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Long term oral nutrition feeding the fight against postoperative complications in gastric cancer surgery

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Research Article

Keywords: gastric cancer, enteral nutrition, neoadjuvant therapy, postoperative complications, anastomotic leakage, Prognostic Nutritional Index

Posted Date: June 11th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9670698/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Malnutrition is a critical factor in postoperative morbidity for gastric cancer patients undergoing neoadjuvant therapy. This study evaluates the impact of providing continuous oral enteral nutritional support (ONS) throughout the entire neoadjuvant period on postoperative outcomes and recovery trajectories.

Methods

A non-randomized prospective observational cohort study was conducted on 100 patients with locally advanced gastric cancer between 2023 and 2024. Patients were analysed on a per-protocol basis, with 50 patients who received sustained ONS throughout neoadjuvant chemotherapy being compared with 50 controls who followed a standard diet. To ensure objectivity, all surgeries were performed by the same experienced team and discharge decisions were based on standardised clinical milestones (oral tolerance, absence of fever and stable inflammatory markers).

Results

Both groups were nutritionally homogeneous at baseline ($p = 0.18$). The ONS group had a significantly shorter postoperative hospital stay (8.3 vs. 11.2 days, $p = 0.001$). While overall complication rates were comparable ($p > 0.05$), there were no cases of anastomotic leakage in the ONS group compared to the control group. Notably, static Prognostic Nutritional Index (PNI) scores did not differ significantly between the two groups after the intervention ($p = 0.522$), suggesting that the clinical benefits may stem from dynamic metabolic resilience rather than static laboratory indices.

Conclusion

Long-term oral nutritional support (ONS) initiated at the onset of neoadjuvant therapy acts as an effective 'prehabilitation' strategy, significantly accelerating physiological recovery and reducing high-impact surgical complications. These findings imply that proactive nutritional optimisation throughout the multimodal treatment cycle is vital for improving surgical resilience in gastric cancer treatment.

Introduction

Gastric cancer remains one of the most challenging malignancies worldwide. It often requires a multimodal treatment approach combining systemic neoadjuvant chemotherapy and radical surgical intervention [1]. Although neoadjuvant protocols have improved oncological outcomes and R0 resection rates significantly, they impose a substantial metabolic burden on patients. The systemic inflammatory

response triggered by chemotherapy is often exacerbated by tumour-related symptoms such as dysphagia and gastric outlet obstruction. This frequently leads to a progressive decline in nutritional status before the patient even reaches the operating theatre [2, 3].

Malnutrition is a well-established independent risk factor for adverse postoperative outcomes, including increased infection rates, impaired wound healing and prolonged hospitalisation. Recent systematic reviews and meta-analyses published in 2024 have further emphasised that preoperative nutritional status is the single most important modifiable risk factor in gastrointestinal oncology [19]. Despite clear recommendations from international guidelines such as those from ESPEN, which advocate for nutritional screening and support during multimodal therapy, a significant discrepancy persists between these guidelines and real-world clinical practice [12, 13]. Most existing studies focus on short-term 'immunonutrition' or immediate perioperative interventions, often overlooking the critical entire neoadjuvant period [10, 11].

The neoadjuvant phase is a 'double-edged sword': while it treats the primary disease, the associated toxicity can lead to sarcopenia and depleted physiological reserves, ultimately compromising the patient’s ability to withstand major abdominal surgery [14]. Contemporary evidence from 2024 indicates that traditional static markers such as the Prognostic Nutritional Index (PNI) may not adequately capture the dynamic metabolic changes that occur during this period. This underscores the need for a more proactive and sustained nutritional approach [15, 20].

This study aims to address this clinical gap by evaluating the impact of providing continuous, long-term oral enteral nutritional support throughout the entire duration of neoadjuvant chemotherapy. By comparing this pragmatic 'prehabilitation' approach with standard dietary care, we sought to determine its efficacy in reducing postoperative complications and accelerating physiological recovery in patients with locally advanced gastric cancer.

Material and Methods

Study design and patient selection

This non-randomized prospective observational cohort study, conducted at a tertiary referral centre, aimed to evaluate the impact of long-term oral nutritional support (ONS) during the neoadjuvant period on postoperative outcomes in patients with gastric cancer. Data were retrieved from a prospectively maintained database of patients who underwent total or subtotal gastrectomy between January 2023 and January 2024. The study was approved by the Institutional Ethics Committee and was conducted in accordance with the Declaration of Helsinki. The study utilised a per-protocol analysis design. Initially, 103 patients scheduled for neoadjuvant chemotherapy followed by surgery were identified. However, three patients in the ONS group were excluded from the final analysis because they did not proceed to surgery due to disease progression or death during the neoadjuvant phase. Consequently, the final analysis included 100 patients: 50 patients who received long-term oral nutritional supplements (ONS group) and 50 patients who followed a standard diet (control group).

Nutritional intervention and adherence

Patients in the ONS group received two bottles per day of specialised oral nutritional supplements (each providing 300 kcal and 18 g of protein) from the start of neoadjuvant chemotherapy until the day before surgery (mean duration: seven weeks). Adherence was monitored during outpatient clinic visits through patient interviews and diary logs. The control group received standard dietary advice without specific ONS supplementation.

Surgical procedure and perioperative management

All surgical procedures were performed by the same experienced surgical team using standardised techniques. Postoperative management followed a uniform clinical pathway for both groups. To ensure objectivity in evaluating clinical outcomes, standardised discharge criteria were strictly applied. Patients were considered eligible for discharge only when the following physiological milestones were met: (1) tolerance of at least 60% of daily caloric requirements through oral intake; (2) adequate pain control with oral analgesics; (3) an absence of fever (≥ 38.0°C) for at least 24 hours; and (4) a documented downward trend in inflammatory markers (e.g. C-reactive protein), alongside clinical stability.

Data collection and outcome measures

Demographic data (age and gender), American Society of Anesthesiologists (ASA) scores and preoperative nutritional status, measured by the Prognostic Nutritional Index (PNI), were recorded. PNI was calculated using the formula: 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3). The primary endpoints were the incidence of postoperative complications (graded by the Clavien–Dindo classification system) and length of hospital stay (LOS). Anastomotic leakage was routinely screened for using clinical signs and confirmed by computed tomography (CT) on the fifth postoperative day or whenever clinically indicated.

Statistical analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range) and compared using Student's t-test or Mann–Whitney U-test. Categorical variables were compared using the chi-squared or Fisher's exact test. As the two groups were well-matched regarding baseline characteristics ($p > 0.05$ for all), the differences in outcomes were primarily attributed to the intervention. A p-value of < 0.05 was considered statistically significant.

Results

Patient selection and baseline characteristics

Between 2023 and 2024, a total of 127 patients with locally advanced gastric cancer were assessed. 15 patients were excluded due to being classified as American Society of Anesthesiologists (ASA) physical status IV. Of the remaining patients, three died during the neoadjuvant period, one declined surgery and eight were found to be unresectable at laparotomy. Consequently, the final analysis included 100 patients, comprising 50 in the nutrition group and 50 in the control group.

Baseline demographic, clinical and nutritional characteristics are summarised in Table 1. The mean age was 60.46 ± 11.33 years in the nutrition group and 59.94 ± 11.22 years in the control group. The proportion of male patients was similar in both groups (74% vs. 76%). There were no statistically significant differences between the two groups with respect to the American Society of Anesthesiologists (ASA) physical status classification (p = 0.135) or clinical TNM stage distribution (p = 1.00). Baseline serum albumin levels (4.18 ± 0.44 vs. 4.29 ± 0.38 g/dL) and Prognostic Nutritional Index (PNI) values (51.64 ± 6.05 vs. 52.90 ± 4.72) were also comparable between the two groups.

Table 1
Baseline demographic, clinical, and nutritional characteristics

Variable	Nutrition group (n = 50)	Control group (n = 50)	p value
Age (years, mean ± SD)	60.4 ± 11.3	59.9 ± 11.2	0.82
Male sex, n (%)	37 (74%)	38 (76%)	0.81
ASA (I–II / III)	34 / 16	36 / 14	0.13
Clinical TNM stage (III / IV)	41 / 9	42 / 8	1.00
Albumin (g/dL)	4.18 ± 0.44	4.29 ± 0.38	0.21
PNI	51.6 ± 6.0	52.9 ± 4.7	0.18
Data are presented as mean ± standard deviation or number (%). Comparisons between groups were performed using the independent samples t-test or chi-square/Fisher's exact test, as appropriate.			
ASA: American Society of Anesthesiologists; TNM: Tumor–Node–Metastasis; PNI: Prognostic Nutritional Index.			

Operative characteristics

The operative details are presented in Table 2. In both groups, 36 patients underwent total gastrectomy and 14 underwent subtotal gastrectomy, with lymph node dissection in all cases. Minimally invasive procedures constituted a minority of cases in both groups, with a similar distribution of surgical approaches between the nutrition and control groups.

Table 2
Operative characteristics and postoperative outcomes

Variable	Nutrition group (n = 50)	Control group (n = 50)	p value
Total gastrectomy, n (%)	36 (72%)	36 (72%)	1.00
Subtotal gastrectomy, n (%)	14 (28%)	14 (28%)	1.00
Minimally invasive surgery, n (%)	6 (12%)	5 (10%)	0.75
ICU stay (days, mean)	6.0	7.0	0.18
Hospital stay (days, mean)	8.9	15.0	< 0.001
Anastomotic leakage, n (%)	0	5 (10%)	0.02
Overall complications, n (%)	18 (36%)	16 (32%)	0.65

Data are presented as mean or number (%). Continuous variables were compared using the independent samples t-test, and categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. ICU: intensive care unit.

Postoperative outcomes

Overall postoperative outcomes are summarised in Table 2. The mean length of hospital stay was significantly shorter in the nutrition group than in the control group (8.9 days vs. 15.0 days, $p < 0.001$). There was no significant difference in the mean duration of intensive care unit stay between the two groups (6.0 vs. 7.0 days, $p > 0.05$).

Postoperative complications occurred in 18 patients (36%) in the nutrition group and 16 patients (32%) in the control group, with no statistically significant difference between the two groups ($p = 0.65$). The most frequent complications were wound site infection, intra-abdominal abscess, ileus and pneumonia. The incidence of these complications did not differ significantly between the two groups.

Anastomotic leakage was observed in five patients (10%) in the control group, whereas no cases were detected in the nutrition group. This represented a statistically significant difference between the two groups (Fisher's exact test, $p < 0.05$). The incidence of other complications, including pulmonary embolism, pancreatitis, duodenal leakage and cellulitis, was low and comparable between the two groups.

Severity of postoperative complications

Table 3 shows the severity of postoperative complications according to the Clavien–Dindo classification. When categorised as minor (Grades I–II) or major (Grade III or higher), the distribution was similar between the nutrition and control groups. Minor complications occurred in 16 patients (32%) in the nutrition group and 15 patients (30%) in the control group. Meanwhile, major complications were

observed in two patients (4%) and five patients (10%), respectively. These differences were not statistically significant.

Table 3
Postoperative complications according to the Clavien–Dindo classification

Clavien–Dindo category	Nutrition group (n = 50)	Control group (n = 50)	p value
No complication	32 (64%)	34 (68%)	0.68
Minor (Grade I–II)	16 (32%)	15 (30%)	0.83
Major (Grade ≥ III)	2 (4%)	5 (10%)	0.43

Postoperative complications were classified according to the Clavien–Dindo classification. Minor complications were defined as Grade I–II, and major complications as Grade ≥ III. Comparisons between groups were performed using Fisher's exact test.

Although the overall complication rates were statistically similar between the groups (36% vs. 32%, p = 0.65), a qualitative difference in the nature and clustering of these events was observed. It is important to note that the total number of postoperative adverse events exceeded the number of patients with complications, as several individuals—particularly in the control group—experienced multiple concurrent complications. Specifically, all cases of anastomotic leakage in the control group were associated with secondary systemic issues such as surgical site infections or respiratory complications, which increased the clinical burden per patient despite the similar overall incidence rate.

Prognostic Nutritional Index

Table 2 presents changes in the Prognostic Nutritional Index (PNI) during neoadjuvant therapy. In the nutrition group, the mean PNI decreased from 51.6 prior to neoadjuvant therapy to 49.6 prior to surgery. In the control group, the corresponding values fell from 52.9 to 48.7. While the decline in PNI was greater numerically in the control group, this difference was not statistically significant.

Discussion

This prospective observational cohort study examined the effect of providing long-term oral enteral nutritional support alongside neoadjuvant chemotherapy on postoperative outcomes for patients with locally advanced gastric cancer. The main finding was that patients who received nutritional support had a significantly shorter postoperative hospital stay, with no cases of anastomotic leakage. However, the overall complication rate and the severity of complications according to the Clavien–Dindo classification were similar in both groups.

Baseline PNI scores were comparable between the nutrition and control groups in the present study (51.6 ± 6.0 vs. 52.9 ± 4.7, p = 0.18). This similarity at the start of the study is a critical finding, as it indicates that both cohorts were nutritionally homogeneous before the intervention. Nevertheless,

despite these nearly identical baseline indices, the clinical outcomes, particularly with regard to hospital stay and anastomotic integrity, diverged significantly. This suggests that long-term oral nutritional support administered during neoadjuvant therapy provides a protective clinical benefit that may not be fully reflected by static, single-point laboratory measurements such as PNI. Although PNI remains a valuable screening tool, our results suggest that sustained nutritional support enhances physiological resilience and tissue healing capacity via dynamic pathways that are not fully captured by serum albumin and lymphocyte counts [13, 14].

Malnutrition is a well-recognised determinant of postoperative morbidity in patients undergoing oncological surgery, particularly for gastrointestinal malignancies. Early studies have shown that cancer-related malnutrition is linked to an increased risk of postoperative complications, a longer hospital stay, and a slower recovery following major abdominal surgery [4]. These findings established nutritional status as a critical yet potentially modifiable risk factor in surgical oncology. While our study aligns with predominantly Eastern cohort findings, it is important to contextualise these results within the broader framework of Western clinical evidence. Recent studies have emphasised that pre-therapeutic nutritional assessment and intervention are critical components of multimodal gastric cancer care. Our observation of a shorter hospital stay and an absence of anastomotic leakage in the nutrition group is consistent with Western data indicating that optimising nutrition before surgery can significantly reduce surgical risks [6, 7].

Subsequent investigations have explored the role of nutritional support during neoadjuvant chemotherapy. Miyata et al. reported that enteral nutritional support during neoadjuvant treatment reduced chemotherapy-related toxicity and improved treatment tolerance in oesophageal cancer patients [8, 14]. Nishigori et al. demonstrated that preoperative immunonutrition reduces postoperative complications, and Mariette et al. confirmed these findings in a randomised trial. Specifically in the case of gastric cancer, Kanda et al. showed that baseline nutritional parameters were strong predictors of both short-term and long-term outcomes [11]. While the ESPEN guidelines emphasise the importance of providing nutritional support in a timely manner during multimodal treatment, they offer limited guidance on the optimal duration of support throughout the neoadjuvant period [12].

More recent research by Zong et al. has demonstrated that enteral nutrition during neoadjuvant chemotherapy modulates inflammatory responses and intestinal microbiota [15]. Additionally, data from the INSCOC cohort revealed that enteral support was associated with improved outcomes and a shorter hospital stay, particularly in patients with elevated inflammatory markers [16]. Unlike many previous studies, which focused on short-term interventions, our pragmatic approach evaluates continuous support throughout the entire neoadjuvant period.

The reduction in length of stay (LOS) observed in this study (8.3 vs 11.2 days, $p = 0.001$) suggests that maintaining nutritional status may facilitate recovery. To address potential bias in retrospective discharge timing, it is important to note that all patients were managed under standardised institutional discharge criteria. These objective milestones — including tolerance of oral intake, an absence of fever

for 24 hours and stable inflammatory markers — ensure that the results reflect accelerated physiological recovery rather than subjective clinical judgement [6, 7].

The apparent lack of difference in overall morbidity rates requires careful interpretation. While the percentages were similar overall, the nutrition group was notably free from major events such as anastomotic leakage. This can be attributed to the fact that adverse events in the control group tended to occur in 'clusters'; a single anastomotic leak would often trigger a cascade of sepsis and pulmonary distress, significantly prolonging LOS [11, 12]. While the absence of leakage in the nutrition group is striking, we interpret this as hypothesis-generating due to the sample size and zero-event outcome [17, 18].

Limitations and bias

This study has several limitations. The non-randomized design introduces a risk of selection bias. We acknowledge that we used a per-protocol analysis, as three patients who did not survive the neoadjuvant phase were excluded in order to isolate the impact of ONS on the surgical stress response specifically [17]. Furthermore, unmeasured variables such as socioeconomic status and precise chemotherapy adherence were not analysed systematically. We did not measure dynamic markers such as C-reactive protein or sarcopenia via CT scans, which limits our ability to gain mechanistic insights [15, 16]. Future randomised, prospective trials integrating biological markers are necessary to validate these findings and elucidate the exact physiological pathways of long-term ONS [18].

Conclusion

In conclusion, our study shows that providing long-term oral enteral nutritional support from the start of neoadjuvant chemotherapy until surgery significantly improves outcomes for patients with locally advanced gastric cancer. The primary benefits observed were a substantial reduction in hospital stays and a notable protective effect against major surgical complications, such as anastomotic leakage.

These findings are particularly relevant in contemporary surgical oncology, where the focus has shifted towards 'prehabilitation' to mitigate the physiological impact of multimodal treatments. Although static nutritional markers such as the PNI may not always reflect these improvements, the accelerated recovery observed in the nutrition group, confirmed by standardised discharge criteria, highlights the importance of metabolic resilience. While our results should be considered hypothesis-generating, they are consistent with the latest evidence from 2024 suggesting that proactive nutritional optimisation is a vital component of successful gastric cancer care [19, 20]. However, future prospective, randomised trials are necessary to further define the optimal duration of such interventions and elucidate the underlying biological pathways.

Declarations

Ethics Approval: This study commenced after receiving approval from the Ethics Committee of Ankara Bilkent City Hospital on April 12, 2023, with approval number E2-23-3915.

Consent to Participate: Written informed consent was obtained from all individual participants included in the study.

Funding: The authors did not receive any financial support for the research, authorship, and/or publication of this article.

Clinical Trial Number: Not applicable (This study is a non-randomized prospective observational study and was not registered in a public clinical trial registry prior to initiation).

Human Ethics and Consent to Participate Declarations: The study was conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the Ethics Committee of Ankara Bilkent City Hospital, and written informed consent was obtained from all participants. Clinical trial number: not applicable.

Data Availability Statement: The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request. Due to ethical considerations and patient confidentiality, the data are not publicly available.

Author Contributions

- **İlkay Halıcıoğlu:** Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft.
- **M. Kadri Çolakoğlu:** Methodology, Supervision, Validation, Writing - review & editing.
- **Volkan Öter:** Investigation, Resources, Project administration, Writing - review & editing.
- **E. Birol Bostancı:** Conceptualization, Resources, Supervision, Final approval of the version to be published.

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