Original Article

Prognostic nutritional index predicts outcomes of gastrectomy in the elderly

Running title: Prognostic nutritional index in elderly gastric cancer.

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Abstract

Background: Owing to the increased life expectancy, elderly patients with gastric cancer is also increasing. Onodera's prognostic nutritional index (PNI) is an assessment tool for nutritional status of surgical patients and possibly predicts prognosis of the patients. Aim of this study is to clarify the predictive and prognostic significance of PNI in elderly patients who underwent gastrectomy for gastric cancer. Methods: Two hundred ninety-five patients, including 196 nonelderly patients under 75 years old (Group NE) and 99 elderly patients (Group E), were eligible. We collected the data on nutritional status and the outcome of gastrectomy, including morbidity, mortality and survival of these patients. A Cox proportional hazards model was used to evaluate the prognostic significance. Results: PNI was significantly lower in E group than in NE group. Both morbidity and mortality rates after gastrectomy were similar between the groups. Although PNI could not predict the postoperative events in NE group, low PNI might be a risk of mortality and morbidity in the elderly. Although survival after gastrectomy was similar among groups divided by the median PNI value (49.2) in NE group, prognosis of PNI-L (<44.7) was significantly poorer than PNI-H (PNI$\geqq$44.7) in E group. Multivariate analysis demonstrated that PNI-L was an independent prognostic factor in the elderly. Conclusion: PNI predicts both short-term and long-term outcomes after

gastrectomy in the elderly.

Introduction

Gastric cancer is one of the most frequent tumors worldwide. Although death from gastric cancer continues to decline[1], the incidence of gastric cancer is still increasing both in Japan and in USA[2]. It is mainly because gastric cancer is a disease of the elderly with its peak incidence occurring in the seventh decade of life[3], while the elderly population is rapidly increasing in the developed countries. The most important part of treatment for curable gastric cancer is gastrectomy and therefore surgical management of gastric cancer in the elderly gains in importance.

Owing to recent advances in diagnostic, surgical and anesthetic techniques, resection rate of gastric cancer in the elderly is increasing[4]. Many articles have reported that postoperative morbidity rates were similar between elderly and nonelderly patients, unless the patients had preexisting comorbidities[5-9]. For postoperative mortality, several authors also reported similar death rates between the elderly and the young[5-9], while the others showed increased hospital mortality in the elderly, especially in cases with preexisting comorbidities[10-11]. The elderly cancer patients often have both malnutrition and comorbidities. Several studies revealed that malnutrition affected poor clinical results in patients with upper gastrointestinal and colorectal cancer[12, 13]. Therefore, preoperative estimation of nutritional status is essential especially for the elderly patients.

Onodera's prognostic nutritional index (PNI) is a simple index calculated by serum albumin and total lymphocyte count. It was proposed as a marker predicting prognosis of patients with gastrointestinal malignancies[14]. Nozoe et al. recently reported that PNI could predict the prognosis and biological aggressiveness of gastric cancer[15]. However, the predictive and prognostic significance of PNI in the elderly patients who undergo gastrectomy for gastric cancer remains unclear. Aim of this study is to clarify the significance of PNI in predicting outcome of gastric cancer in the elderly.

Patients and methods

Patients

Two hundred and ninety-five patients who underwent curative intent gastrectomy from April 2005 to March 2011 in Kumamoto University Hospital were eligible. Among these patients, 99 were aged 75 or more, including 46 patients aged 80 or more. The Local Ethics Committee of Kumamoto University approved the study.

Tumor staging and type of gastrectomy

Disease stage was classified according to the Japanese classification of gastric carcinoma (3rd English edition)[16], while surgical procedures including extent of both

gastrectomy and lymph node dissection were based on the Japanese Gastric Cancer Treatment Guidelines 2010 (ver.3)[17]. There were 147 patients with early cancer and 148 with advanced cancer. Total gastrectomy and distal or proximal partial gastrectomy was performed for 131 and 181 patients, respectively. D1+ and D2 lymph node dissection was performed for 161 and 134 patients, respectively.

Nutritional assessment

We collected data of preoperative blood test, including serum albumin (Alb) and total lymphocyte count of the peripheral blood (TLC) from the patients' records. Then PNI was calculated by $10 \times$Alb$+0.005 \times$TLC[14].

Evaluation for outcome

Data on outcome of the patients, including morbidity, mortality and survival, was also collected from patients' records. Follow-up of the patients was carried out in our clinic or affiliated hospitals at least every 6 months for 5 years.

Statistical analysis

All quantitative data are expressed as mean±one standard deviation. Statistical analyses were performed using the Stat View software program (SAS Institute, Cary, NC, USA). The differences in Alb, TLC and PNI among three age groups were determined by one-way analysis of variance and post-hoc comparisons were performed using Tukey-Kramer method. The difference in clinicopathologic features between groups divided by PNI was determined using a Student's *t* test for age and Fisher's exact test for the other variables. Survival rates after gastrectomy were calculated by the Kaplan-Meyer method and the statistical significance was determined by Log-lank test. A Cox proportional-hazards model was used for univariate and multivariate analysis on the prognosis after gastrectomy in the elderly. A *P*-value less than 0.05 was considered to be statistically significant.

Results

Effect of aging on the nutritional parameters

To evaluate effects of aging on the nutritional status, we compared Alb, TLC and PNI among the groups divided by age (Figure 1): The nonelderly, age younger than 75; the elderly, age with 75 to 79; and the very elderly, age 80 or over. Alb in both the elderly and the very elderly were significantly lower than that in the nonelderly. TLC in the very elderly was significantly lower than those in the nonelderly. PNI in the elderly was significantly lower than that in the nonelderly, whereas there was no significant difference in PNI between the elderly and the very elderly. Therefore, the following comparison was performed between the nonelderly group (NE; age younger than 75)

and the elderly group (E; age 75 or older). PNI of NE group was significantly higher than that of E group (P<0.0001). The distribution of PNIs in NE and E groups was demonstrated in Figure 2. The mean PNI values were 48.6 and 44.3 in NE and E groups, respectively.

Morbidity and mortality after gastrectomy

Morbidity and mortality after gastrectomy in each group is summarized in Table 1. Morbidity rates of NE and E group were 24.0% and 27.3%, respectively. Plural complications were observed in 2 patients in NE group. There was no significant difference in both the incidence of postoperative complication and hospital death between NE and E groups. The respiratory complication was more frequent in E group than in NE group but the difference was not significant (P=0.07).

Correlation between PNI and surgical result

Difference in PNI between patients with and without complication is shown in Figure 3. PNI was similar between patients with and without complication in NE group, while patients with complication displayed lower PNI compared to those without in E group. Although the incidence of surgery related complication was comparable between NE group and E group, medical events were more frequent in E group than in NE group. Especially, respiratory complication was more than 3 times frequent in E group compared to NE group. In E group, PNI was lower in patients who experienced medical events than those who did not (41.0 vs. 44.7, *P*=0.11). Although PNI could not predict the hospital death in NE group, both of the dead in E group had displayed low PNIs less than 40 preoperatively (Figure 4).

Correlation between PNI and prognosis

We evaluated the prognostic significance of PNI in NE and E groups (Figure 5). The follow-up time ranged from 156 to 2133 days, and the median was 1046 days. The mortality included both operative death and hospital death more than 30 days after surgery. In order to clarify the prognostic significance, PNIs in each of NE and E group were divided into quartiles: In NE group; Q1 (≥56.9, N=49), Q2 (49.3-56.8, N=49), Q3 (44.2-49.2, N=49), and Q4 (<44.2, N=49); in E group; Q1 (≥49.2, N=25), Q2 (44.7-49.1, N=25), Q3 (39.6-44.6, N=24), and Q4 (<39.6, N=25). There was no significant difference in overall survival among Q1 to Q4 in NE group, while survival of Q3-4 was significantly poorer than Q1-2 in E group. Therefore, as far as the long-term outcome is concerned, the median PNI value can be a cutoff value between low and high PNIs in E group. Then, we analyzed overall and disease-specific survivals between PNI-H (≥44.7) and PNI-L (<44.7) subgroups in E group (Figure 5). Similarly, in NE group, survival analysis was performed between subgroups divided by the median PNI value (49.2). In

E group, PNI-L demonstrated significantly worse overall and cause-specific survivals than PNI-H, whereas the survival rates in NE group were similar irrespective of PNI. These results indicate that PNI can predict the prognosis of elderly patients but is not a prognostic marker for the nonelderly.

Clinicopathologic background in the elderly

Background parameters were compared between PNI-H and PNI-L in the elderly (Table 2). There were several differences in background factors between the groups. Diffuse-type carcinoma tended to be frequent in PNI-L compared to PNI-H. Tumor depth and nodal status indicate that PNI-L included significantly more advanced cases than PNI-H, but percentage of patients who suffered from gastric obstruction was similar between the groups. Preexisting comorbidities tended to be more frequent in PNI-L than PNI-H. Patients who underwent neoadjuvant chemotherapy were observed only in PNI-L. Incidence of postoperative complication was significantly higher in PNI-L than PNI-H.

Univariate and multivariate analysis on overall survival after gastrectomy in the elderly (Table 3)

The univariate analysis revealed that histology (diffuse type), tumor depth (pT3), nodal metastasis (positive), neoadjuvant chemotherapy (present), adjuvant chemotherapy (present) and PNI-L were the significant factors related to poor prognosis. The multivariate analysis among these variables revealed that PNI-L was an independent prognostic factor in the elderly.

Cause of death without recurrence of gastric cancer in both age groups

Cause of death other than gastric cancer in each group is shown in Table 4. There were 9 (4.6%) and 17 (17.2%) events in NE and E groups, respectively. The most common cause of death in E group was respiratory failure due to pneumonia (35.3%) or emphysema (11.8%).

Discussion

In this study, we revealed that PNI was a predictor of both short-term and long-term outcomes after gastrectomy for gastric cancer in the elderly. First, we demonstrated that PNI in the elderly was significantly lower than that in the nonelderly. Next we revealed that PNI might be a predictor of both postoperative complication and hospital mortality in the elderly. Then, at last, we disclosed that PNI-L was an independent prognostic factor after gastrectomy in the elderly.

Polanczyk et al. reported that advanced age was an independent predictor for morbidity, mortality, and prolonged hospital stay in patients undergoing non-cardiac

surgery[18]. On the contrary, Giner et al. described that the most important preoperative risk factor for poor postoperative outcome was not chronological age but the sum of comorbidities[19]. The definition of the elderly differs among studies. There were several studies which defined the elderly as patients aged 70 or more. However, according to the aging of the society in Japan, aging of gastric cancer patients is also in progress. The mean age of patients included in this study was 67.8 years old and nowadays patients aged over 70 are not rare. Therefore, in this study, patients aged 75 or more were defined as E group. Both the morbidity and mortality rates after gastrectomy were similar between the elderly and the nonelderly. The result is consistent with several previous reports concerning gastrectomy for the elderly[5-11]. Although these findings may be a result from selection bias, gastrectomy for the elderly can be performed safely if surgeons made appropriate decisions on indication.

Studies have revealed that malnutrition might influence the postoperative results of cancer patients[20, 21]. Older people often have malnutrition because of a decline in both biological and physiologic functions of the digestive system[22]. Besides, accompanying disorders such as chronic diseases, malignancies and psychological illness can be causes of malnutrition in the elderly. In this study, we have demonstrated that elderly patients presented significantly lower Alb, TLC and PNI than the nonelderly.

There are several assessment tools applied to nutritional evaluation, such as the Subjective Global Assessment (SGA)[23], the Mini-Nutritional Assessment[24], and Nutritional Risk Scoring 2002 (NRS2002)[25]. Onodera's PNI is a simple index calculated by only two parameters including Alb and TLC. Alb is a main component of plasma protein that preserves colloid osmotic pressure, and reflects nutritional status. Garth et al. reported that low Alb, as well as preoperative weight loss, was a predictive of prolonged hospital stay in gastrointestinal surgical patients[26]. TLC is also proposed as a useful indicator of nutritional status as well as host immunity[27]. TLC is well known to decrease with age[28]. TLC is also reported to decrease with progressive malnutrition and to correlate with morbidity and mortality in hospitalized patients[29, 30].

Previous studies have already reported the prognostic significance of PNI in esophageal and gastric cancer[18]. In this study, PNI tended to correlate with morbidity and mortality after gastrectomy especially in the elderly. In the elderly, medical events such as pneumonia were frequently observed. As PNI reflects both nutritional and immunologic status, it may be a good predictor for short term outcome, especially for medical events in the elderly. Although we have tried to figure out the demarcation value of PNI to predict short-term outcome after gastrectomy in the elderly, we could

not get the ROC curve because of the small case number. A large scale multicentric study is needed to detrermine the appropriate cutoff value.

As for long-term outcome, the median PNI value was a good demarcation value to predict survival in E group. Moreover, PNI was an independent prognostic factor in the gastrectomized elderly patients, while it could not predict the prognosis of nonelderly patients. As shown in Figure 6, difference in survival rate between PNI-H and PNI-L was closer in cause-specific survival than in overall survival, suggesting that more patients died of diseases other than gastric cancer in PNI-L than in PNI-H. When we looked at the cause of death other than gastric cancer in the PNI-L patients, there were many patients who died from respiratory failure due to pneumonia. These findings suggest that less immunoresistance may be a cause of poor prognosis in PNI-L patients in the elderly.

Limitation of this study is that it is a retrospective study conducted in a single institute. Besides, indication for surgery in the elderly depended on decision of the attending physicians. Recently, research has shown that perioperative immunonutrition improve both nutritional and immunologic status of surgical patients and thus reduce postoperative morbidity and mortality[13, 31]. It is still unknown if such a nutritional intervention could improve result of patients with low PNI. A prospective validation of the significance of PNI as well as an analysis on the effect of nutritional intervention for the low PNI cases should be performed in the future..

In conclusion, nutritional assessment using PNI is useful in predicting both short-term and long-term outcome after gastrectomy in the elderly. Screening of nutritional status by PNI may assure the safety of gastrectomy and achieve prolonged survival in the elderly.

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Figure legends

Figure 1. Nutiritiional parameters in gastric cancer patients among the age groups. PNI in both the elderly and the very elderly was significantly lower than that in the nonelderly. PNI in E group (age 75 or older) was significantly lower than that in NE group (age young than 75).

Figure 2. Distribution of PNIs in NE and E groups. The mean PNI values were 48.6 and 44.3 in NE and E groups, respectively.

Figure 3. Correlation between PNI and the occurrence of postoperative complication. PNI was similar between patients with and without complication in NE group, while PNI of patients with complication tended to be lower than that without complication in E group (*P*=0.074).

Figure 4. Correlation between PNI and hospital death. Although PNI was similar irrespective of the occurrence of hospital death in NE group, the patients with hospital mortality presented very low PNI in E group.

Figure 5. Overall survival of patients after gastrectomy among the groups divided by PNI. PNIs in each of NE and E group were divided into quartiles: In NE group; Q1 (≥ 56.9, N=49), Q2 (49.3-56.8, N=49), Q3 (44.2-49.2, N=49), and Q4 (<44.2, N=49); in E group; Q1 (≥49.2, N=25), Q2 (44.7-49.1, N=25), Q3 (39.6-44.6, N=24), and Q4 (<39.6, N=25). Significant difference in the survival was observed between Q1-2 and Q3-4 in E group (*P*=0.0089).

Figure 6. Overall and cause-specific survivals after gastrectomy between PNI-H and PNI-L divided by the median PNI values in each age group. Significant difference in the survival was observed between PNI-H and PNI-L only in E group but not in NE group.