ORIGINAL

The number of teeth is a prognostic indicator for chemotherapy in colorectal cancer

Toshihiro Nakao, Mitsuo Shimada, Takuya Tokunaga, Masaaki Nishi, Hideya Kashihara, Chie Takasu, Yuma Wada, and Toshiaki Yoshimoto

Department of Digestive and Transplant Surgery, Tokushima University Hospital, Tokushima, Japan

Abstract : Background : The oral and gut microbiomes are linked to prognosis in colorectal cancer patients undergoing surgery, chemotherapy, or radiotherapy. Dysbiosis in the oral microbiome can lead to tooth decay, periodontitis, and gingivitis, resulting in tooth loss. This study examined the relationship between tooth count and chemotherapy outcomes in colorectal cancer patients. Method : This retrospective cohort study involved 42 patients receiving chemotherapy for unresectable advanced or metastatic colorectal cancer at Tokushima University Hospital between October 2016 and December 2021. Prior to chemotherapy, dental panoramic radiographs were taken to determine tooth count. Patients were grouped based on the number of teeth (≥17 vs. ≤16), and overall survival (OS), progression-free survival (PFS), and adverse events were compared. Results : Patients with ≤16 teeth had significantly worse OS than those with ≥17 teeth (p = 0.024). PFS tended to be worse in patients with ≤16 teeth, albeit without significance (p = 0.097). The incidence of various adverse events did not differ between the groups. Anemia was the most common adverse event in patients with ≤16 teeth. Conversely, neutropenia was the most common adverse event in patients with ≥17 teeth. Conclusion : The number of teeth could be easily examined prognostic factor for chemotherapy in colorectal cancer. J. Med. Invest. 72 : 134-138, February, 2025

Keywords **:** *number of teeth, chemotherapy, FOLFOXIRI, rectal cancer, prognostic factor*

INTRODUCTION

Comprising more than 700 species of microorganisms residing in the human oral cavity, the oral microbiome is one of the most significant and complex communities in the human body (1). Dysbiosis of the oral microbiome is associated with oral diseases such as dental caries, periodontitis, gingivitis, and oral cancer as well as various chronic diseases such as cardiovascular disease, inflammatory bowel disease, diabetes, and Alzheimer's disease (2-5). Oral dysbiosis has also been reported to be associated with cancers such as gastrointestinal, esophageal, gastric, pancreatic, and colorectal cancers (6-9). Recent studies revealed that *Fusobacterium nucleatum* is commonly found in the biopsies and stool samples of patients with colorectal cancer (10, 11). Recent studies also reported that a high abundance of *F. nucleatum* in colorectal cancer tissue is associated with shorter overall survival (OS), recurrence, and chemoresistance (12, 13). Another study demonstrated that the synergistic effects of oral and intestinal bacteria could affect the prognosis of colorectal cancer and the effectiveness of radiotherapy (14). Dysbiosis in the oral cavity can lead to caries, periodontitis, and gingivitis, resulting in the loss of healthy teeth. Previous studies observed a positive association between the number of teeth and the risk of oral cancer (15). Other studies reported an association between the number of teeth and the risks of head and neck, esophageal, lung, stomach, pancreatic, and colorectal cancers (16-19). However, no report has evaluated the association between the number of teeth and the efficacy of chemotherapy in colorectal cancer to our knowledge. This is the first study to report the association between the dental status and the efficacy of chemotherapy in colorectal cancer.

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Address correspondence and reprint requests to Toshihiro Nakao, MD, PhD, FACS, Department of Digestive and Transplant Surgery, Tokushima University Hospital, 3-18-15 Kuramoto-cho, Tokushima City, Tokushima 7708503, Japan and Fax : +81-88-631-9698. E-mail : nakao.toshihiro@tokushima-u.ac.jp

METHODS

Patients

This retrospective cohort study included 42 patients who received chemotherapy for unresectable advanced and metastatic colorectal cancer at Tokushima University Hospital from October 2016 to December 2021. The primary endpoint was OS. The secondary endpoints were performance-free survival (PFS) and chemotherapy-induced adverse event rates. The inclusion criteria were as follows : age > 20 years ; a diagnosis of unresectable advanced and metastatic colorectal cancer ; receipt of chemotherapy ; a checkup with a dentist and dental panoramic radiographs obtained before chemotherapy ; and absence of other malignant diseases. The study protocol was approved by the Ethics Committee of Tokushima University (approval number : 3215-1) and conducted in accordance with the provisions of the Declaration of Helsinki. All patients provided informed consent for the use of their data.

Number of teeth

All patients were checked by a dentist, and dental panoramic radiographs were taken prior to chemotherapy. The number of healthy teeth without loss or evidence of treatment was counted on the radiographs.

Chemotherapy

The FOLFOXIRI regimen was used as the first-line chemotherapy for unresectable advanced and metastatic colorectal cancer. The regimen consisted of an intravenous infusion of irinotecan at a dose of 150 mg/m^2 for 90 min, intravenous infusion of leucovorin at a dose of 200 mg/m^2 for 120 min, intravenous infusion of oxaliplatin at a dose of 85 mg/m^2 for 120

min, and continuous intravenous infusion of 5-fluorouracil at a dose of 2400 mg/m^2 for 44 h (7, 8). Immediately prior to irinotecan, patients received panitumumab at a dose of 60 mg/kg for 60 min, cetuximab at a dose of 250 mg/m^2 for 60 min, or bevacizumab at a dose of 5 mg/kg for 90 min. All patients were pretreated intravenously with palonosetron hydrochloride (0.75 mg), dexamethasone sodium phosphate (6.6 mg), and fosaprepitant meglumine (150 mg) 1 h prior to irinotecan administration. Chemotherapy was administered essentially every 2 weeks until cancer progressed, an unacceptable adverse event occurred, or the patient refused further chemotherapy. Toxicity was assessed immediately prior to each cycle using the Common Terminology Criteria for Adverse Events version 5.0 (9). The second-line and subsequent treatments after FOLFOXIRI were administered in accordance with the guidelines (20).

Statistical analysis

Categorical variables were analyzed using Fisher's exact test, and continuous variables were analyzed using Student's *t*-test. Kaplan–Meier curves were used to visualize differences in OS and PFS according to the number of teeth (≥17 teeth vs. ≤16 teeth), and their significance was assessed by univariate analysis using the log-rank test. OS was defined as the time from the date of curative surgery to that of death or the last follow-up with no restriction on the cause of death. PFS was defined as the duration from the date of primary treatment to that of the first evidence of disease progression or death.

All statistical analyses were performed using EZR version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (version 4.03, R Foundation for Statistical Computing, Vienna, Austria) (21). EZR is a modified version of R commander (version 2.7-1) designed to add statistical functions frequently used in biostatistics. $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

In total, 42 patients were enrolled in the study. The median follow-up duration was 16.2 months (interquartile range = 1.7–36.5), and the median number of healthy teeth was 13 (interquartile range = 7–17.75). Patients were divided into two groups using a cutoff of 16 teeth, half of the maximum number of adult teeth. The characteristics of all patients, those with ≥17 teeth, and those with ≤16 teeth are summarized in Table 1. Patients

Table 1. Patient characteristics

		Number of teeth		
	Total (n = 42)	≤16 (n = 30)	17≤ (n = 12)	*p*
Age, years	61.5 (34-85)	66.5 (34-85)	50.5 (37-70)	0.003
Sex				0.158
Male	26	21	5	
Female	16	9	7	
ASA-PS				0.030
1	19	10	9	
2	19	17	2	
3	4	3	1	
BMI, kg/m^2	22.7 ± 3.7	22.8 ± 3.8	22.6 ± 3.5	0.738
Stage				0.290
II	5	5	0	
III	13	7	6	
IV	13	10	3	
Recurrence	11	8	3	
Location				0.298
Right side	5	5	0	
Left side	37	25	12	
Molecular targeted therapy				0.290
Anti-EGFR monoclonal antibody	17	10	7	
Anti-VEGF monoclonal antibody	23	18	5	
None	2	2	0	
Total cycles	5.5 (2-22)	5.5 (2-18)	5.5 (2-22)	0.955
Blood examination at start of chemotherapy				
WBC (/μL)	6,557 ± 2,064	6,536 ± 2,015	6,608 ± 2,358	0.967
Neut (/μL)	4,474 ± 1,886	4,407 ± 1,640	4,638 ± 2,525	0.989
Hemoglobin (g/dL)	12.3 ± 2.6	12.4 ± 2.9	12.1 ± 1.8	0.933
Plt (10,000/μL)	29.5 ± 21.0	29.4 ± 24.4	29.7 ± 10.5	0.303
CEA (ng/mL)	11.1 (0.7-3760)	11.8 (1.4-3760)	8.6 (0.7-423)	0.422
CA19-9 (U/mL)	44 (0.85-776)	49 (0.85-776)	26 (1-49)	0.688

ASA-PS, American Society of Anesthesiologists physical status ; BMI, body mass index ; EGFR, epidermal growth factor receptor ; VEGF, vascular endothelial growth factor ; WBC, white blood cells ; Neut, neutrophils ; Plt, platelets ; CEA, carcinoembryonic antigen ; CA19-9, carbohydrate antigen 19-9

with ≤16 teeth were significantly older than those with ≥17 teeth (p = 0.003). The American Society of Anesthesiologists physical status was significantly worse in patients with ≤16 teeth than in those with ≥17 teeth (p = 0.030). There were no differences between the groups regarding sex, oncologic factors, the use of molecular targeted therapies, the total number of administered cycles, or pre-chemotherapy blood examination data.

Long-term outcomes

OS was significantly worse in patients with ≤16 teeth than in those with ≥17 teeth (p = 0.024, Fig. 1). Similarly, PFS tended to be worse in patients with ≤16 teeth (p = 0.097, Fig. 2).

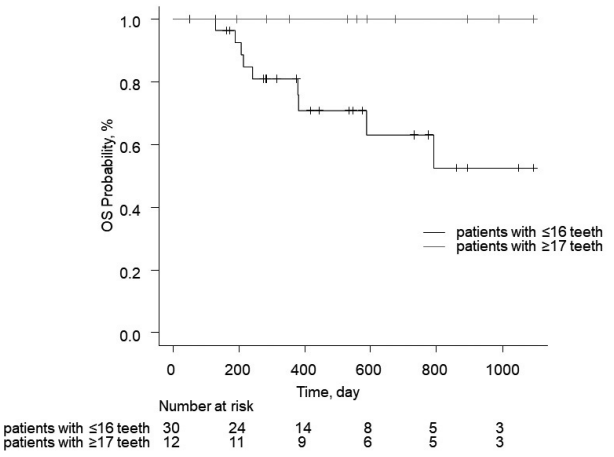

Fig. 1. Comparison of overall survival between patients with ≥17 teeth and those with ≤16 teeth.

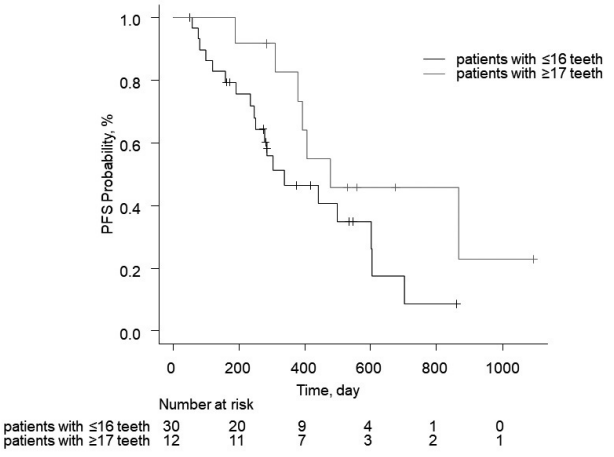

Fig. 2. Comparison of performance-free survival between patients with ≥17 teeth and those with ≤16 teeth.

Adverse events of chemotherapy

Table 2 summarizes the adverse events that occurred during chemotherapy. The most common adverse event was anemia, which occurred in 88.1% of all patients, followed by neutropenia (83.3%) and anorexia (59.5%). The most common Grade 3 or higher adverse event was neutropenia, which occurred in 38.1% of all patients. There was no significant difference in the incidence of various adverse events between patients with ≤16 teeth and those with ≥17 teeth. Anemia was the most common adverse event in patients with ≤16 teeth, followed by neutropenia and anorexia. Meanwhile, neutropenia was the most common adverse event in patients with ≥17 teeth, followed by anemia, whereas neutropenia and anorexia were equally common in this group.

DISCUSSION

In this study, patients with colorectal cancer and fewer teeth had worse OS and PFS following chemotherapy than those with more teeth. To the best of our knowledge, no prior reports discussed the relationship between the number of teeth and the efficacy of chemotherapy in colorectal cancer. When the balance of the oral microbiome is disrupted, oral diseases such as caries, periodontitis, and gingivitis can occur, potentially leading to tooth loss. Koliarakis *et al*. proposed a relationship between oral bacteria and the development of colorectal cancer (6). Oral pathogens such as *F. nucleatum* and *Porphyromonas gingivalis*, the counts of which are increased by periodontal disease, are ingested and incorporated into the intestinal microbiota of the colon, causing intestinal dysbiosis. A chronic inflammatory condition develops via the activation of macrophages, disruption of the mucosal barrier, and the activation of inflammatory cytokines, which in turn injure the colonic epithelium and promote carcinogenesis. Yu *et al*. reported that *F. nucleatum* was abundant in the colorectal cancer tissues of patients with recurrence after chemotherapy and that a molecular network of Toll-like receptors, microRNAs, and autophagy that clinically, biologically, and mechanistically promoted resistance to chemotherapy was established (13). Dong *et al*. found that *F. nucleatum* in the oral microbiome migrates to colorectal cancer lesions, reduces the efficacy of radiotherapy, and negatively affects prognosis (14). According to their report, oral bacteria can influence tumor development by migrating to the tumor via the intestinal tract. The number of teeth might indirectly reflect this.

In this study, there was no significant correlation between the number of teeth and the adverse events of chemotherapy. However, neurotoxicity was more common in patients with ≥17 teeth than in patients with ≤16 teeth. Shen *et al*. demonstrated the role of the gut microbiome in the development of oxaliplatin-induced neurotoxicity (22). They found that oxaliplatin-induced mechanical hyperalgesia was reduced in germ-free mice and in mice pretreated with antibiotics, and restoring the microbiota of germ-free mice abrogated this protection. Changes in the oral microbiota might influence the development of neurotoxicity, and the number of teeth could indirectly reflect this change.

In conclusion, the number of teeth might be an easily examined prognostic factor for chemotherapy in patients with colorectal cancer. This study had several limitations. The most important limitation was the small sample size because the study was conducted in a single institution. A multicenter study is needed to overcome this limitation. The second limitation was that that this was a retrospective study, and prospective research is needed. The third limitation was that only FOLFOXIRI was used as chemotherapy in this study. FOLFIXIRI is used as the first-line regimen for colorectal cancer in our institution, but this problem can also be overcome by conducting a multicenter study. The fourth limitation was that the oral microbiome was not examined. Examination of the oral microbiome before treatment would better demonstrate the relationship among the oral microbiome, number of teeth, and prognosis of chemotherapy.

Table 2. Adverse events during chemotherapy

	Total (n=42)		
	All grades	Grade 1–2	Grade 3–4
Alopecia	5 (11.9%)	5 (11.9%)	0 (0.0%)
Anemia	37 (88.1%)	33 (78.6%)	4 (9.5%)
Anorexia	25 (59.5%)	24 (57.1%)	1 (2.4%)
Asthenia	9 (21.4%)	9 (21.4%)	0 (0.0%)
Diarrhea	12 (28.6%)	12 (28.6%)	0 (0.0%)
Dysgeusia	5 (11.9%)	5 (11.9%)	0 (0.0%)
Hypertension	2 (4.8%)	2 (4.8%)	0 (0.0%)
Nausea	22 (52.4%)	20 (47.6%)	2 (4.8%)
Neurotoxicity	14 (33.3%)	14 (33.3%)	0 (0.0%)
Neutropenia	35 (83.3%)	19 (45.2%)	16 (38.1%)
Hand-foot syndrome	1 (2.4%)	1 (2.4%)	0 (0.0%)
Platelet count decreased	21 (50.0%)	19 (45.2%)	2 (4.8%)
Proteinuria	2 (4.8%)	2 (4.8%)	0 (0.0%)
Skin toxicity	8 (19.0%)	8 (19.0%)	0 (0.0%)
Stomatitis	7 (16.7%)	6 (14.3%)	1 (2.4%)

	≤16 teeth (n = 30)			≥17 teeth (n = 12)			*p*	
	All grades	Grade 1–2	Grade 3–4	All grades	Grade 1–2	Grade 3–4	All grades	Grades 3–4
Alopecia	4 (13.3%)	4 (13.3%)	0 (0.0%)	1 (9.3%)	1 (9.3%)	0 (0.0%)	1.000	-
Anemia	28 (93.3%)	26 (86.7%)	2 (6.6%)	9 (75.0%)	7 (58.3%)	2 (16.7%)	0.131	0.565
Anorexia	19 (63.3%)	18 (60.0%)	1 (3.3%)	6 (50.0%)	6 (50.0%)	0 (0.0%)	0.498	1.000
Asthenia	10 (33.3%)	10 (33.3%)	0 (0.0%)	5 (41.7%)	5 (41.7%)	0 (0.0%)	0.726	-
Diarrhea	8 (26.7%)	8 (26.7%)	0 (0.0%)	4 (33.3%)	4 (33.3%)	0 (0.0%)	0.715	-
Dysgeusia	3 (10.0%)	3 (10.0%)	0 (0.0%)	2 (16.7%)	2 (16.7%)	0 (0.0%)	0.613	-
Hypertension	1 (3.3%)	1 (3.3%)	0 (0.0%)	1 (9.3%)	1 (9.3%)	0 (0.0%)	0.495	-
Nausea	14 (46.6%)	12 (40.0%)	2 (6.6%)	8 (66.7%)	8 (66.7%)	0 (0.0%)	0.169	1.000
Neurotoxicity	8 (26.7%)	8 (26.7%)	0 (0.0%)	6 (50.0%)	6 (50.0%)	0 (0.0%)	0.169	-
Neutropenia	24 (80.0%)	14 (46.7%)	10 (33.3%)	11 (91.7%)	5 (41.7%)	6 (50.0%)	0.651	0.483
Hand-foot syndrome	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000	-
Platelet count decreased	16 (53.2%)	14 (46.6%)	2 (6.6%)	5 (41.7%)	5 (41.7%)	0 (0.0%)	0.743	1.000
Proteinuria	2 (6.6%)	2 (6.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000	-
Skin toxicity	4 (13.3%)	4 (13.3%)	0 (0.0%)	4 (33.3%)	4 (33.3%)	0 (0.0%)	0.195	-
Stomatitis	5 (16.7%)	4 (13.3%)	1 (3.3%)	2 (16.7%)	2 (16.7%)	0 (0.0%)	1.000	1.000

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AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

The authors declare no conflict of interest relevant to this research.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol for this research project was approved by the Tokushima University Ethics Committee (approval number 3215-1) and was performed in accordance with the provisions of the Declaration of Helsinki. Informed consent was obtained from all patients.

PATIENT CONSENT FOR PUBLICATION

All patients provided informed consent for their information to be published.

AUTHOR CONTRIBUTIONS

TN and MS were involved in the study design and data interpretation. TT, MN, HK, CT, YW, and TY were involved in the data analysis. All authors revised the manuscript, approved the manuscript to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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