# Association of dental occlusal support with the Prognostic Nutritional Index in patients with esophageal cancer who underwent esophagectomy

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Reiko Yamanaka-Kohno designed the study, obtained research funds, performed data collection, analysis and interpretation of data, and wrote the initial draft of the manuscript. Yasuhiro Shirakawa, Shunsuke Tanabe, and Toshiyoshi Fujiwara contributed to the analysis and interpretation of data from the perspective of esophageal surgeons and assisted in the preparation of the manuscript. Mami Inoue-Minakuchi and Aya Yokoi contributed to data collection, analysis and interpretation of data, and assisted in the preparation of the manuscript. Misato Muro and Hirotaka Kosaki contributed to data collection. Manabu Morita contributed to analysis and interpretation of the data from the perspective of a dentist, epidemiologist, and statistician, and assisted in the preparation of the manuscript. All authors contributed to interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree 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.

**Abstract**

Background

The Prognostic Nutritional Index is useful for predicting surgical risk and overall survival based on preoperative immunological and nutritional status in patients undergoing digestive organ cancer surgery. The purpose of this study was to examine the association between the Prognostic Nutritional Index and dental status in patients with esophageal cancer who underwent esophagectomy.

Methods

This retrospective case-control study included 73 patients who underwent resection of esophageal cancer (69 males, 4 females; age 36-83). General and dental status were evaluated. The Prognostic Nutritional Index was calculated based on the serum albumin concentration and the total lymphocyte count, and subjects were divided into two groups based on index scores: a higher group, characterized by scores ≥ 45 (n = 54); and a lower group, characterized by scores < 45 (n = 19). Univariate analysis and multiple logistic regression analysis were used to compare between groups.

Results

Total protein, C-reactive protein, the number of sound and total decayed, missing and filled teeth, and the rate of patients with poor dental occlusal support showed significant differences between the lower and higher Prognostic Nutritional Index groups ($p < 0.05$). Stepwise logistic regression analysis by backward selection approach showed that low total protein, few sound teeth and poor status of dental occlusal support were significantly associated with the lower Prognostic Nutritional Index ($p = 0.007$, 0.042 and 0.009, respectively).

Conclusion

Dental status, especially dental occlusal support and the number of sound teeth, showed a positive relationship with the Prognostic Nutritional Index in esophageal cancer patients who underwent esophagectomy.

**Key Words:** Esophageal cancer surgery, Prognostic factor, Nutrition

## Introduction

Esophageal cancer is the eighth most common cancer worldwide and the sixth cancer-related cause of death [1]. The global incidence rate and mortality of esophageal cancer are expected to increase in the coming decades [2]. Esophageal cancer has a comparatively poor prognosis, with a 5-year survival rate ranging from 11.4% to 79.7% depending on the stage of cancer progression, and an overall 5-year survival of 43.7% at designated cancer care hospitals in Japan [3]. Although complete resection of esophageal cancer is one of the favorable prognostic factors, esophagectomy has been identified as a particularly complex surgical procedure due to the documented high rates of perioperative complications and mortality [4].

Prediction of surgical risk and survival by evaluating preoperative status can be a useful strategy to prevent postoperative complications and improve overall survival for patients with esophageal cancer. Onodera's Prognostic Nutritional Index (PNI) was found to be one of the predictors of outcomes after gastrectomy [5]. In 1984, Onodera *et al*. proposed a linear predictive model relating the risk of operative complications, mortality, or both to nutritional status using the following equation: PNI = 10 × serum albumin level (Alb) (g/dl) + 0.005 × total lymphocyte count (TLC)/$mm^3$ in peripheral blood [5]. The PNI is simple to calculate, easy to interpret, and has been widely used to assess the preoperative immunological and nutritional status of patients undergoing digestive surgery [6,7].

Previous studies demonstrated the relationship between nutritional status and occlusal support. It has been reported that posterior natural tooth contact loss affected the intake of vitamins and dietary fiber [8]. Moreover, a large-scale, cross-sectional survey showed that loss of occlusion of natural teeth

was a risk factor for malnutrition in community-dwelling frail elderly persons [9]. In addition, Wakabayashi *et al.* reported that occlusal support is directly associated with dysphagia and indirectly with malnutrition and activities of daily living via dysphagia in aged individuals needing long-term care [10]. Loss of posterior dental occlusion could be associated with decreased oral intake of vitamins and dietary fiber, dysphagia, and malnutrition.

Given this background, we thought that the dental status of esophageal cancer patients could be associated with the PNI. We hypothesized that dental status, especially occlusal support status, is associated with the PNI in patients with esophageal cancer undergoing esophagectomy. The purpose of this study was to examine the relationship between dental status and the PNI of patients with esophageal cancer who underwent esophagectomy.

## Materials and Methods

### *Human rights statement*

This retrospective, observational study was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital (No. Ken1907-014). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. All patients received the right to opt out from this observational study and patient anonymity was preserved.

### *Subjects*

A total of 73 patients who underwent esophageal cancer surgery (M/F: 68/5, 68.5±9.1 y) in Okayama University Hospital from January to December 2012 were enrolled in this study. Our university hospital has a Perioperative Management Center (PERIO) that consists of a multidisciplinary team including dental staff who perform oral management in the perioperative period. All esophageal cancer patients who underwent esophagectomy were under the management of this center; therefore, the detailed dental records of esophageal cancer patients who underwent esophagectomy were available.

***Data collection***

All subjects underwent esophagectomy with PERIO management. The patients who underwent second-stage surgery were excluded. Medical data, except blood data, and dental data were collected for all subjects on the day of the first dental examination for perioperative oral management. The first dental examination was performed before surgery. The data from blood tests performed immediately before surgery were analyzed.

***Parameters of general status***

Age, sex, cancer stage, body mass index (BMI), drinking and smoking habits, presence or absence of neoadjuvant chemotherapy and operative procedures were recorded. Operative procedures were divided in 4 groups which were Right thoracotomy, Thoracoscopic surgery, Transhiatal esophagectomy and Left thoracolaparotomy (lower esophagectomy). Drinking and smoking habits were divided into 2 categories, “Yes” and “No”. “Yes” included current and former drinkers and smokers. Never drinkers and never smokers were assigned to “No”. The following data were obtained from blood tests performed immediately before surgery: total white blood cell (WBC)count, TLC, total protein (TP), Alb, and C-reactive protein (CRP).

***Parameters of dental status***

The following dental status indicators were evaluated: numbers of present, sound, decayed (D), missing (M), filled (F), and total decayed, missing, and filled (DMF) teeth [11], the Community Periodontal Index (CPI) [12], and the number of functional tooth units (FTUs) [12-14]. The CPI was used to record periodontal status. The scores of the CPI index are as follows: healthy periodontal conditions (Score 0); gingival bleeding (Score 1); dental calculus and bleeding (Score 2); shallow periodontal pockets (4 to 5 mm) (Score 3); and deep periodontal pockets (6 mm or more) (Score 4). Periodontal status was divided into 2 categories, “Healthy or mild periodontitis” (CPI 0,1,2) and “Moderate or severe periodontitis” (CPI 3, 4). Patients without teeth were assigned to “Healthy or mild periodontitis”, because they had no periodontal pockets and no periodontitis at the time. The number of FTUs was used to evaluate posterior occlusal support without wisdom teeth, which is widely used for evaluating dental occlusal support [12-14]. The number of FTUs was defined as the numbers of pairs of opposing posterior natural teeth and artificial teeth that are implant-supported, fixed (bridge pontics), and removable prostheses. Dental carious teeth with extensive coronal destruction, and missing teeth were regarded as non-functional. Two opposing premolars were defined as one FTU, and two opposing molars were defined as two FTUs. Therefore, the score ranged from 0 to 12, and a person with complete posterior occlusal support received a score of 12; higher scores represented better posterior occlusal support, namely dental occlusal support. The patients were divided into two groups by the number of FTUs, with 3 as a cut-off value; individuals with $\leq 2$ FTUs were defined as having poor dental occlusal support, because the frequency distribution of FTUs was not a normal distribution by the Kolmogorov-Smirnov test ($p < 0.001$), and there were no patients with FTU = 3.

***PNI calculation and grouping into higher and lower levels***

PNI was calculated according to Onodera's method: PNI = 10 × Alb (g/dl) + 0.005 × TLC (/$mm^3$) in peripheral blood [5]. The patients were divided into two groups based on the previous studies: the higher PNI group (PNI ≥ 45, n = 54) and the lower PNI group (PNI < 45, n = 19) [15, 16~~, 17~~].

***Statistical analyses***

Parameters of medical and dental status were compared between the higher and lower PNI groups with Mann-Whitney *U* test, Fisher's exact test, and the Chi-squared test. Logistic regression analysis with stepwise regression manner by backward selection approach was used to determine the characteristics of the PNI. In the stepwise method, all parameters were regarded as the independent variables at first, and each parameter were removed from the model at $p < 0.10$ and added to the model at $p < 0.05$. Results were considered significant at $p < 0.05$. All statistical analyses were performed using SPSS for Windows version 20 (SPSS Inc., Chicago, IL).

**Results**

***Characteristics of subjects in the lower and higher PNI groups***

Nineteen of the 73 patients were in the lower PNI (< 45) group, and 54 patients were in the higher PNI (≥ 45) group. The characteristics of the subjects in the lower and higher PNI groups are shown in Table 1. There were no significant differences between the groups in age, sex, cancer stage, BMI, drinking and smoking habits, presence or absence of neoadjuvant chemotherapy and operative procedures. The WBC count showed no significant difference, while TP and CRP showed significant differences between the

lower and higher PNI groups ($p < 0.05$) (Table 2).

***Dental status and PNI***

The dental status of subjects in the lower and higher PNI groups is shown in Table 3. The number of sound teeth was significantly less in the lower PNI group than in the higher PNI group, whereas the number of DMF teeth was significantly greater in the lower PNI group than in the higher PNI group. The rate of patients with poor dental occlusal support was higher in the lower PNI group than in the higher PNI group. There were no significant differences between the groups in numbers of present, D, M, and F teeth, respectively, and in periodontal status.

***Factors related to the PNI***

In the stepwise logistic regression model by backward selection approach, low TP, few sound teeth and poor dental occlusal support were significantly associated with lower PNI after adjusting for other parameters (Table 4).

## Discussion

In this study, low TP, few sound teeth and poor dental occlusal support were found to be significantly associated with the lower PNI on logistic regression analysis with stepwise method by backward selection approach. This result supports our hypothesis that dental status, especially sound teeth and dental occlusal support, is related to the PNI in patients with esophageal cancer who undergo esophagectomy.

The most important finding of this study is that dental occlusal support showed a positive

relationship with the PNI in esophageal cancer patients who underwent esophagectomy. This finding is novel and significant. A cross-sectional observational study reported that loss of posterior teeth occlusion was independently associated with dysphagia risk, and maintaining and restoring posterior teeth occlusion may be an effective measure to prevent dysphagia in older nursing home residents [17]. Although a causal relationship between dental occlusal support and PNI remains unclear, we propose that dental occlusal support may be clinically useful, as a potential risk factor for postoperative complications, particularly pneumonia after esophagectomy. Furtherer studies are required to clarify the causal relationship between maintaining or providing an appropriate dental prosthesis and prognosis.

Recently, the PNI has been increasingly recognized as the best prognostic score for predicting surgical risk and overall survival in esophageal cancer patients among other prognostic scores, such as the modified Glasgow Prognostic Score (mGPS), the Neutrophil Lymphocyte Ratio (NLR), the Platelet Lymphocyte Ratio (PLR), and the Prognostic Index (PI) [16, 18, 19]. It is interesting that the PNI, which has high accuracy in predicting the prognosis of patients with esophageal cancer, was associated with dental occlusal support. This is the first study demonstrating a relationship between dental occlusal support status and a prognostic factor in patients with esophageal cancer who underwent esophagectomy.

In this study, the number of FTUs was used as an indicator of dental occlusal support. Previous studies reported a positive relationship between the number of FTUs and masticatory ability [20, 21]. Iwasaki *et al.* reported the temporal association of impaired dentition with decreases in selected nutrient and food group intakes among older Japanese adults for five years using FTUs [22]. Moreover, a systematic review reported that the number of FTUs was significantly associated with nutritional status in

elderly persons [23]. It was shown that well-nourished subjects had significantly more FTUs than individuals at risk of malnutrition. Persons with more FTUs might have better nutritional status and PNI, because they have better masticatory ability and more variety in their nutrient and food intakes.

Enhanced recovery after surgery (ERAS) programs pay attention to reducing the length of hospital stay for patients undergoing digestive tract surgery [4, 24]. Oral nutrition is set as one goal of ERAS programs. We sometimes experience that nutritional status clinically improves after appropriate dental prostheses are provided for perioperative patients [25]. Dental occlusal support is indispensable for swallowing and having a normal diet. The number of FTUs is an indicator for evaluating posterior occlusal support that includes artificial teeth. Providing appropriate dental prostheses might accelerate enhanced recovery after surgery, especially for patients without natural dental occlusal support. Perioperative oral care intended to control dental infection can reduce postoperative pneumonia in patients with esophageal cancer [26, 27]. We proposed another important role for dental intervention, providing an appropriate dental prosthesis in addition to infection control in esophageal cancer patients who undergo esophagectomy.

PNI was significantly associated with the number of sound teeth. There are no reports which showed a relationship between number of sound teeth and systemic condition, to our knowledge. On the other hand, there are several reports which showed the relationship between the numbers of present teeth or missing teeth and cancer occurrence [28]. To evaluate the number of present teeth and missing teeth might be relatively easy, because only judging whether tooth exist or not. As to evaluate the numbers of sound or DMF teeth, diagnosis by dentists is essential and cumbersome, there might be few studies which

treated the numbers of sound or DMF teeth as parameters. The number of DMF teeth have almost opposite meaning to the number of sound teeth, and presents dental caries experience in them life. Although there are no evidence of relationship DMF and cancer incidence or survival rate of cancer, so on, a positive association between caries experience and metabolic syndrome in Japanese adults were reported recently [29]. In the future, studies which showed the relationship between caries experience or the number of sound teeth and incidence or prognosis of cancer might increase gradually. Further studies are required, and this study is the first report which showed a positive relationship between PNI and the number of sound teeth in the esophageal cancer patients who underwent esophagectomy.

In addition to poor dental occlusal support and few sound teeth, low TP was associated with the lower PNI after adjusting for potential confounders. PNI is a prognostic factor based on immunity and nutrition used to predict surgical risk and overall survival in esophageal cancers patients, and it is calculated using serum Alb and TLC. TP is mainly divided into Alb and globulin. Alb generally accounts for more than half of TP, and TP is positively correlated with Alb. Thus, in the present study, the result that low TP has a significantly correlation with the lower PNI appears reasonable. On the other hand, CRP is an indicator of chronic inflammation. It was reported that an increasing CRP level was associated with a decreasing survival rate and an increasing mortality rate in advanced cancer patients [30]. Since there are clear dose-effect relationships between elevated CRP levels and outcomes, CRP is considered useful for predicting prognoses in patients with advanced cancer. However, in this study, no significant relationship between high CRP and lower PNI was identified from logistic regression analysis. This result might have been affected by the fact that cancer stage in 60% of subjects (n = 44/73) was 0, I or II and

relatively early stages.

There are some limitations in this study. First, the subjects of this study were few, from only one hospital, and only Japanese. Further studies are required to investigate the relationship between the PNI and dental occlusal support. Second, a causal relationship between the PNI and dental occlusal support cannot be deduced from this study because it was observational. Further interventional research is necessary to clarify the causal relationship between providing an appropriate dental prosthesis and nutritional status, prognosis, and incidence of postoperative complications in esophageal cancer patients who underwent esophagectomy. If the nutritional status of esophageal cancer patients with poor dental occlusion were to improve after providing appropriate dental prostheses in intervention studies, dental treatment might give such patients a better prognosis. Finally, the relationship between actual prognosis and dental occlusal support is not clear, because the PNI, which is a prognostic index, was used as an objective variable in the present study. Further studies are required to clarify the relationship between actual prognosis, including postoperative complications, weight loss, length of hospital stay, and overall survival rate etc. and dental status.

Dental status, especially poor dental occlusal support and few sound teeth, was associated with a lower PNI in the present study. This result suggests that poor dental occlusal support and few sound teeth might be related to immunological and nutritional problems leading to higher surgical risk and lower survival in patients with esophageal cancer undergoing esophagectomy.

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**Conflicts of Interest**

The authors declare that they have no conflict of interest to report.

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Table 1. Characteristics of the study population

| Parameter | Lower PNI group (n = 19) | Higher PNI group (n = 54) | Total (n = 73) | P value[†] |
|---|---|---|---|---|
| Age (y) | 71.0 (61.0, 74.0)[‡] | 64.0 (60.0, 69.5) | 65.0 (60.0, 71.5) | 0.06 |
| Sex (n) | | | | 0.60 |
| Male/Female | 17/2 | 51/3 | 68/5 | |
| Cancer stage (n) | | | | |
| 0, I and II | 8 | 36 | 44 | 0.10 |
| III and IV | 11 | 18 | 29 | |
| BMI (kg/mm$^2$) | 21.1 (17.6, 26.8) | 21.4 (19.1, 25.1) | 21.1 (18.9, 25.4) | 0.83 |
| Drinking habit (n) Yes/No | 16/3 | 49/5 | 65/8 | 0.42 |
| Smoking habit (n) Yes/No | 18/1 | 51/3 | 69/4 | 1.00 |
| Neoadjuvant chemotherapy (n) Present/Absent | 10/9 | 25/29 | 35/38 | 0.79 |
| Operative procedures | | | | |
| Right thoracotomy | 5 | 10 | 15 | 0.07 |
| Thoracoscopic surgery | 10 | 42 | 52 | |
| Transhiatal esophagectomy | 3 | 1 | 4 | |
| Left thoracolaparotomy (lower esophagectomy) | 1 | 1 | 2 | |

[†]Mann-Whitney *U* test or Fisher's exact test, [‡]Median (25%, 75%).

Table 2. Distribution of serum parameters

| Parameter | Lower PNI group (n = 19) | Higher PNI group (n = 54) | Total (n = 73) | P value† |
|---|---|---|---|---|
| WBC ($10^3$/μl) | 6.6 (4.3, 9.0)‡ | 5.6 (4.6, 7.3) | 5.7 (4.5, 7.5) | 0.481 |
| TP (g/dl) | 6.4 (5.9, 7.1) | 6.8 (6.5, 7.1) | 6.7 (6.4, 7.1) | 0.029* |
| CRP (mg/dl) | 0.60 (0.13, 1.72) | 0.10 (0.05, 0.28) | 0.15 (0.05, 0.53) | 0.005** |

†Mann-Whitney *U* test, ‡Median (25%, 75%).

*P < 0.05, **P < 0.01

Table 3. Dental status of subjects in the lower and higher PNI groups

| Parameter | Lower PNI group (n = 19) | Higher PNI group (n = 54) | Total (n = 73) | P value† |
|---|---|---|---|---|
| Number of present teeth | 22.0 (13.0, 23.0)‡ | 21.0 (12.0, 27.0) | 21.0 (13.0, 27.0) | 0.354 |
| Number of sound teeth | 4.0 (0.0-10.0) | 8.0 (3.8, 16.0) | 7.0 (1.5, 14.0) | 0.025* |
| Number of D teeth | 1.0 (0.0, 5.0) | 0.0 (0.0, 2.0) | 0.0 (0.0, 2.0) | 0.175 |
| Number of M teeth | 9.0 (6.0, 16.0) | 7.0 (1.0, 16.8) | 7.0 (2.0, 16.0) | 0.313 |
| Number of F teeth | 8.0 (3.0, 13.0) | 7.5 (2.0, 13.0) | 8.0 (2.5, 13.0) | 0.830 |
| Number of DMF teeth | 24.0 (19.0, 28.0) | 20.0 (12.8, 25.0) | 21.0 (15.0, 27.0) | 0.021* |
| Dental occlusal support (n) | | | | |
| Poor: FTUs 0-2 | 6 | 5 | 11 | 0.029* |
| Good: FTUs 4-12 | 13 | 49 | 62 | |
| Periodontal status (n) | | | | |
| Healthy or mild periodontitis: No teeth or CPI 0,1, 2 | 8 | 16 | 24 | 0.236 |
| Moderate or severe periodontitis: CPI 3 or 4 | 11 | 38 | 49 | |

†Mann-Whitney *U* test or Fisher's exact test, ‡Median (25%, 75%).

*P < 0.05

Table 4. Stepwise Logistic Regression Analysis by Backward Selection Approach with the Lower PNI (< 45) as the Dependent Variables

| Factor | Odds Ratio | 95% CI | P value |
|---|---|---|---|
| TP | 0.189 | 0.056 – 0.631 | 0.007* |
| Number of sound teeth | 0.899 | 0.811 – 0.996 | 0.042* |
| Dental occlusal support (poor) | 9.363 | 1.769 – 49.565 | 0.009* |

CI = confidence interval.

*P < 0.05