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Do total parenteral nutrition and bowel rest reduce the risk for perforation in patients with gastrointestinal tract lymphoma receiving chemotherapy?

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ABSTRACT

Objectives: Gastrointestinal tract (GIT) lymphoma is associated with a risk for perforation while the patient is receiving chemotherapy. The role of total parenteral nutrition (TPN) and bowel rest in preventing perforation is unknown. The aim of this study was to examine the clinical outcomes of TPN and bowel rest in patients with GIT lymphoma who were receiving chemotherapy.
Methods: We reviewed all patients with GIT biopsy-proven lymphoma in our institution between 2013 and 2017. Patients were stratified into two groups, with and without TPN and bowel rest during chemotherapy. We identified 158 patients with GIT lymphoma. Of these, 47 (29.7%) received TPN and bowel rest before chemotherapy. Patients who received TPN were younger, more likely to have aggressive lymphoma in the small or large bowel. The primary outcome was to compare the perforation rate between the two groups. Secondary outcome analysis included infection rate and survival.
Results: Patients with perforation had significantly poorer survival. Perforation rate was similar between the TPN and the non-TPN groups (8.5% versus 2.7%, $P = 0.197$). Overall survival was similar between the two groups ($P = 0.659$). The TPN group had a higher infection rate (odds ratio, 5.32; 95% confidence interval, 1.36–20.8) after adjustment for covariates (age, types of lymphoma, and location of lymphoma).
Conclusion: The present study demonstrated that TPN and bowel rest did not reduce the risk for perforation among patients with GIT lymphoma who were receiving chemotherapy. As the practice of prophylactic TPN and bowel rest was associated with higher infection risk and longer hospitalization, we do not recommend such practice for all patients with GIT lymphoma receiving chemotherapy.

Introduction

Perforation is a life-threatening complication that occurs in 9% of patients with lymphoma involving the gastrointestinal tract (GIT) [1]. Retrospective studies have shown that perforation negatively affects the survival outcome among patients with GIT lymphoma [2,3]. Risk factors associated with perforation among patients with GIT lymphoma included the types and location of lymphoma. Aggressive lymphoma such as Burkitt's lymphoma and high-grade B-cell lymphoma carried a six times higher risk for perforation than indolent B-cell lymphoma. GIT lymphoma located at the small bowel was shown to have a higher risk for perforation than gastric or colonic lymphoma [1].

It has been postulated that GIT perforation occurs as a result of a transmural involvement of a tumor or tissue necrosis after chemotherapy. The reported risk for perforation of GIT lymphoma ranged from 0% to 9%, depending on location and histology [1,4–6]. Due to the significant morbidity associated with perforation, some physicians advocate the use of total parenteral nutrition (TPN) and bowel rest as a strategy for reducing the risk for perforation and peritoneal contamination in the event of perforation. However, because TPN carries an inherent risk for infection and higher cost, the benefit of such practice remains controversial.

To address this controversy, we retrospectively reviewed the medical records of all patients with GIT lymphoma receiving the

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first cycle of chemotherapy in our institution. The primary aim of the present study was to determine whether TPN and bowel rest reduced the perforation risk among these patients. The secondary outcome analysis included infection rate and survival between patients with and without TPN and bowel rest.

Methods

Study design

In this retrospective study, we included all patients with GIT lymphoma treated in Singapore General Hospital and National Cancer Centre Singapore between January 2013 and January 2017. The study protocol was approved by the Singhealth Centralized Institutional Review Board.

Study population

Patients who were >18 y of age with an initial presentation of biopsy-proven GIT lymphoma treated with the first cycle of chemotherapy were included. Patients with only radiologic evidence suggestive of lymphoma were excluded. We stratified patients into two groups: those receiving TPN and bowel rest while receiving chemotherapy and those not receiving the two strategies. We subsequently compared the clinical outcomes (perforation, infection, and survival) between the two groups.

We collected information on patient demographics and clinical, radiologic, and histologic data from the electronic medical record system. Perforation was confirmed either intraoperatively or radiologically (defined as the presence of free air intraabdominally in radiology imaging). To investigate the effects of TPN in perforation risk for GIT lymphoma, patients with perforation as initial presentation were excluded from this analysis. Infection was defined by either presence of positive culture (blood, tissue, or fluid) for microorganism, or, radiologic evidence of infection (consolidation/collection/abscess) as reported by the duty radiologist, detected 24 h after initiation of chemotherapy until the date of discharge.

Statistical analysis

Continuous variables were summarized using mean and SD (normally distributed variables) or median and interquartile range (non-normally distributed variable). Categorical variables were expressed as numbers and percentage. Univariate analysis of baseline characteristics was performed to identify differences between the two cohorts. All variables with $P < 0.10$ on univariate analysis were retained and integrated into the multivariate models to adjust for potential confounding effect. A 2-sided $P < 0.05$ was considered statistically significant. Multivariate logistic regression was performed to assess the effect of TPN on the outcomes of perforation, infection, and hospital length of stay (LOS), adjusting for confounding factors. As LOS has a skewed distribution, logistic regression with log link was used to assess the effect of TPN, with adjustment made for confounders. Kaplan–Meier was performed to compare the survival of patients in the two groups. This was followed by Cox regression analysis to compare the survival of the two groups, adjusting for confounding factors. All data analysis was performed using SPSS version 21 (IBM, Armonk, NY, USA).

Results

Patients

We identified 158 patients with GIT lymphoma who were receiving the first cycle of chemotherapy (Fig. 1). During the study period, three patients presented with perforation as initial presentation and were promptly started on TPN. These patients were excluded from the study analysis. Baseline characteristics of the 158 patients are summarized in Table 1. The mean age was 66 y (range: 14.8–97 y) and 39.2% were men. GIT lymphomas were found in the stomach (64.6%), small bowel (17.1%), large bowel (14.6%), and multiple sites (3.8%). Marginal zone lymphoma (mucosa-associated lymphoid tissue [MALT]) was the most common histologic type of lymphoma (44.3%). Aggressive lymphomas were found in 52.5% of patients. Among 86 patients (52.5%) treated on an inpatient basis, 90.7% had aggressive lymphoma. The most common reasons for admission were observation during chemotherapy (79.1%), first presentation of GIT lymphoma (14%), and others (7%).

During the median follow-up duration of 22 ± 31.5 mo, 7 cases of perforation (4.4%) were reported. The most common site for perforation was the small bowel (n = 4), followed by the stomach (n = 2) and the large bowel (n = 1). Of the seven perforations, six occurred in patients with aggressive lymphoma. All patients with perforation underwent surgical repair. Patients with aggressive lymphoma (10.5 versus 1.3%, $P = 0.01$) or small bowel involvement (18.2% versus 3.1%, $P < 0.01$), and those treated on an inpatient basis (11.6% versus 0%, $P < 0.01$) had higher risk for perforation. Gastric involvement was associated with lower risk for perforation (1.9% versus 9.4%, $P = 0.43$).

Forty-seven patients received prophylactic TPN and bowel rest (29.7%), whereas the rest received standard oral/enteral tube feeding as per the physician's discretion. Baseline characteristics of patients with and without TPN are summarized in Table 2. sex, race and types of lymphoma were similar for both groups. Patients who received TPN were younger (mean age 56.3 ± 13.4 vs 67.8 ± 14.0 years, $P < 0.01$) and was associated with more aggressive lymphoma (55.4% vs 1.3%, $P < 0.01$) and small bowel involvement (34% vs 13.5%, $P < 0.01$).

The perforation rate among GIT lymphoma was similar with and without TPN and bowel rest (8.5% versus 2.7%, $P = 0.197$), even after adjusting for covariates by multivariate analysis (odds ratio [OR], 0.87; 95% confidence interval [CI], 0.1–5.9; Table 3). Overall median time from initiation of chemotherapy to perforation was 33.6 d (range: 2–78 d). Perforation was significantly associated with higher risk for infection (71.4% versus 10.6%, $P < 0.01$) and poorer survival (median survival 13 mo; 95% CI, 7.2–18.8 versus 158; 95% CI, 95.8–220.8 mo; log rank $P < 0.01$; Fig. 2). TPN and bowel rest did not reduce the risk for perforation when subgroup analysis was performed among patients with aggressive lymphoma (TPN versus no TPN: 8.7% versus 5.4%, $P = 0.45$), small bowel involvement (TPN versus no TPN: 12.5% versus 18.5%, $P = 0.56$), and those treated as inpatient (TPN versus no TPN: 8.5% versus 8.3%, $P = 0.98$). The details of all patients with perforation are summarized in Table 4.

The TPN group had a higher risk for infection (hazard ratio [HR], 6.02; 95% CI, 1.58–22.92) after adjustment for age, types of lymphoma, and small bowel involvement in multivariate analysis. When subgroup analysis was performed among patients treated on an inpatient basis, the TPN group demonstrated an almost four-fold higher risk for infection (HR, 3.8; 95% CI, 1.04–13.70) and 80% longer hospital LOS (mean LOS ratio 1.8; 95% CI, 1.04–3.03). The most frequently reported types of infection were pneumonia (30%) and urinary tract infection (20%). Six patients had bacteremia with an uncertain source, with blood culture positive for *Enterococcus* sp. (n = 4) and *Escherichia coli* (n = 2). Catheter-related bloodstream infection occurred in one patient. The overall survival was similar with and without TPN and bowel rest (OR, 1.23; 95% CI, 0.50–3.03) after adjustment for covariates using Cox regression; Kaplan–Meier survival curve is shown in Figure 3.

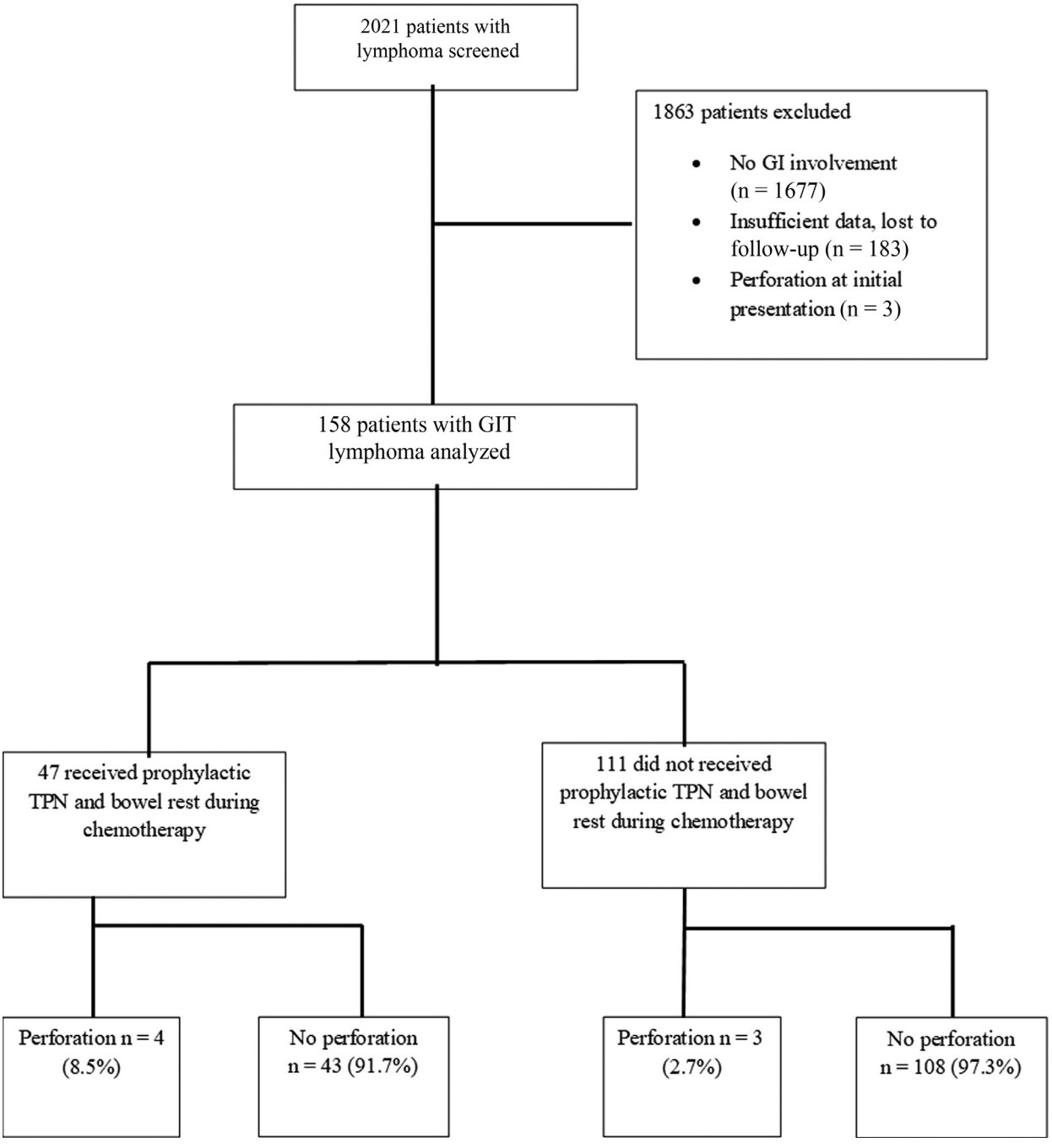

Fig. 1. CONSORT diagram. GIT, gastrointestinal tumor; TPN, total parenteral nutrition.

Discussion

Perforation in GIT lymphoma can result in peritonitis, septic shock, multiorgan failure, delayed initiation of chemotherapy, and death. Whether TPN and bowel rest reduces the risk for perforation among patients with GIT lymphoma receiving chemotherapy remains controversial. The present study demonstrated that TPN and bowel rest did not reduce the risk for perforation among this group of patients (Table 3). The overall number of perforation cases reported in the present cohort (4.4%) was lower than in the reported literature [1,7]. Only four patients in the TPN group had perforation as opposed to three in the non-TPN group. The present finding is consistent with Chin et al. who showed that TPN and bowel rest did not reduce the risk for perforation among this patient population [7]. However, unlike Chin et al. who observed a similar perforation risk between their inpatient and outpatient cohorts, none of our outpatients with GIT lymphoma had perforation, which reflects the patient selection for prophylactic TPN and bowel rest in the present cohort. The variation in clinical practice is apparent among managing physicians. Although more patients with aggressive lymphoma were given TPN and bowel rest while receiving their first cycle of chemotherapy (55.4% versus 1.3%, $P < 0.01$), not all patients with aggressive lymphoma or small bowel involvement were treated the same. To our knowledge, there

Table 1
Baseline demographic characteristics of GIT lymphoma patients receiving chemotherapy (N = 158)

Characteristics		% (n)
Age, mean ± SD in y		66 ± 14.8
Sex	Male	39.2 (62)
Race	Chinese	73.4 (116)
	Malay	18.4 (29)
	Indian	3.2 (5)
	Others	5 (8)
Types of lymphoma		
Aggressive lymphoma	DLBCL	41.1 (65)
	Burkitt's lymphoma	8.2 (13)
	Enteropathy-associated T-cell lymphoma	2.5 (4)
	Plasmablastic lymphoma	0.6 (1)
Indolent lymphoma	Marginal zone lymphoma	44.3 (70)
	Follicular lymphoma	3.2 (5)
Location of lymphoma	Stomach	64.6 (102)
	Small intestine	17.1 (27)
	Large intestine	14.6 (23)
	Multiple sites	3.7 (6)
TPN and bowel rest		29.7 (47)

DLBCL, diffuse large B-cell lymphoma; GIT, gastrointestinal tumor; TPN, total parenteral nutrition.

Table 2
Baseline demographic characteristics of GIT lymphoma patients with and without TPN (N = 158)

Characteristics		TPN (n = 47)	No TPN (n = 111)	*P*-value
Age, mean ± SD in y		56.3 ± 13.4	67.8 ± 14	<0.01
Sex, % (n)	Male	29.8 (14)	43.2 (48)	0.154
Race, % (n)	Chinese	61.7 (29)	78.4 (87)	0.170
	Malay	29.8 (14)	13.5 (15)	
	Indian	2.1 (1)	3.6 (4)	
	Others	6.4 (3)	4.5 (5)	
Types of lymphoma, % (n)				<0.01
Aggressive lymphoma	DLBCL	66 (31)	30.6 (34)	
	Burkitts lymphoma	23.4 (11)	1.8 (2)	
	Enteropathy-associated T-cell lymphoma	8.5 (4)	0.0 (0)	
	Plasmablastic lymphoma	0.0 (0)	0.9 (1)	
Indolent lymphoma	Marginal zone lymphoma	0.0 (0)	63.1 (70)	
	Follicular lymphoma	2.1 (1)	3.6 (4)	
Location of lymphoma, % (n)	Stomach	34 (16)	77.5 (86)	<0.01
	Small intestine	34 (16)	9.9 (11)	<0.01
	Large intestine	29.8 (14)	8.1 (9)	<0.01
	Multiple sites	2.1 (1)	4.5 (5)	
Perforation		8.5 (4)	2.7 (3)	0.197
Infection		34 (16)	4.5 (5)	<0.01

DLBCL, diffuse large B-cell lymphoma; GIT, gastrointestinal tumor; TPN, total parenteral nutrition.

currently is no standard guideline to recommend TPN and bowel rest in GIT lymphoma before chemotherapy. The present findings questioned the routine strategy of starting TPN and bowel rest in patients with GIT lymphoma who were receiving chemotherapy.

The present study reported a higher risk for perforation among patients with small bowel lymphoma, which is consistent with previous retrospective studies [1,8]. In contrast, no perforation was observed among 52 Japanese patients with gastric diffuse large B-cell lymphoma receiving chemotherapy [6]. The higher risk for perforation seen in small bowel lymphoma is likely anatomic, with the small bowel having a thinner luminal wall than the stomach.

Perforation is a serious complication that negatively impact the outcome of GIT lymphoma in patients receiving chemotherapy. The present study shows that perforation results in higher risk for infection and is associated with poorer survival among patients with GIT lymphoma receiving the first cycle of chemotherapy (Fig. 2). Additionally, systemic chemotherapy before GIT perforation can attenuate immune response to counter sepsis; overwhelming infection also can interrupt subsequent chemotherapy, which further affects these the survival of these patients. In patients with high risk for perforation such as those having an aggressive lymphoma localized to a segment of small bowel, surgical resection followed by rituximab-based chemotherapy may be a reasonable approach to avoid perforation upon completion of chemotherapy [9].

The present study also showed that the TPN group had higher risk for infection and inadvertently longer median LOS. The study reported an overall infection risk of 13.3%, with higher infection risk observed among patients receiving TPN and bowel rest during chemotherapy. Nosocomial infections, such as pneumonia and urinary tract infection, constitute about half of the infection. One patient reported having a catheter-related infection while on TPN. About 30% of patients with infection had bacteremia without a specific source of infection. We postulate the following reasons for bacterial translocation being the most likely source of infection in these patients

- presence of typical GIT normoflora such as *Enterococcus* sp. and *E. coli* in blood culture;
- disrupted mucosal barrier permeability as a result of GIT lymphoma;
- absence of trophic feeding increasing bacterial translocation; and
- absence of another source of infection [10–13].

With more patients with aggressive lymphoma in the TPN group, bowel rest may lead to intestinal mucosa atrophy, bacteremia, and higher risk for infection among the TPN group. Furthermore, mandatory inpatient admission during TPN also increases

Table 3
Association of outcomes of GIT lymphoma with and without TPN

			Univariate analysis		Multivariate analysis	
Outcome	TPN (n = 47)	No TPN (n = 111)	*P*-value	Unadjusted OR/HR* (95% CI)	*P*-value	Adjusted OR/HR* (95% CI)†
Infection, n (%)	16 (34)	5 (4.5)	<0.001	10.9 (3.71–32.25)	0.016	5.32 (1.36–20.76)
Perforation, n (%)	4 (8.5)	3 (2.7)	0.124	3.35 (0.72–15.59)	0.869	0.87 (0.13–5.90)
Survival, mean mo (95% CI)	67.4 (54.8–80.1)	139.7 (118.7–160.7)	0.118	1.75 (0.87–3.52)	0.659	1.23 (0.50–3.03)

GIT, gastrointestinal tumor; TPN, total parenteral nutrition.
*OR reported for outcomes of infection and perforation; HR reported for survival outcome.
†Multivariate analysis performed with adjustment for age, types of lymphoma (aggressive/indolent), and location of lymphoma (stomach, small and large bowel involvement, stomach as reference category). Reference group: non-TPN.

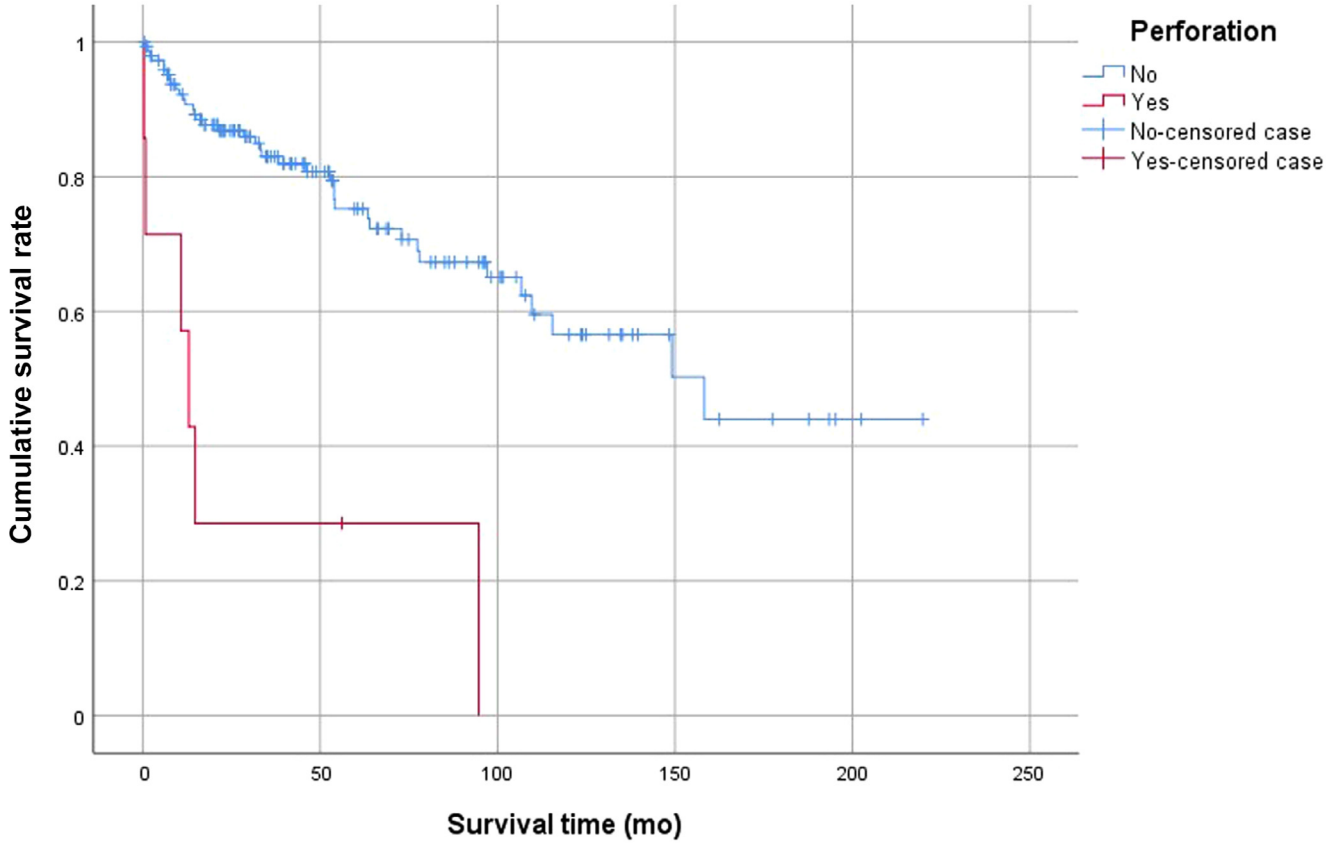

Fig. 2. Kaplan–Meier survival curves in patients with gastrointestinal tumor lymphoma with and without perforation.

Table 4
Demographic of patients with GIT lymphoma and perforation

Patient	Age, y/Sex	Location of lymphoma	Type of lymphoma	Type of chemotherapy	Time to perforation (median, d)	TPN	Infection	Outcome	Cause of death
1	69/F	Stomach	DLBCL	R-CHOP	39	No	Pneumonia	Dead	Lymphoma
2	61/M	Stomach	DLBCL	Dexamethasone	2	Yes	Gram-negative bacteremia	Dead	Lymphoma
3	24/F	Small bowel	DLBCL	Hyper-CVAD	50	Yes	Gram-negative bacteremia	Dead	Lymphoma
4	60/M	Small bowel	DLBCL	R-CHOP	15	No	Pneumonia	Alive	–
5	48/M	Small bowel	Follicular lymphoma	R-Benda	78	No	–	Dead	Lymphoma
6	70/M	Small bowel	Enteropathy-associated T-cell lymphoma	CHOP	39	Yes	–	Dead	Lymphoma
7	55/M	Large bowel	Enteropathy-associated T-cell lymphoma	CHOP	23	Yes	Pneumonia	Dead	Lymphoma

CHOP, cyclphosphamide, doxorubicin, vincristine, and prednisone; CVAD, cyclophosphamide, vincristine, doxorubicin, dexaethasone; DLBCL, diffuse large B-cell lymphoma; GIT, gastrointestinal tumor; R-CHOP, rituximab-cyclphosphamide, doxorubicin, vincristine, and prednisone; TPN, total parenteral nutrition.

the risk for nosocomial infection. Unlike patients who were discharged after completion of chemotherapy without TPN and bowel rest, patients receiving TPN and bowel rest were monitored until they achieved nadir of neutropenia subsequent to chemotherapy. The median onset of GIT perforation after chemotherapy is 33.6 d, suggesting half of the perforation can still occur after discharge following TPN and bowel rest.

The present study was limited by its retrospective and non-randomized design. Due to the nature of a non-randomized retrospective study, a cause-and-effect relationship cannot be established between TPN and infection. This was especially true when other factors such as glycemic control, nutritional status, baseline comorbidities, and performance status were not adjusted. We tried to address these limitations by adjusting all findings to account for differences in baseline characteristics and potential selection bias. Furthermore, we applied stringent inclusion criteria to include only biopsy-proven lymphoma from GIT and clearly defined clinical outcomes in the present study. Second, to evaluate perforation risk after chemotherapy, patients with GIT lymphoma not undergoing chemotherapy were excluded, thus potentially underreporting the overall perforation risk for GIT lymphoma. Third, although perforation after chemotherapy is assumed to be caused by chemotherapy-induced necrosis, the exact cause of GIT perforation at this time

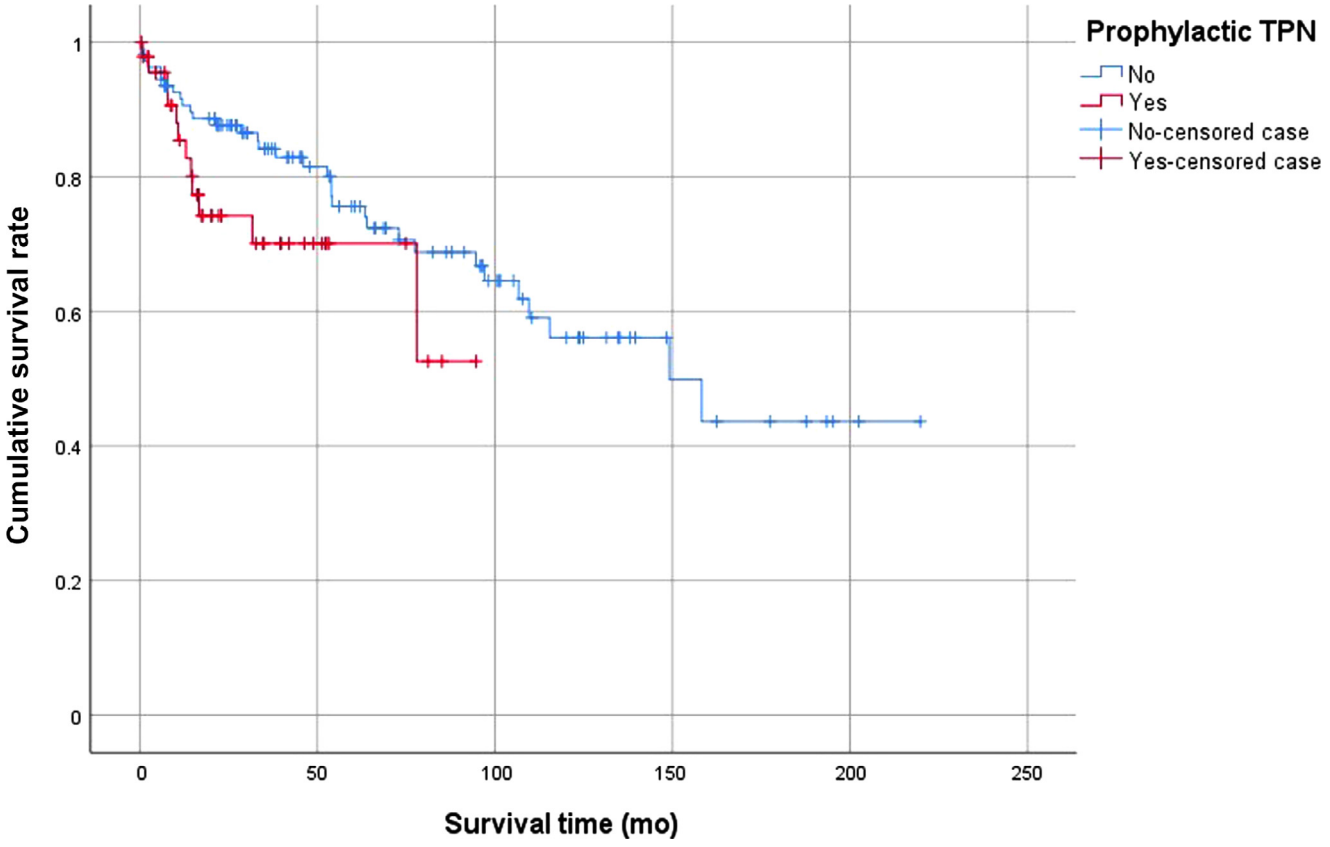

Fig. 3. Kaplan–Meier survival curve of patients with gastrointestinal tumor lymphoma with and without TPN and bowel rest. TPN, total parenteral nutrition.

point can be difficult even after reviewing histologic results. Finally, owing to the limited events of perforation, the power to detect outcomes related to perforations might be limited. A prospective randomized study, although being ideal, is resource intensive. Before this study, subjecting patients with GIT lymphoma to the potential morbidity of perforation without TPN and bowel rest in prospective randomized study raised ethical concerns among physicians. Such ethical concern is now addressed with the findings of the present study showing that TPN and bowel rest did not reduce perforation risk among patients with GIT lymphoma receiving chemotherapy.

Conclusion

In the present study, we demonstrated that TPN and bowel rest do not reduce risk for perforation among patients with GIT lymphoma receiving chemotherapy. Because the practice of prophylactic TPN and bowel rest was associated with higher infection risk and prolonged LOS, we do not recommend such practice for all patients with GIT lymphoma receiving chemotherapy. Future randomized studies are required to clarify these findings.

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