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Significance of Preoperative Tooth Loss in Patients Who Underwent Gastrectomy for Gastric Cancer

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Abstract. *Background/Aim:* The relationship between gastric cancer and oral health has been reported in several studies. This study aimed to determine the relationship between the postoperative prognosis of gastric cancer and oral health using preoperative tooth loss as a simple index. *Patients and Methods:* We conducted a single-center retrospective cohort study. Patients were divided into two groups according to the number of tooth losses. The survival curve was constructed using the Kaplan–Meier method. We also performed univariate and multivariate analyses of overall survival based on Cox proportional hazard regression to determine prognostic factors. *Results:* A total of 191 patients were divided into two groups: those with seven or more tooth losses and those with less than seven tooth losses. The three-year overall survival rate was 71.5% in the group with seven or more tooth losses and 87.0% in the group with less than seven tooth losses. The group with seven or more tooth losses had a significantly lower overall survival rate compared to the group with less than seven tooth losses ($p=0.0014$). However, in multivariate analysis, tooth loss was

not identified as an independent prognostic factor whereas age, clinical T stage, CEA level, and serum albumin level were independent poor prognostic factors. *Conclusion:* Preoperative tooth loss was not a prognostic factor for gastric cancer after gastrectomy, but tooth loss may be a simple and useful method for evaluating frailty in patients.

Although the number of patients with gastric cancer has decreased with the improved management of *Helicobacter pylori* infection (1), gastric cancer is still the fifth most common cancer type and the fourth most common cause of cancer-related death worldwide (2). With the eradication of *Helicobacter pylori*, the majority of patients with gastric cancer are elderly. Systemic conditions and comorbidities are problematic in the treatment of gastric cancer in the elderly population. Establishing a useful scale for the preoperative evaluation of these facts and prognosis is necessary.

Oral health is affected by many daily aspects, such as smoking, drinking, obesity, and poor nutrition (3, 4). Many diseases, such as pneumonia, cardiovascular disease, stroke, and diabetes, are associated with oral health (5-8). Several studies have reported the relationship between periodontal disease and malignant tumors, including oral squamous cell carcinoma, esophageal squamous cell carcinoma, head and neck cancer, lung cancer, and pancreatic cancer (9-12). Tooth loss, which mostly occurs from periodontal disease (13), is a simple and useful method to assess oral health. We have previously reported tooth loss as an independent prognostic factor of esophageal cancer after esophagectomy (14). It has also been reported that there is a relationship between tooth loss and the occurrence of gastric adenocarcinomas (15-17). Recently, the relationship between tooth loss and gastric cancer has been discussed, and it has been reported that the type of oral microbiota differs between healthy people and those with gastric cancer (18, 19). However, the relationship between the

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Key Words: Tooth loss, gastric cancer, prognosis, frailty.

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Table I. Clinical characteristics of the patients.

	Tooth loss ≥ 7 TL-High group (n=95) n (%)	Tooth loss < 7 TL-Low group (n=77) n (%)	p-Value
Age, years	73, 58-93	70, 35-89	<0.0001
Sex (Male/Female)	72 (75.8)/23 (24.2)	54 (70.1)/23 (29.9)	0.40
Clinical T stage (T1,2/T3,4)	65 (68.4)/30 (31.6)	64 (83.1)/13 (16.9)	0.027
Clinical N stage (N0/N1-3)	74 (77.9)/21 (22.1)	64 (83.1)/13 (16.9)	0.39
Clinical stage (I/II, III)	60 (63.2)/35 (36.8)	60 (77.9)/17 (22.1)	0.036
Smoking history (Yes/No)	69 (72.6)/26 (27.4)	49 (63.6)/28 (36.4)	0.21
Drinking history (Yes/No)	52 (54.7)/43 (45.3))	48 (62.3)/29 (37.7)	0.32
Body Mass Index, kg/m ² ($<18.5/\geq 18.5$)	6 (6.3)/89 (93.7)	5 (6.5)/72 (93.5)	0.96
Comorbidity			
Hypertension	41 (43.2)	30 (39.0)	0.58
Diabetes	20 (21.1)	15 (19.5)	0.80
Other cancer	43 (45.3)	19 (24.7)	0.0052
CEA, ng/ml ($>5.0/\leq 5.0$)	20 (21.1)/75 (78.9)	9 (11.7)/68 (88.3)	0.10
CA19-9, U/ml ($>37.0/\leq 37.0$)	16 (16.8)/79 (83.2)	5 (6.5)/72 (93.5)	0.039
Serum hemoglobin, g/dl ($\leq 13.0/>13.0$)	48 (50.5)/47 (49.5))	36 (46.8)/41 (53.2)	0.62
Serum Albumin, g/dl ($\leq 4.0/>4.0$)	49 (51.6)/46 (48.4)	19 (24.7)/58 (75.3)	0.0003
Tooth loss, number	15, 7-28	1, 0-6	-

Continuous data are presented as medians with ranges.

outcome of gastric cancer after gastrectomy and tooth loss remains unclear. Furthermore, in patients undergoing gastrectomy, tooth loss may have an impact on postoperative complications, quality of life, and prognosis. Hence, in this study, we evaluated the relationship between tooth loss and the prognosis of gastric cancer after gastrectomy.

Patients and Methods

Patients. This was a retrospective study of 191 patients who underwent gastrectomy to achieve R0 resection for pathological stage I to III gastric cancer at Kobe University Hospital between January 2013 and December 2017. Patients with records of the preoperative number of teeth were included in the study, and those who received preoperative chemotherapy or underwent a palliative operation were excluded. In total, 172 patients were recruited for the analysis. The preoperative number of teeth was evaluated by dentists at our hospital as part of preoperative oral care before admission.

This study was approved by Kobe University Clinical Research Ethics Committee. All patients provided informed consent for the use of anonymized data using an opt-out methodology.

Diagnosis and treatment. Preoperative diagnosis and staging of gastric cancer were performed using computed tomography (CT) and endoscopic examination. Patients were classified according to the TNM classification of malignant tumors, eighth edition (20). Blood samples for hemoglobin, serum albumin, and tumor markers (CEA and CA 19-9) were obtained at the first visit to the hospital. Clinicopathologic data (*e.g.*, age, sex, and preoperative complications) were obtained from the patients' medical records.

Surgical outcomes. The surgery performed was either distal gastrectomy, total gastrectomy, or proximal gastrectomy. Mortality

was defined as postoperative death within 90 days after surgery, and morbidity was defined as postoperative complication of Clavien–Dindo (21) grade II or higher. Postoperative surveillance for disease recurrence was performed using CT every six months and esophagogastroduodenoscopy annually for at least five years after surgery (22). The causes of death were classified as gastric cancer or other diseases.

Statistical analysis. We used JMP version 10 (SAS Institute Inc., Cary, NC, USA) for the statistical analysis. Statistical significance was set at $p < 0.05$. We determined the appropriate number of tooth losses for the occurrence of death using the receiver operating characteristic (ROC) analysis and divided the patients into two groups based on the cutoff value. Differences between the two groups were analyzed using a two-sided *t*-test or Pearson's chi-square test. Survival curves for overall survival (OS), cumulative recurrence, and cause-specific survival (CSS) were constructed using the Kaplan–Meier method. The results of the two groups were compared using the log-rank test. Univariate and OS analyses were performed using Cox proportional hazard regression to adjust for confounding factors and to determine prognostic factors. The factors evaluated in the univariate analysis were age, sex, clinical T stage (T1-2/3-4), clinical N stage (N0/N1-3), smoking history (yes/no), drinking history (yes/no), preoperative body mass index (BMI) ($\leq 18.5/>18.5$ kg/m²), preoperative serum level of CEA ($5.0>/\leq 5.0$ ng/ml), preoperative serum level of CA 19-9 ($>37/\leq 37$ U/ml), preoperative serum hemoglobin ($\leq 13.0/>13.0$ g/dl), preoperative serum albumin ($\leq 4.0/>4.0$ g/dl), and preoperative tooth loss ($\geq 7/<7$).

Results

ROC analysis. ROC analysis indicated seven was the appropriate cutoff value for the number of tooth losses. We

classified patients with seven or more tooth losses as the TL-High group and those with six or less tooth losses as the TL-Low group.

Clinical characteristics. The preoperative patient characteristics are shown in Table I. The median number of teeth lost was 15 (7-28) in the TL-High group and one (0-6) in the TL-Low group. Patients in the TL-High group were significantly older (median age: 73 vs. 70, $p<0.0001$), had a higher prevalence of other cancers (45.5% vs. 24.7%, $p=0.0052$), and were more likely to have advanced gastric cancer ($p=0.036$) compared to those in the TL-Low group.

Surgical outcomes. The TL-High group had a significantly worse OS rate than the TL-Low group ($p=0.0014$) (Figure 1A). There were no significant differences in the cumulative recurrence rates and CSS rates between the two groups ($p=0.12$ and $p=0.14$, respectively) (Figure 1B and C).

Surgical outcomes of the patients are summarized in Table II. There was no difference in the proportion of surgical procedures between the two groups ($p=0.71$). The TL-High group had a higher proportion of patients with lymph node metastases (40.0% vs. 24.7%, $p=0.033$). More patients died in the TL-High group (44.2% vs. 19.5%, $p=0.0006$), but the proportion of deaths attributed to causes other than gastric cancer was also higher in the TL-High group (28.4% vs. 10.4%, $p=0.0023$). Although the TL-High group tended to have more pneumonia complications (12.6% vs. 6.5%, $p=0.18$), there was no significant difference in the overall incidence of complications between the two groups (40.0% vs. 39.0%, $p=0.89$).

Univariate and multivariate analysis. Table III shows the univariate and multivariate analyses of OS. In the univariate analysis, age, clinical T stage, CEA, serum albumin level, and tooth loss were significant prognostic factors. In the multivariate analysis, age [hazard ratio (HR)=2.18, 95% confidence interval (CI)=1.22-3.94], clinical T stage (HR=3.08, 95%CI=1.66-5.75), CEA (HR=1.90, 95%CI=1.03-3.48) and serum albumin level (HR=2.37, 95%CI=1.24-4.53) were significant independent prognostic factors. Tooth loss itself was not an independent prognostic factor.

Discussion

The study determined that a cutoff value of seven tooth losses was appropriate, consistent with a previous study on esophageal cancer and tooth loss (14).

Although this study showed that tooth losses of seven or more was associated with poor prognostic factors and worse OS compared to less than seven tooth losses, tooth loss itself was not identified as an independent prognostic factor for patients after elective gastrectomy for gastric cancer. Clinical

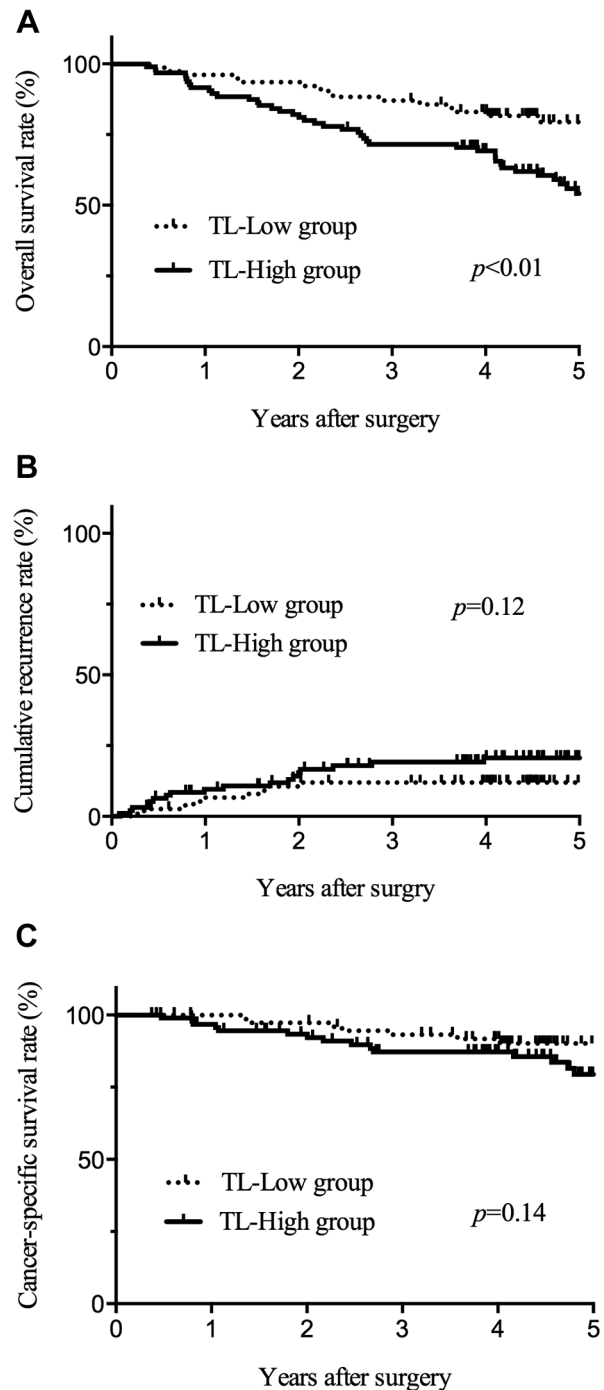


Figure 1. Kaplan-Meier curves of the two groups. A) Overall survival of the patients. B) Cumulative recurrence of the patients. C) Cancer-specific survival of the patients.

characteristics showed that older age, lower serum albumin level, and more advanced tumors were associated with a higher degree of tooth loss. We considered that these patients' fragility and malignancy affected the poor prognosis in the

Table II. *Surgical outcomes of the patients.*

	Tooth loss ≥ 7 TL-High group (n=95) n (%)	Tooth loss < 7 TL-Low group (n=77) n (%)	p-Value
Operation (DG/PG/TG)	61 (64.2)/4 (4.2)/30 (31.6)	47 (61.0)/2 (2.6)/28 (36.4)	0.71
Mortality	0	0	1.00
Morbidity (CD grade ≥ 2)			
All	38 (40.0)	30 (39.0)	0.89
Pneumonia	12 (12.6)	5 (6.5)	0.18
Delayed gastric emptying	5 (5.3)	3 (3.9)	0.67
Anastomosis leak	3 (3.2)	2 (2.6)	0.83
Pathological T stage (T1/T2-4)	56 (58.9)/39 (41.1)	53 (68.8)/24 (31.2)	0.18
Pathological N stage (N0/N1-3)	57 (60.0)/38 (40.0)	58 (75.3)/19 (24.7)	0.033
Pathological stage (I/II, III)	60 (63.2)/35 (36.8)	55 (71.4)/22 (28.6)	0.25
Death	42 (44.2)	15 (19.5)	0.0006
Cause of death (Gastric cancer/Others)	15 (15.8)/27 (28.4)	7 (9.1)/8 (10.4)	0.0023
Recurrence	19 (20.0)	9 (11.7)	0.14

DG: Distal gastrectomy; PG: proximal gastrectomy; TG: total gastrectomy; CD: Clavien–Dindo.

Table III. *Univariate and multivariate analysis of prognostic factors for overall survival.*

Factors	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	p-Value	Hazard ratio	95%CI	p-Value
Age, years (≥ 75 / < 75)	2.51	1.49-4.22	0.0005	2.18	1.22-3.94	0.0088
Sex (Male/female)	1.29	0.70-2.40	0.42			
Clinical T stage (T3,4/T1,2)	3.34	1.98-5.64	< 0.0001	3.08	1.65-5.75	0.0004
Clinical N stage (N1-3/N0)	2.26	1.28-3.99	0.0050	1.18	0.61-2.29	0.62
Smoking history (Yes/No)	1.15	0.65-2.02	0.64			
Drinking history (Yes/No)	0.69	0.41-1.15	0.15			
Body mass index, kg/m ² (< 18.5 / ≥ 18.5)	2.09	0.90-4.89	0.088			
CEA, ng/ml (> 5 / ≤ 5)	1.9	1.03-3.48	0.037	1.9	1.03-3.52	0.041
CA19-9, U/ml (> 37 / ≤ 37)	2.21	1.14-4.27	0.019	0.9	0.44-1.84	0.77
Serum hemoglobin, g/dl (≤ 13.0 / > 13.0)	2.63	1.51-4.60	0.0007	1.41	0.74-2.68	0.29
Serum albumin, g/dl (≤ 4.0 / > 4.0)	3.93	2.27-682	< 0.0001	2.37	1.24-4.53	0.0089
Tooth loss (≥ 7 / < 7)	2.52	1.40-4.56	0.0021	1.37	0.72-2.62	0.34

CI: Confidence interval.

group with a high number of tooth losses. However, the cancer-specific outcomes did not differ with respect to the extent of tooth loss. This may be due to the fact that the effects of death from other diseases, such as pneumonia, cardiovascular diseases, and stroke, which have been reported to be associated with tooth loss, have been eliminated (5-7).

Tooth loss was an independent poor prognostic factor in patients with esophageal cancer (14), but not in patients with gastric cancer in this study. This difference may be related to the minimal invasiveness of the procedure and the less malignant nature of gastric cancer compared to esophageal cancer. One possible reason for this could be the higher incidence of postoperative pneumonia in head and neck

cancer and esophageal cancer patients (10.6-22.3%) (23-28) than that in gastric cancer patients (9.9%) in this study. In fact, it has been reported that preoperative oral care could reduce postoperative pneumonia after surgery in patients with esophageal and colorectal cancer (29, 30). In addition, pneumonia has been reported to be a poor prognostic factor for patients with head and neck and esophageal cancers (31, 32). Preoperative oral care has been reported to improve surgical outcomes in several cancers.

Since tooth loss is affected by malnutrition and old age, in addition to their association with comorbidities other than gastric cancer, it can serve as a comprehensive marker of patient vulnerability. In patients with gastric cancer, the

status of missing teeth can be used to make decisions to recommend aggressive interventions, such as preoperative oral care, nutritional management, and rehabilitation.

Study limitations. First, this was a retrospective study conducted at a single hospital. A prospective large-scale study with postoperative oral care intervention is required to evaluate whether the intervention will improve the prognosis of gastric cancer after gastrectomy. Second, we did not consider details of oral conditions, such as the cause of tooth loss or whether the patients had artificial teeth. Periodontitis is the major cause of tooth loss, but some of the patients in our study lost their teeth to some degree of physical damage. In addition, records of oral treatment or use of artificial teeth were not included. Third, the difference in clinical characteristics between the two groups most likely acted as a confounding factor. Adjustment for these factors using a larger sample size is required.

Conclusion

Although our study could not demonstrate the use of preoperative tooth loss as an independent prognostic factor in gastric cancer, tooth loss may be a simple and useful method to evaluate frailty associated with the poor prognosis of patients who underwent elective gastrectomy for gastric cancer.

Conflicts of Interest

All Authors have no conflicts of interest or financial ties to disclose in relation to this study.

Authors' Contributions

Study conceptualization: Shingo Kanaji, Naoki Urakawa; Acquisition of data: Ryuichiro Sawada, Hitoshi Harada; Analysis and interpretation of data: Hironobu Goto, Hiroshi Hasegawa; Supervision: Yoshihiro Kakeji; Writing - original draft: Yuki Azumi; Writing - review and editing: Shingo Kanaji, Kimihiro Yamashita, Takeru Matsuda, Taro Oshikiri. All Authors read and approved the final manuscript.

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