

# Preoperative malnutrition and prognosis after neoadjuvant chemotherapy followed by subsequent esophagectomy

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Preoperative malnutrition has been reported to correlate with unfavorable long-term outcomes in patients who undergo surgery for gastroenterological cancers, including esophageal (1-4), gastric (5), colorectal (6), and pancreatic (7) cancers and hepatocellular carcinoma (8). Appropriate methods are needed to preoperatively assess malnutrition likely to adversely affect long-term outcome. Although blood test data, such as serum albumin, transthyretin, transferrin, and cholesterol concentrations and total lymphocyte count (TLC) are candidate markers of nutritional status, suitable comprehensive indicators to estimate long-term postoperative outcomes have not been identified. Prognostic nutritional index (PNI), calculated as  $10 \times \text{albumin (g/dL)} + 0.005 \times \text{TLC (/}\mu\text{L)}$ , was the first nutrition-related indicator of the risk of complications after gastrointestinal cancers surgery (9) and is a useful predictor of long-term outcome after surgery for various gastrointestinal cancers (3,4,7,8,10). Predictive markers of prognosis after esophagectomy in patients with esophageal cancer include preoperative sarcopenia (11), body mass index (12), controlling nutritional status (CONUT) (1,2) and PNI (3,4).

In the current study, Nakatani *et al.* retrospectively investigated 66 patients with squamous cell esophageal cancer who underwent neoadjuvant chemotherapy (NAC) with docetaxel, cisplatin, and 5-fluorouracil, followed by esophagectomy. All patients had resectable advanced esophageal cancer (stage II and III, not T4), and most (97%) completed two courses of NAC. Patients who underwent

R1 or R2 resection and those who died in-hospital were excluded. The mean follow-up duration was 31.9 months. The study showed that preoperative PNI was significantly worse than pre-NAC PNI and that preoperative PNI (<45) was an independent unfavorable prognostic factor after NAC followed by esophagectomy, whereas pre-NAC PNI was not.

This study is clinically meaningful, because it is the first to demonstrate the usefulness of preoperative PNI as a prognostic indicator after NAC followed by esophagectomy. Current standard treatment for resectable advanced esophageal cancer consists of neoadjuvant therapy followed by surgery (13-15). Although, preoperative PNI was previously reported useful to predict prognosis after esophagectomy (3,4), those studies were not designed solely for patients who received NAC.

Although it is interesting to use PNI to preoperatively estimate unfavorable long-term outcomes, it is more important to determine whether preoperative nutritional intervention during NAC can improve both PNI and long-term outcomes after esophagectomy. Several studies have shown that preoperative nutritional intervention may reduce the incidence of postoperative morbidities (16,17). However, no studies to date showed that these nutritional interventions could improve long-term outcomes after esophagectomy. As indicated by Nakatani *et al.*, maintaining or improving nutrition during NAC is important. In addition to conventional interventions, several novel approaches were suggested. Esophageal stenting in patients

with stenosis during preoperative chemotherapy has been shown effective in maintaining preoperative nutrition (18,19). In addition, ghrelin administration may help maintain body weight and minimize the deterioration of nutritional status during chemotherapy (20).

It remains unclear whether PNI can serve as a nutritional or prognostic marker in patients who undergo esophagectomy for esophageal cancer. Albumin concentration and TLC may not accurately reflect nutritional status, as these parameters are affected by other factors, including systemic inflammation, liver function, changes in body fluid volume, and preoperative treatment, resulting albumin concentration and TLC having low sensitivity and specificity for assessing changes in nutritional status (21). Nutritional status can be reliably determined by nutritional risk screening (22) or by subjective global assessment in cancer patients (23), indices that focus on health history and physical examination and eliminate the ambiguity of non-specific, relatively insensitive laboratory values. Thus, although PNI may not be a reliable marker of malnutrition, it probably has prognostic value, as shown in this study.

The study by Nakatani *et al.* had several limitations. It was a retrospective study based on the medical records at a single institute. Sample size was small. Indications and methods of nutritional intervention during NAC were not fixed. In addition, the parameters used for univariate and multivariate analyses were unknown. Poor PNI may only reflect anorexia caused by cancer progression or organ dysfunction. Thus, interactions between PNI (<45 *vs.* ≥45) and other parameters should be examined.

In conclusion, to our knowledge, the current study is the first to demonstrate the usefulness of preoperative PNI (<45 *vs.* ≥45) as a prognostic indicator after NAC followed by esophagectomy. However, further research is needed to firmly establish the usefulness and reliability of PNI.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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