%)			0.114
<13.0	22 (29.7)	7 (53.8)	
≥13.0	52 (70.3)	6 (46.2)	
Requirement of soft/liquid style diet – No. (%)			0.004
Yes	19 (26.0)	9 (69.2)	
No	54 (74.0)	4 (30.8)	
Location of primary tumor – No. (%)			0.285
Cervival	8 (10.8)	2 (15.4)	
Upper thoracic	14 (18.9)	0 (0.0)	
Middle thoracic	30 (40.5)	7 (53.8)	
Lower thoracic	20 (27.0)	3 (23.1)	
Abdominal	2 (2.7)	1 (7.7)	
Macroscopic type of primary tumor – No. (%)			0.535
Type 3	22 (30.1)	5 (38.5)	
Other	51 (69.9)	8 (61.5)	
Perimeter – No. (%)			0.005
<3/4	37 (50.0)	1 (7.7)	
≥3/4	37 (50.0)	12 (92.3)	
Longitude of primary tumor by CT – No. (%)			1.000
<50 mm	19 (31.7)	4 (33.3)	
≥50 mm	41 (68.3)	8 (66.7)	
Ability of endosope passage before treatment – No. (%)			<0.001
yes	70 (94.6)	6 (46.2)	
no	4 (5.4)	7 (53.8)	
Total irradiation dose to the primary tumor – No. (%)			0.700
50.4 Gy	13 (17.6)	3 (23.1)	
60.0 Gy	61 (82.4)	10 (76.9)	

diagnosed with SBCS according to the following criteria: 1) inability to pass a 9-mm diameter endoscope (IPE); or 2) presence of symptoms due to stricture requiring interventional treatment.

Data collection. The following data were collected from medical records until data cut-off (August 2016): 1) patient characteristics at the initiation of dCRT, such as Eastern Cooperative Oncology Group (ECOG) performance status (PS), style of ingestible diet (*i.e.*, solid/soft/liquid/none) and laboratory data; 2) characteristics of the PT: perimeter (≤1/3, 1/2, 2/3, 3/4, subtotal, or total circumference), macroscopic type according to the Japanese Classification of Esophageal Cancer, 11th Edition (7, 8), longitude measured by CT, ability to pass a 9-mm diameter endoscope, location (cervical/upper thoracic/middle thoracic/lower thoracic/abdominal); 3) total irradiation dose; and 4) maximal grade of toxicities according to the Common Terminology Criteria for Adverse Events version 4.0 (9).

Statistical analysis. The objective of the analysis was to estimate the incidence and identify the RFs of SBCS. The non-parametric cumulative incidence function estimator for competing risks was

used to estimate the cumulative incidence of SBCS. Temporal strictures which resolved spontaneously were not regarded as SBCS. Death prior to the occurrence of SBCS was considered a competing risk event. Crude and adjusted cause-specific hazard ratios (HRs) were estimated using univariate and multivariate cause-specific Cox proportional hazards models to explore RFs of SBCS.

Patient characteristics were compared between patients with and without SBCS using Fisher's exact test. The median follow-up was calculated using the reverse Kaplan–Meier method. The overall and progression-free survival were estimated using the Kaplan–Meier method, and the confidence interval (CI) of the median survival time was calculated using the Brookmeyer–Crowley method. All *p*-values are two-sided and 95%CIs were calculated. A $p<0.05$ indicated statistical significance. All statistical analyses were performed using the SAS software version 9.4 (SAS Institute, NC, USA).

Results

Patient characteristics. A total of 197 patients with cSt II/III ESCC with T3 PT received dCRT. Ninety-one patients (46.2%) achieved CR. After excluding four patients due to insufficient data, 87 patients were analyzed.

Patient characteristics are shown in Table I. The median age was 63 years (range=42-78 years), ECOG PS was 0-1 in most cases, and 64 patients (73.6%) had cSt III disease. At the initiation of dCRT, IPE was present in eleven patients (12.6%). Two types of dCRT regimens were used in this study: i) 5FU 700 mg/m^2, days 1-4 plus CDDP 70 mg/m^2, day 1 plus RT 60 Gy (700/70-60 Gy); and ii) 5FU: 1,000 mg/m^2 plus CDDP 75 mg/m^2 plus RT 50.4 Gy (1,000/75-50.4 Gy). The regimen of dCRT was 1,000/75-50.4 Gy in 16 patients (18.4%) and 700/70-60 Gy in 70 patients (80.5%).

Toxicity of dCRT. Adverse events during dCRT are listed in Table II. The most common grade 3-4 hematologic events were leukopenia (36.8%). Febrile neutropenia was observed in 5.7% of the patients. Gastrointestinal toxicities and radiation esophagitis (RE) (46.0%) were major grade 2-4 non-hematologic events.

Survival analysis and cumulative incidence of SBCS. The median survival time of the patients was 7.01 years (95%CI=5.37-not reached) with a median follow-up time of 7.45 years (95%CI=0.91-13.77) (Figure 1). The 5-year progression-free survival rate was 45.6% (95%CI=34.8-55.7). Thirteen patients (14.9%) developed SBCS prior to data cut-off (Figure 2). The cumulative incidence of SBCS was estimated as 10.4% (95%CI=5.1-17.9) within one year and 15.2% (95%CI=8.5-23.7%) within 2 years (Figure 3). There were no newly diagnosed cases of SBCS after two years.

Risk factor analysis of SBCS. Univariate analyses identified the following RFs of SBCS at the initiation of dCRT: female sex (HR=3.17; 95%CI=1.04-9.67: $p=0.042$), PT occupying ≥3/4 of the perimeter (HR=8.46; 95%CI=1.46-49.12; $p=0.017$), IPE (HR=11.36; 95%CI=3.77-34.21; $p<0.001$), and requirement of soft/liquid diet (HR=5.59; 95%CI=1.74-17.93; $p=0.004$). Hypoalbuminemia (serum albumin <4.0) showed a marginal association with an increased risk of SBCS (HR=2.60; 95%CI=0.87-7.75: $p=0.086$) (Table III). Multivariate analysis using these five parameters as covariates identified hypoalbuminemia (HR=5.65; 95%CI=1.51-21.28; $p=0.010$) and IPE (HR=5.90; 95%CI=1.52-22.85; $p=0.010$) as RFs of SBCS.

Table II. *Adverse events*.

Hematologic adverse events	Grade 3-4	
	n	%
Leukopenia	32	36.8
Neutropenia	23	26.4
Anemia	1	1.1
Thrombocytopenia	4	4.6
Febrile neutropenia	5	5.7
Non-hematologic adverse events	**Grade 2-4**	
	n	%
Creatinine increase	14	16.1
Anorexia	49	56.3
Nausea	21	24.1
Vomitting	6	6.9
Diarrhea	1	1.1
Fatigue	15	17.2
Oral mucositis	7	8.0
Radiation dermatitis	5	5.7
Radiation esophagitis	40	46.0

Discussion

Pre-operative chemotherapy or CRT followed by surgery is the current standard of care for patients with localized ESCC. However, dCRT is a treatment option for those who are unfit or unwilling to undergo surgery. A proportion of patients who are complicated with dysphasia due to bulky disease prior to dCRT may achieve complete disappearance of symptoms; whereas, patients without dysphasia may occasionally develop SBCS, causing difficulty in oral intake and eventually leading to malnutrition.

Several reports have shown that approximately 19-37% of the patients with head and neck SCC (HNSCC) experienced dysphasia due to mechanical strictures after dCRT (10, 11). A Japanese phase II trial applying FP-RT (700/70-60 Gy) for the treatment of cSt II/III ESCC revealed that grade 3-4 chronic esophagus-related toxicity occurred in 13% of the patients (12). In our study, SBCS occurred in 15.2% of the patients with cST II/III ESCC with T3 PT who achieved CR.

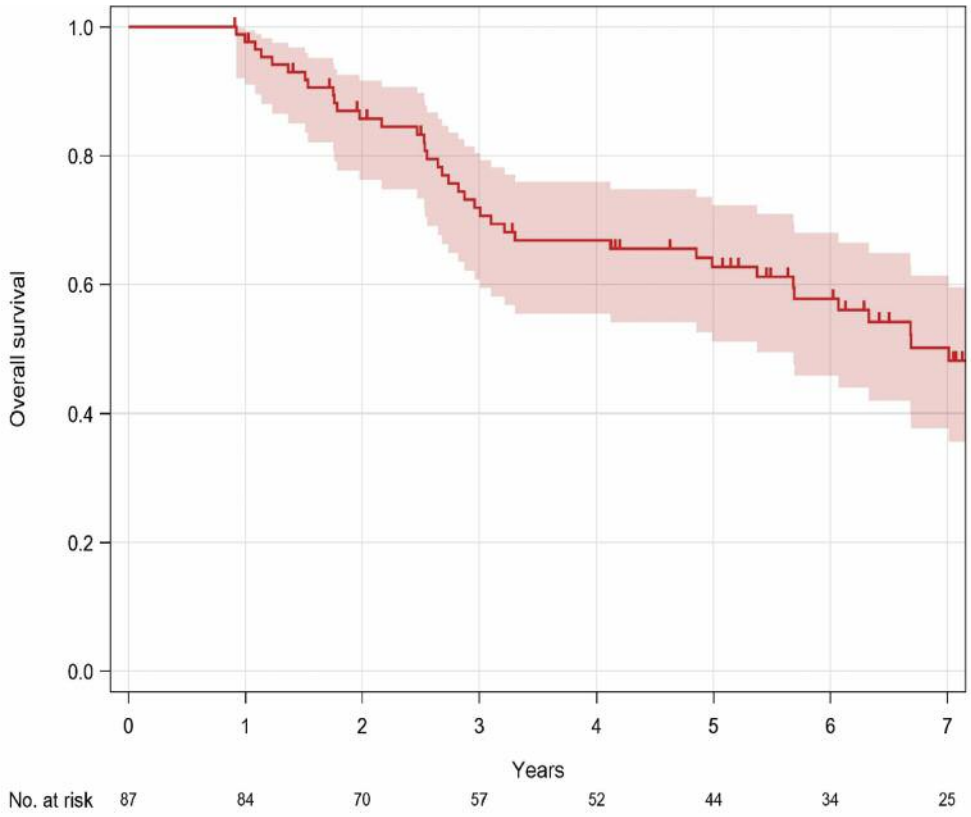

Figure 1. *Overall survival of the patients who achieved complete response (CR). The median survival time of the 87 patients who achieved CR was 7.01 years (95%CI=5.37-NR), with a median follow-up time of 7.45 years (95%CI=0.91-13.77). The 5-year overall survival was 62.7% (95%CI=51.1-72.3).*

Although the incidence of SBCS in this study cannot be compared with these previous reports, it appears to be consistent.

This study revealed that SBCS occurred within two years from the initiation of dCRT. Based on our findings, a careful interview of the patients regarding dysphasia and observation through endoscopy are essential, especially within two years after the initiation of dCRT.

Thus far, RFs of SBCS after dCRT for ESCC have not been established. Previous studies classified RFs of pharyngo-esophageal stricture in radiation-related (RR) and non-radiation-related (nRR) RFs in HNSCC (11, 13-16). This study identified the IPE at the initiation of dCRT as a nRR-RF of SBCS. This finding suggests the presence of a large PT occupying the inner cavity of the esophagus and/or tumors with intrinsically abundant fibrosis causing stricture. A large defect of the esophageal wall may cause severe fibrosis during tissue repair. Moreover, intrinsic fibrosis is not resolved by the disappearance of tumor cells. In contrast, the relatively standardized dosage and method of RT, as well as the simple structure and function of the esophagus may explain the absence of RR-RFs.

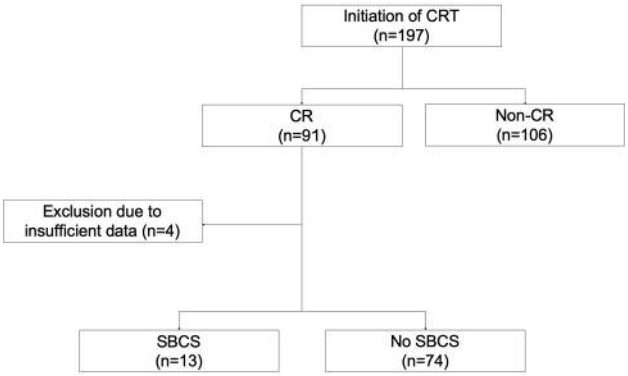

Figure 2. *Patient allocation. A total of 197 patients received definitive chemoradiation therapy (dCRT) and 91 of those achieved complete response (CR). Four patients were excluded from the analysis due to insufficient data. Thirteen patients developed severe benign cicatricial stricture (SBCS).*

A number of studies have reported that the most important RF of pharyngo-esophageal stricture after dCRT for HNSCC is mucosal or submucosal injury (10). One of the major

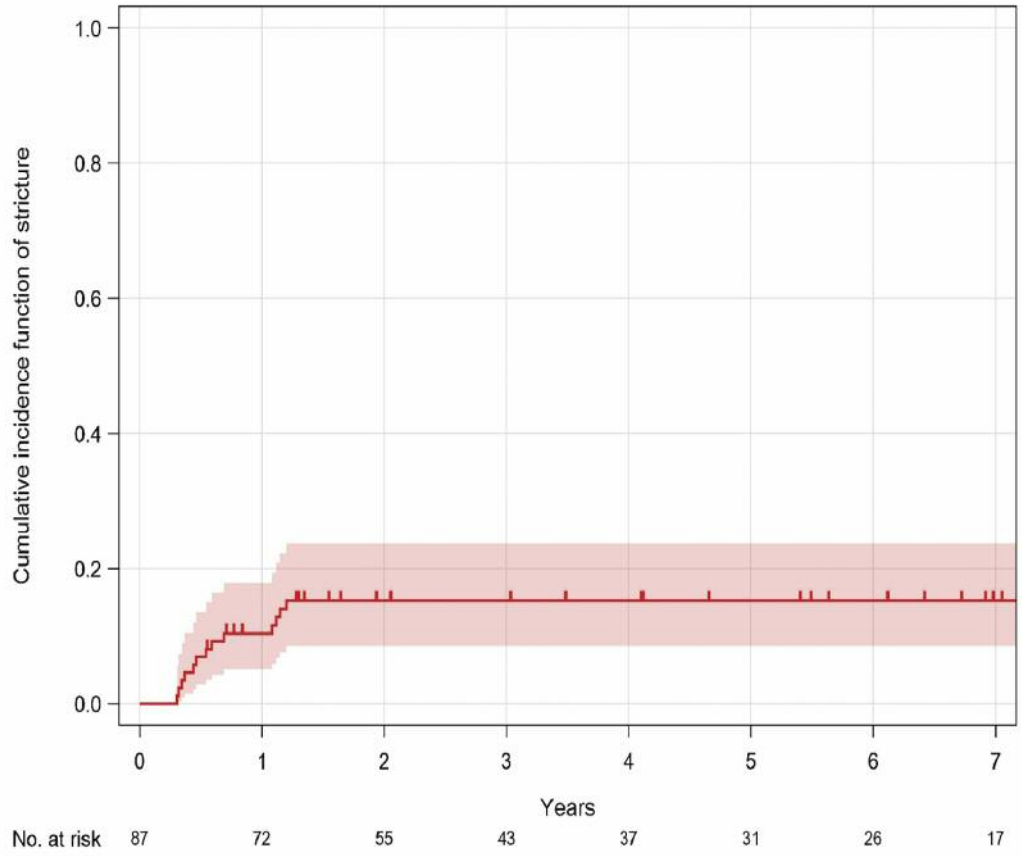

Figure 3. *Cumulative incidence of severe benign cicatricial stricture (SBCS) in patients who achieved complete response (CR). The cumulative incidence of SBCS in patients who achieved CR was 10.4% (95%CI=5.1-17.9) within 1 year from the initiation of definitive chemoradiation therapy (dCRT) and 15.2% (95%CI=8.5-23.7%) within two years.*

Table III. *Univariate and multivariate analysis for SBCS using cause-specific Cox regression models.*

Covariate	Univariate analysis (n=83)				Multivariate analysis (n=83)			
	HR	95%CI		*p*-Value	HR	95%CI		*p*-Value
Gender								
Male	Reference				Reference			
Female	3.172	1.041	9.670	0.042	3.251	0.864	12.230	0.081
Alb								
<4.0	Reference				Reference			
≥4.0	0.384	0.129	1.144	0.086	0.177	0.047	0.663	0.010
Perimeter								
<3/4	Reference				Reference			
≥3/4	8.455	1.455	49.121	0.017	2.692	0.367	19.777	0.330
Ability of endosope passage before treatment								
Yes	Reference				Reference			
No	11.359	3.771	34.213	<0.001	5.897	1.522	22.852	0.010
Requirement of soft/liquid style diet								
No	Reference				Reference			
Yes	5.586	1.740	17.928	0.004	3.974	0.977	16.171	0.054

adverse events of dCRT for ESCC is esophagitis, causing mucosal injury, which may eventually develop radiation-induced fibrosis (RIF). The mechanism of RIF has been reported as misguided wound healing response (17). Ionized radiation generates reactive oxygen and nitrogen species, leading to injury of the tissue. Thereafter, inflammatory cytokines released from inflammatory cells recruit stromal fibroblasts, resulting in RIF (17). Therefore, factors which exacerbate RE or prolong wound healing may be potential RFs of SBCS. Of note, the relationship between the occurrence of adverse events during dCRT and SBCS was not investigated in this study. Hypoalbuminemia was identified as the first-ever reported RF of SBCS. Human serum albumin demonstrates anti-inflammatory activity by scavenging free radicals (18). This mechanism suggests that hypoalbuminemia may exacerbate RE and delay its healing. Prolonged RE may lead to the formation of reactive fibroblasts, causing severe stricture at the site of injury. Therefore, it is considered that hypoalbuminemia and esophagitis may synergistically increase the risk of SBCS.

Hypoalbuminemia can be prevented or resolved through intensive nutritional support. Thus, it is speculated that prophylactic management against malnutrition may prevent SBCS. In this study, the effectiveness of prophylactic nutritional support could not be assessed. Thus, prospective studies are warranted to investigate the efficacy of prophylactic nutritional intervention for the prevention of SBCS.

The limitation of this study is that SBCS were defined retrospectively and that adverse events during dCRT, which represent injury of the esophagus, were not included in the analysis. Moreover, the deterioration of quality of life in patients who developed SBCS remains to be determined. Thus, prospective observational studies with pre-specified endpoints of SBCS are warranted.

In conclusion, SBCS after dCRT for cSt II/III ESCC with T3 PT occurred in 15.2% of the patients within two years from the initiation of treatment. The major RFs of SBCS were IPE and hypoalbuminemia at baseline. These results may facilitate the selection of the most appropriate treatment strategy for patients with cSt II/III ESCC with T3 PT.

Conflicts of Interest

All Authors do not have conflicts of interest to disclose regarding this study.

Authors' Contributions

All Authors contributed to the study conception and design. Data collection were performed by Natsuko Satomi-Tsushita. Analysis were performed by Kengo Nagashima. The first draft of the manuscript was written by Natsuko Satomi-Tsushita and all Authors commented on previous versions of the manuscript. All Authors read and approved the final manuscript.

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