

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2020 September 27; 12(9): 377-406



ORIGINAL ARTICLE

Retrospective Study

- 377 Impact of palliative therapies in metastatic esophageal cancer patients not receiving chemotherapy

Kim S, DiPeri TP, Guan M, Placencio-Hickok VR, Kim H, Liu JY, Hendifar A, Klempner SJ, Nipp R, Gangi A, Burch M, Waters K, Cho M, Chao J, Atkins K, Kamrava M, Tuli R, Gong J

Observational Study

- 390 Predictive significance of cancer related-inflammatory markers in locally advanced rectal cancer

Timudom K, Akaraviputh T, Chinswangwatanakul V, Pongpaibul A, Korpraphong P, Petsuksiri J, Ithimakin S, Trakarnsanga A

CASE REPORT

- 397 Distal gastric tube resection with vascular preservation for gastric tube cancer: A case report and review of literature

Yura M, Koyanagi K, Adachi K, Hara A, Hayashi K, Tajima Y, Kaneko Y, Fujisaki H, Hirata A, Takano K, Hongo K, Yo K, Yoneyama K, Dehari R, Nakagawa M

ABOUT COVER

Editorial board member of *World Journal of Gastrointestinal Surgery*, Dr. Ying Fan is a Professor at China Medical University. Dr. Fan was promoted to Associate Professor & Deputy Chief Surgeon without exception in 2011. He has published more than 40 articles in Chinese and 20 SCI-indexed articles as first author or corresponding author. Currently, he is Deputy Director of the Second Department of General Surgery, Shengjing Hospital of China Medical University, member of the Expert Committee of Biliary Calculi Surgery of the Chinese Branch of the International Hepatobiliary and Pancreatic Association, member of the International College of Surgeons (ICS) for Biliary Surgery and Minimally Invasive Surgery, and review expert for the National Natural Science Foundation of China. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (WJGS, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, pancreatectomy, pancreaticoduodenectomy, and pancreaticojejunostomy, etc.

INDEXING/ABSTRACTING

The WJGS is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 edition of Journal Citation Reports® cites the 2019 impact factor (IF) for WJGS as 1.863; IF without journal self cites: 1.824; Ranking: 109 among 210 journals in surgery; Quartile category: Q3; Ranking: 77 among 88 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Liang Zhang; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ping Yan.

NAME OF JOURNAL

World Journal of Gastrointestinal Surgery

ISSN

ISSN 1948-9366 (online)

LAUNCH DATE

November 30, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Shu-You Peng, Varut Lohsiriwat, Jin Gu

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9366/editorialboard.htm>

PUBLICATION DATE

September 27, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Retrospective Study

Impact of palliative therapies in metastatic esophageal cancer patients not receiving chemotherapy

Sungjin Kim, Timothy P DiPeri, Michelle Guan, Veronica R Placencio-Hickok, Haesoo Kim, Jar-Yee Liu, Andrew Hendifar, Samuel J Klempner, Ryan Nipp, Alexandra Gangi, Miguel Burch, Kevin Waters, May Cho, Joseph Chao, Katelyn Atkins, Mitchell Kamrava, Richard Tuli, Jun Gong

ORCID number: Sungjin Kim 0000-0002-1150-703X; Timothy P DiPeri 0000-0003-1190-1640; Michelle Guan 0000-0003-3285-2120; Veronica R Placencio-Hickok 0000-0002-0463-8867; Haesoo Kim 0000-0002-7821-264X; Jar-Yee Liu 0000-0003-0448-2978; Andrew Hendifar 0000-0002-2079-9177; Samuel J Klempner 0000-0002-4062-0808; Ryan Nipp 0000-0002-4577-3248; Alexandra Gangi 0000-0002-9512-7973; Miguel Burch 0000-0001-5357-0718; Kevin Waters 0000-0003-3828-8647; May Cho 0000-0003-3445-6690; Joseph Chao 0000-0002-1809-504X; Katelyn Atkins 0000-0002-3165-4803; Mitchell Kamrava 0000-0003-1744-6271; Richard Tuli 0000-0002-3525-687X; Jun Gong 0000-0001-8713-1406.

Author contributions: Kim S and Gong J designed the research; Kim S, Guan M, Placencio-Hickok VR, Kim H, Liu JY, and Gong J collected and analyzed the data; Kim S, DiPeri TP, and Gong J wrote the paper; all authors edited and approved the final paper.

Institutional review board statement: The data used in the study are derived from a de-identified National Cancer Database file. As all patient identification variables have been removed, no institutional review

Sungjin Kim, Biostatistics and Bioinformatics Research Center, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, United States

Timothy P DiPeri, Alexandra Gangi, Miguel Burch, Division of Surgical Oncology, Department of Surgery, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, United States

Michelle Guan, Veronica R Placencio-Hickok, Haesoo Kim, Jar-Yee Liu, Andrew Hendifar, Jun Gong, Department of Medicine, Division of Hematology and Oncology, Samuel Oschin Comprehensive Cancer Institute, Cedars Sinai Medical Center, Los Angeles, CA 90048, United States

Samuel J Klempner, Ryan Nipp, Department of Medicine, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA 02114, United States

Kevin Waters, Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA 90048, United States

May Cho, Division of Hematology and Oncology, Department of Medicine, University of California, Davis, Sacramento, CA 95817, United States

Joseph Chao, Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA 91010, United States

Katelyn Atkins, Mitchell Kamrava, Department of Radiation Oncology, Cedars Sinai Medical Center, Los Angeles, CA 90048, United States

Richard Tuli, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, United States

Corresponding author: Jun Gong, MD, Assistant Professor, Department of Medicine, Division of Hematology and Oncology, Samuel Oschin Comprehensive Cancer Institute, Cedars Sinai Medical Center, 8700 Beverly Blvd, AC 1042B, Los Angeles, CA 90048, United States.
jun.gong@cshs.org

board (IRB) review was needed.

Informed consent statement: The data used in the study are derived from a de-identified National Cancer Database file. As all subject identification variables have been removed, no informed consent was needed.

Conflict-of-interest statement: No conflict of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: June 3, 2020

Peer-review started: June 3, 2020

First decision: June 15, 2020

Revised: July 2, 2020

Accepted: September 8, 2020

Article in press: September 8, 2020

Published online: September 27, 2020

P-Reviewer: Sommariva A

S-Editor: Wang JL

L-Editor: A

P-Editor: Li JH



Abstract

BACKGROUND

Palliative therapy has been associated with improved overall survival (OS) in several tumor types. Not all patients with metastatic esophageal cancer receive palliative chemotherapy, and the roles of other palliative therapies in these patients are limited.

AIM

To investigate the impact of other palliative therapies in patients with metastatic esophageal cancer not receiving chemotherapy.

METHODS

The National Cancer Database was used to identify patients between 2004-2015. Patients with M1 disease who declined chemotherapy and had known palliative therapy status [palliative therapies were defined as surgery, radiotherapy (RT), pain management, or any combination thereof] were included. Cases with unknown chemotherapy, RT, or nonprimary surgery status were excluded. Kaplan-Meier estimates of OS were calculated. Cox proportional hazards regression models were employed to examine factors influencing survival.

RESULTS

Among 140234 esophageal cancer cases, we identified 1493 patients who did not receive chemotherapy and had complete data. Median age was 70 years, most (66.3%) had a Charlson Comorbidity Index (CCI) of 0, and 37.1% were treated at an academic center. The majority (72.7%) did not receive other palliative therapies. On both univariate and multivariable analyses, there was no difference in OS between those receiving other palliative therapy (median 2.83 mo, 95%CI: 2.53-3.12) vs no palliative therapy (2.37 mo, 95%CI: 2.2-2.56; multivariable $P = 0.290$). On univariate, but not multivariable analysis, treatment at an academic center was predictive of improved OS [Hazard ratio (HR) 0.90, 95%CI: 0.80-1.00; $P = 0.047$]. On multivariable analysis, female sex (HR 0.81, 95%CI: 0.71-0.92) and non-black, other race compared to white race (HR 0.72, 95%CI: 0.56-0.93) were associated with reduced mortality, while South geographic region relative to West region (HR 1.23, 95%CI: 1.04-1.46) and CCI of 1 relative to CCI of 0 (HR 1.17, 95%CI: 1.03-1.32) were associated with increased mortality. Higher histologic grade and T-stage were also associated with worse OS ($P < 0.05$).

CONCLUSION

Palliative therapies other than chemotherapy conferred a numerically higher, but not statistically significant difference in OS among patients with metastatic esophageal cancer not receiving chemotherapy. Quality of life metrics, inpatient status, and subgroup analyses are important for examining the role of palliative therapies other than chemotherapy in metastatic esophageal cancer and future studies are warranted.

Key Words: Esophageal cancer; Metastatic; Palliative; Chemotherapy; Radiotherapy; Survival

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: We evaluated the impact of non-chemotherapy-based palliative treatments in patients with metastatic esophageal cancer not receiving chemotherapy. A remarkably small fraction of these patients does not receive any palliative therapy. These findings merit further investigation to identify those at greatest risk who may benefit from risk-tailored management approaches. There was a numerically higher but not statistically significant difference in overall survival among those who received other palliative therapies vs those who did not (median overall survival 2.83 mo vs 2.37 mo). Our analysis was limited by lack of ability to account for patients at different stages of presentation or severity of disease.

Citation: Kim S, DiPeri TP, Guan M, Placencio-Hickok VR, Kim H, Liu JY, Hendifar A,

Klempner SJ, Nipp R, Gangi A, Burch M, Waters K, Cho M, Chao J, Atkins K, Kamrava M, Tuli R, Gong J. Impact of palliative therapies in metastatic esophageal cancer patients not receiving chemotherapy. *World J Gastrointest Surg* 2020; 12(9): 377-389

URL: <https://www.wjgnet.com/1948-9366/full/v12/i9/377.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v12.i9.377>

INTRODUCTION

Esophageal cancer is the 8th most common cause of cancer worldwide and a majority of Western patients present with advanced disease at the time of diagnosis^[1]. In 2014 alone, the total esophageal cancer-related deaths were estimated to be greater than 15000 in the United States^[2]. The two primary subtypes of esophageal cancer are adenocarcinoma and squamous cell carcinoma, with adenocarcinoma representing the most common pathologic subtype in the Western world^[3]. Most patients present with advanced disease, and many of those who are initially eligible for surgical resection ultimately have disease recurrence^[4]. Nearly 50%-60% of patients present with locally advanced disease with invasion into adjacent structures (T4b), extensive nodal disease, or distant metastatic disease (M1) which preclude upfront surgical management^[3]. In patients who are not considered for surgical therapy, other treatment options such as palliative chemotherapy, palliative radiation, and supportive care for symptoms are available^[5].

Seminal studies have shown that early integration of palliative care can improve patient outcomes, including quality of life, mood, and potentially overall survival (OS)^[6-8]. These enhanced patient outcomes occurred despite patients receiving less aggressive care^[9]. Based on these findings from important studies in palliative medicine, practice guidelines have been developed that recommend all patients with advanced cancer should receive dedicated palliative care services early in the disease course and concurrent with active treatment^[10]. However, data are lacking regarding the optimal pathway that would allow for integration of palliative care into the metastatic esophageal cancer patient treatment algorithm^[5].

The systemic toxicity of cytotoxic chemotherapy in patients with metastatic gastroesophageal cancer is high, with an estimated median survival of less than one year in this population^[3]. Despite the high rates of advanced disease and considerable symptom burden in this population, data are lacking about how to best integrate palliative therapies into the care of patients with advanced esophageal cancer^[11]. In a recent series of advanced gastroesophageal cancer patients, only 18% of patients received chemotherapy whereas the most common treatment choice was supportive care alone (21%)^[12]. In this study, even among those who agreed to palliative chemotherapy, considerable heterogeneity existed regarding the choice of first-line chemotherapy, as fluorouracil and oxaliplatin represented the only regimen exceeding 10% utilization in the first-line setting^[13]. These results suggest that a remarkable proportion of patients with metastatic esophageal cancer do not receive palliative chemotherapy, and the role of other forms of palliative therapy in this population are also poorly described.

The goal of the current study was to describe outcomes among patients with metastatic esophageal cancer who did not receive chemotherapy. We sought to compare patient characteristics and outcomes between those who did or did not receive other palliative therapy. Specifically, we placed an emphasis on patient and disease factors that were independently associated with OS with a comparison of survival between those with metastatic esophageal cancer declining chemotherapy who received palliative therapy and those declining chemotherapy who did not receive any palliative therapy.

MATERIALS AND METHODS

The National Cancer Database (NCDB) was queried for patients with esophageal cancer ($n = 140234$) between 2004-2015 and the subgroup of patients with M1 disease who were not receiving chemotherapy and had known palliative therapy status ($n = 1493$ patients) were included in this retrospective analysis. Data were extracted and defined using the existing NCDB data dictionary (<http://ncdbpuf.facs.org/node/259?q=print-pdf-all>). In particular, the Charlson Comorbidity Index (CCI) is a

weighted score of comorbid conditions modified by Deyo *et al*^[14] from the original Charlson score that has been validated to independently predict for patient outcomes (e.g., mortality) as based on International Classification of Diseases codes found in administrative data such as hospital abstracts data^[15]. Palliative therapy was defined as surgery, radiation therapy (RT), and/or other pain management therapy provided to prolong the patient's life by controlling symptoms, to alleviate pain, or to make the patient comfortable as per the NCDB data dictionary. Cases with unknown chemotherapy, RT, or nonprimary surgery status were excluded ($n = 138741$).

Missing data patterns for variables with missing values such as treatment site (missing rate: 0.67%), geographic location (0.67%), race (0.47%), insurance type (1.81%), income (3.48%), education level (3.48%), residence area type (2.88%), grade (24.38%), American Joint Committee on Cancer (AJCC) clinical T stage (50.90%) and N stage (24.25%) were examined using the method proposed by Little^[16] and was not missing completely at random. To reduce the chance of bias from missing data, missing values were imputed using fully conditional specification implemented by the multivariate imputation by chained equations algorithm under the missing at random assumption^[17,18]. We generated thirty complete data sets, which were analyzed separately and then the results were combined using the formula in Rubin^[19].

OS was calculated from diagnosis to the date of death or censored at the date of last follow-up. Baseline characteristics in patients who did and did not receive palliative treatment were compared using Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables. Median follow-up was calculated using the reverse Kaplan-Meier method^[20]. Survival functions were estimated by the Kaplan-Meier method and compared using a log-rank test^[21]. Univariate and multivariable survival analyses were carried out using Cox proportional hazards regression models^[22]. Multivariable analyses were performed using a stepwise variable selection procedure based on Akaike Information Criterion (AIC) while receipt of palliative treatment was forced into the models^[23]. Final multivariable models were returned by the lowest AIC value. The proportional hazards assumption was assessed graphically and analytically with scaled Schoenfeld residuals^[24]. Variables included in the multivariable model in Table 1 were common to all 30 models fitted to the 30 imputed data sets. Each multivariable model had between 0-3 additional variables. Likelihood ratio tests were carried out to compare each full model to the reduced model and the results were not statistically significant. Possibility of multi-collinearity was assessed by tolerance and the variance inflation factor. Analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina) and R package version 3.5.3 with two-sided tests at a significance level of 0.05.

RESULTS

Baseline characteristics

Among the 140234 cases of esophageal cancer screened from the NCDB between 2004-2015, we identified a final 1493 patients with metastatic disease who declined chemotherapy and had complete data. In these patients, the median follow-up was 40.71 mo (95% CI: 33.81-59.47). A total of 407 patients with metastatic esophageal cancer did not receive chemotherapy but received some form of palliative therapy, while 1086 (73%) did not receive chemotherapy or any palliative therapy. We examined the baseline characteristics of patients who did or did not receive any palliative treatments (Table 2). In all patients, the median age was 70 years (interquartile range 62-79) and the majority were white (85%) and male (77%). In the overall cohort, the majority of cases had Medicare for insurance (63%), were treated at non-academic sites (63%) as defined by the Commission on Cancer Accreditation program, and resided in a metropolitan county (79%) as defined by population size by the U.S. Department of Agriculture Economic Research Service. Higher CCI scores (≥ 2) have been shown to be poor prognostic indicators in esophageal cancer patients undergoing curative intent esophagectomy^[25]. In our cohort of metastatic esophageal cancer patients, most (66%) had a CCI of 0.

Across all patients and those not receiving palliative chemotherapy with or without other palliative therapies, there were no statistically significant differences by age, gender, race, insurance type, income quartiles, education level, treatment site (academic *vs* non-academic), residence area type, CCI, year of diagnosis, grade, and AJCC T stage (Table 2). Notably, a higher proportion of cases from U.S. South geographic region (31%) not receiving chemotherapy and palliative therapy *vs* 24% who were not receiving chemotherapy but did receive palliative therapy ($P = 0.003$).

Table 1 Univariate and multivariable analysis of overall survival in cohort of patients with advanced esophageal cancer

Variable	n	Univariate		Multivariable	
		HR (95%CI)	P value	HR (95%CI)	P value
Treatment received					
No chemotherapy/received palliative therapy	407	0.94 (0.84-1.05)	0.288	0.94 (0.83-1.06)	0.290
No chemotherapy/no palliative therapy	1086	1 (Reference)		1 (Reference)	
Age (yr)	1493	1.00 (1.00-1.00)	0.773	²	
Gender					
Female	340	0.82 (0.73-0.93)	0.002	0.81 (0.71-0.92)	0.002
Male	1153	1 (Reference)		1 (Reference)	
Race ¹					
Black	142	0.87 (0.73-1.04)	0.136	0.87 (0.72-1.05)	0.136
Other	82	0.76 (0.60-0.97)	0.026	0.72 (0.56-0.93)	0.011
White	1270	1 (Reference)		1 (Reference)	
Insurance type ¹					
Medicaid	134	1.00 (0.81-1.24)	0.977	²	
Medicare	944	1.04 (0.91-1.18)	0.605		
Not insured	89	0.99 (0.77-1.28)	0.963		
Other government	21	1.01 (0.63-1.64)	0.956		
Private	305	1 (Reference)			
Income quartiles for place of residence ¹					
\$30000-\$34999	291	1.03 (0.86-1.24)	0.723	1.04 (0.86-1.25)	0.710
\$35000-\$45999	452	1.19 (1.01-1.41)	0.034	1.21 (1.01-1.44)	0.035
\$46000+	514	1.04 (0.89-1.23)	0.593	1.06 (0.89-1.26)	0.518
Less than \$30000	236	1 (Reference)		1 (Reference)	
Education level ^{1,3}					
14%-19.9%	372	1.03 (0.90-1.18)	0.679	²	
20%-28.9%	369	1.01 (0.88-1.16)	0.871		
29% or more	263	0.96 (0.82-1.12)	0.580		
Less than 14%	489	1 (Reference)			
Treatment site ¹					
Academic	554	0.90 (0.80-1.00)	0.047	²	
Non-Academic	939	1 (Reference)			
Geographic location in United States ¹					
Midwest	487	1.10 (0.93-1.29)	0.259	1.10 (0.94-1.30)	0.232
Northeast	341	1.12 (0.94-1.32)	0.203	1.17 (0.98-1.39)	0.076
South	431	1.20 (1.02-1.42)	0.026	1.23 (1.04-1.46)	0.017
West	234	1 (Reference)		1 (Reference)	
Residence area type ¹					
Metro	1183	1.06 (0.92-1.21)	0.431	²	
Rural	31	1.07 (0.73-1.57)	0.719		
Urban	279	1 (Reference)			
Number of comorbidities ⁴					

1	351	1.17 (1.03-1.32)	0.014	1.17 (1.03-1.32)	0.018
≥ 2	152	1.20 (1.00-1.42)	0.044	1.12 (0.94-1.35)	0.200
0	990	1 (Reference)		1 (Reference)	
Year of diagnosis					
2010-2014	889	1.06 (0.96-1.18)	0.249	²	
2004-2009	604	1 (Reference)			
Grade ^{1,5}					
1	50	0.64 (0.37-1.09)	0.101	0.58 (0.33-1.01)	0.054
2	513	0.60 (0.38-0.93)	0.023	0.58 (0.37-0.92)	0.020
3	901	0.73 (0.47-1.13)	0.153	0.71 (0.45-1.11)	0.133
4	29	1 (Reference)		1 (Reference)	
AJCC T stage ¹					
T0	17	0.69 (0.35-1.35)	0.280	0.64 (0.33-1.25)	0.192
T1	335	0.89 (0.74-1.07)	0.199	0.89 (0.73-1.08)	0.223
T2	162	0.73 (0.59-0.91)	0.005	0.72 (0.58-0.90)	0.003
T3	499	0.77 (0.66-0.89)	< 0.001	0.76 (0.66-0.89)	< 0.001
T4	480	1 (Reference)		1 (Reference)	
AJCC N stage ¹					
Positive	1083	0.92 (0.81-1.04)	0.187	²	
Negative	410	1 (Reference)			

¹Missing data were imputed by multiple imputation.

²Dropped out of the model.

³% of adults in the patient's zip code who did not graduate from high school.

⁴Per Charlson/Deyo *et al*^[14].

⁵Grade 1, well-differentiated; grade 2, moderately differentiated; grade 3, poorly differentiated; grade 4, undifferentiated. AJCC: American Joint Committee on Cancer; HR: Hazard ratio for mortality.

The only other clinical variable showing a statistically significant difference was AJCC node positivity whereby 78% of node-positive patients did not receive chemotherapy but did receive palliative therapy compared with 70% of node-positive patients who did not receive either chemotherapy or palliative therapy ($P = 0.006$).

Univariate analyses of OS

The median OS was 2.53 mo (95%CI: 2.33-2.66) in our overall cohort of patients with advanced esophageal cancer not receiving palliative chemotherapy. There was no statistically significant difference in OS between those receiving other palliative therapies (median OS 2.83 mo, 95%CI: 2.53-3.12) *vs* those who did not receive other palliative therapies (median OS 2.37 mo, 95%CI: 2.2-2.56, $P = 0.288$, **Figure 1**). The 6-mo and 12-mo OS rates were also similar in patients declining chemotherapy who received and did not receive palliative therapy.

We next performed univariate analyses of these same patient and clinicopathologic variables using Cox proportional hazards regression models for OS (**Table 1**). In metastatic esophageal cancer patients not receiving chemotherapy, there was no difference in OS between those who received and those who did not receive other palliative therapies [Hazard ratio (HR) 0.94, 95%CI: 0.84-1.05, $P = 0.288$]. On univariate analyses, female gender (HR 0.82, 95%CI: 0.73-0.93, $P = 0.002$), non-black, other race relative to white race (HR 0.76, 95%CI: 0.60-0.97, $P = 0.026$), treatment at an academic site (HR 0.90, 95%CI: 0.80-1.00, $P = 0.047$), and grade 2 histology relative to grade 4 (HR 0.60, 95%CI: 0.38-0.93, $P = 0.023$) were all significantly associated with reduced risk of death (**Table 1**). An income quartile of \$35000-\$45999 annually (HR 1.19, 95%CI: 1.01-1.41, $P = 0.034$), residing in the South compared to the West (HR 1.20, 95%CI: 1.02-1.42, $P = 0.026$), and higher CCI ≥ 2 (HR 1.20, 95%CI: 1.00-1.42, $P = 0.044$) were associated with poor OS. Compared to AJCC T4 stage, T3 (HR 0.77, 95%CI: 0.66-0.89, $P < 0.001$) and T2 (HR 0.73, 95%CI: 0.59-0.91, $P = 0.005$) were associated with

Table 2 Baseline characteristics of patients with advanced esophageal cancer who refused chemotherapy with and without receiving palliative treatment, *n* (%)

Variable	All patients (<i>n</i> = 1493)	No chemotherapy/received palliative therapy (<i>n</i> = 407)	No chemotherapy/no palliative therapy (<i>n</i> = 1086)	<i>P</i> value
Age (yr)				0.775
Median (IQR)	70 (62-79)	71 (62-79)	70 (62-79)	
Gender				0.748
Female	340 (22.77)	95 (23.34)	245 (22.56)	
Male	1153 (77.23)	312 (76.66)	841 (77.44)	
Race ¹				0.727
Black	142 (9.50)	38 (9.36)	104 (9.58)	
Other	82 (5.46)	19 (4.71)	62 (5.71)	
White	1270 (85.04)	350 (85.93)	920 (84.71)	
Insurance type ¹				0.398
Medicaid	134 (8.98)	33 (8.11)	101 (9.30)	
Medicare	944 (63.30)	255 (62.65)	689 (63.45)	
Not insured	89 (5.96)	19 (4.67)	70 (6.44)	
Other government	21 (1.41)	7 (1.72)	14 (1.29)	
Private	305 (20.43)	93 (22.85)	212 (19.52)	
Income quartiles for place of residence ¹				0.282
Less than \$30000	236 (15.79)	70 (17.20)	166 (15.29)	
\$30000-\$34999	291 (19.51)	87 (21.38)	204 (18.78)	
\$35000-\$45999	452 (30.29)	125 (30.71)	327 (30.11)	
\$46000+	514 (34.41)	125 (30.71)	389 (35.82)	
Education level ^{1,2}				0.971
Less than 14%	489 (32.73)	134 (32.92)	355 (32.69)	
14%-19.9%	372 (24.94)	101 (24.82)	271 (24.95)	
20%-28.9%	369 (24.73)	97 (23.83)	272 (25.05)	
29% or more	263 (17.60)	75 (18.43)	188 (17.31)	
Treatment site ¹				0.118
Academic	554 (37.11)	164 (40.29)	390 (35.91)	
Non-Academic	939 (62.89)	243 (59.71)	696 (64.09)	
Geographic location in United States ¹				0.003
Midwest	487 (32.62)	128 (31.45)	359 (33.05)	
Northeast	341 (22.84)	116 (28.50)	225 (20.72)	
South	431 (28.87)	96 (23.59)	335 (30.85)	
West	234 (15.67)	67 (16.46)	167 (15.38)	
Residence area type ¹				0.637
Metro	1183 (79.25)	316 (77.61)	867 (79.83)	
Rural	31 (2.07)	9 (2.28)	22 (2.02)	
Urban	279 (18.68)	82 (20.11)	197 (18.15)	
Number of comorbidities ³				0.759

0	990 (66.31)	266 (65.36)	724 (66.67)	
1	351 (23.51)	101 (24.82)	250 (23.02)	
≥ 2	152 (10.18)	40 (9.83)	112 (10.31)	
Year of diagnosis				0.753
2004-2009	604 (40.46)	162 (39.8)	442 (40.7)	
2010-2014	889 (59.54)	245 (60.2)	644 (59.3)	
Grade ^{1,4}				0.395
1	50 (3.35)	16 (3.93)	34 (3.13)	
2	513 (34.36)	127 (31.20)	386 (35.54)	
3	901 (60.35)	254 (62.41)	647 (59.58)	
4	29 (1.94)	10 (2.46)	19 (1.75)	
AJCC T stage ¹				0.091
T0	17 (1.14)	3 (0.74)	14 (1.29)	
T1	335 (22.44)	80 (19.65)	255 (23.48)	
T2	162 (10.85)	37 (9.09)	125 (11.51)	
T3	499 (33.42)	160 (39.31)	339 (31.21)	
T4	480 (32.20)	127 (31.20)	353 (32.50)	
AJCC N stage ¹				0.006
Positive	1083 (72.54)	319 (78.38)	764 (70.35)	
Negative	410 (27.46)	88 (21.62)	322 (29.65)	

¹Missing data were imputed by multiple imputation.

²% of adults in the patient's zip code who did not graduate from high school.

³Per Charlson/Deyo *et al*^[14].

⁴Grade 1, well-differentiated; grade 2, moderately differentiated; grade 3, poorly differentiated; grade 4, undifferentiated. *P* value is calculated by Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables. AJCC: American Joint Committee on Cancer.

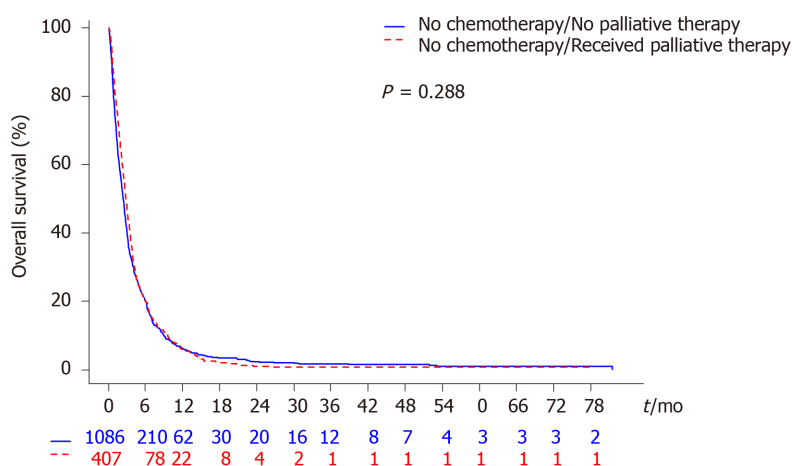
significantly improved OS. No other variables were predictive of OS on univariate analyses (Table 1).

Multivariable analyses of OS

On multivariable analyses, in metastatic esophageal cancer patients not receiving chemotherapy, receipt of other palliative therapies remained not associated with OS (HR 0.94, 95%CI: 0.83-1.06, *P* = 0.290; Table 1). Female gender (HR 0.81, 95%CI: 0.71-0.92, *P* = 0.002) and non-black, other race compared to white race (HR 0.72, 95%CI: 0.56-0.93, *P* = 0.011) independently predicted for reduced risk of death. Compared to grade 4, grade 2 histology (HR 0.58, 95%CI: 0.37-0.92) predicted for improved OS (*P* = 0.020). Compared to T4 stage, T3 (HR 0.76, 95%CI: 0.66-0.89, *P* < 0.001) and T2 (HR 0.72, 95%CI: 0.58-0.90, *P* = 0.003) were significantly associated with reduced risk of death. Compared to a CCI of 0, a score of 1 (HR 1.17, 95%CI: 1.03-1.32) predicted for increased mortality (*P* = 0.018). Residing in the South (HR 1.23, 95%CI: 1.04-1.46, *P* = 0.017) and an income quartile of \$35000-\$45999 annually (HR 1.21, 95%CI: 1.01-1.44, *P* = 0.035) predicted for worse OS. All other variables dropped out of the multivariable model (Table 1).

DISCUSSION

In patients diagnosed with advanced esophageal cancer, a clinically significant proportion of patients decline did not receive chemotherapy and often opt for best supportive care^[12]. Palliative chemotherapy in this population has been positively associated with an OS benefit, but grade 3-5 toxicity rates have been shown to be a relevant 33%-48% with platinum-based doublet regimens^[26,27]. Other palliative modalities for esophageal cancer have historically included surgery, radiation therapy,



Treatment received	n	Events	Censored	Median OS month (95%CI)	Estimated 6-month OS rate (95%CI)	Estimated 1-year OS rate (95%CI)
No chemotherapy/no palliative therapy	1086	1042 (96%)	44 (4%)	2.37 (2.2-2.56)	20.20% (17.84%-22.67%)	6.25% (4.88%-7.84%)
No chemotherapy/received palliative therapy	407	396 (97%)	11 (3%)	2.83 (2.53-3.12)	19.98% (16.22%-24.04%)	5.64% (3.65%-8.22%)

Figure 1 Kaplan-Meier estimates of overall survival for advanced esophageal cancer patients not receiving chemotherapy with and without palliative treatment. OS: Overall survival.

nutritional optimization, relief of obstruction, pain control, or a combination of the above^[28]. However, in patients with metastatic esophageal cancer who do not receive chemotherapy, our understanding of disease related outcomes is fairly limited. We are among the first groups to specifically look at patient and disease factors associated with treatment with palliative therapy and OS in those with metastatic esophageal cancer not receiving chemotherapy.

From a large retrospective cohort of 1493 patients with metastatic esophageal cancer who did not receive chemotherapy, we identified a surprisingly high 72.7% of cases who also did not receive any other palliative therapies. This is quite surprising given that a majority (66.7%) of these patients not receiving chemotherapy or any other palliative therapy had a no comorbidities, suggesting that this is a group who might be able to tolerate certain treatments. In another large cohort of 11,242 patients with gastrointestinal (GI) cancers (17% who had esophageal cancer), 22% did not receive outpatient palliative care, which is largely discordant with our findings^[29]. It is worthwhile to note that this study included a variety of GI cancers and evaluated outpatient palliative care encounters only.

Importantly, our survival analysis showed that patients with metastatic esophageal cancer who received any palliative therapy but no chemotherapy had a numerically higher, but not statistically significant OS compared to those who did not receive chemotherapy or any other palliative therapies (Table 1). These findings are important, as they suggest that other palliative therapies do not provide significant survival benefits to patients who are not receiving chemotherapy. Data is lacking on whether these palliative therapies influence other important factors, such as symptom burden and quality of life. Additionally, although the use of formal palliative care consultation was not directly investigated, integration of palliative care along with usual oncologic care is now a widely recommended approach across national practice guidelines in oncology^[10]. Early initiation of palliative care and beyond the outpatient setting is important as nearly 40% of patients with gastroesophageal cancer die within the first 6 months of presentation, reflective of a population with aggressive tumors or a disease state that is too advanced for curative therapy^[30]. In advanced esophageal cancer, greater implementation of this practice is certainly warranted. One manner to increase widespread implementation could involve more multidisciplinary discussions, *e.g.* tumor boards, as multidisciplinary discussions of gastroesophageal cancer patients resulted in more referrals for treatment with palliative therapies including radiation therapy and chemotherapy compared to those cases not discussed in a multidisciplinary setting^[31]. Furthermore, application of palliative care needs to come from an integrative approach encompassing a comprehensive assessment of biological,

psychological, social, and spiritual concerns, communication and decision-making domains, physical domains including pain, fatigue, nausea, and other symptoms, and ethical domains including advanced care planning^[32].

Several patient-related factors were associated with OS. For example, treatment at an academic center (HR 0.90 on univariate, $P = 0.047$), non-black, other race compared to white race (HR 0.72 on multivariable, $P = 0.011$), and female gender (HR 0.81 on multivariable, $P = 0.002$) were significantly associated with decreased mortality in our cohort. We found sex disparities in our current study, which contrasts findings from a retrospective series of esophageal cancer patients referred to a specialist UK cancer center by 6 National Health Service sites and multiple primary care referral centers whereby there were no statistically significant differences in survival between men and women^[30]. However, advancing age and socioeconomic deprivation was impaired to poorer OS in this study. A worse prognosis has been associated with black individuals with esophageal cancer, but this has not held true when adjusting for socioeconomic status, while blacks, Asians, and Hispanics have been shown to undergo lower rates of surgery, when compared to whites, in localized esophageal cancer^[33]. In addition, there were more patients from the geographic Southern region who did not receive any palliative therapy (30.9%) compared to those who received palliative therapy (23.6%, $P = 0.003$), and notably being from the South was significantly associated with a worse OS on both univariate and multivariable analyses (Table 1). Not surprisingly, having a higher T stage, histologic grade, and CCI were predictive of worse OS and were statistically significant on multivariable analysis (Table 1).

Although not statistically significant, having an income quartile of $> \$46000$ was associated with a lower HR of 1.06, while having an income quartile of $\$35000$ – $\$45999$ annually was significantly associated with poorer survival (HR 1.21, Table 1) on multivariable analysis. It has been shown that the presence of modifiable risk factors such as smoking, poor diet, impaired physical activity, and increased BMI are more commonly found in socioeconomically deprived groups, which can attribute to reduced survival outcomes in multiple studies on cancer^[30]. In other studies of esophageal cancer, lower socioeconomic status has been associated with poorer prognosis, while the incidence and mortality rates for esophageal cancer were higher in rural areas compared to urban areas across multiple nations^[33].

Our study has several limitations. It is worthwhile to mention that our retrospective analysis limited our ability to attribute differences in OS across demographic factors as we cannot account for delays in diagnosis and treatment or access to treatment, which can all contribute significantly to patient outcomes^[34]. However, our fairly large sample size and restriction to metastatic esophageal cancer patients who are not receiving chemotherapy offers an initial glimpse into potential socioeconomic, racial, and sex disparities that exist and can factor into prognosis in this population. Further investigation may help identify those with metastatic esophageal cancer who have declined or unable to receive chemotherapy having these demographic factors associated with poorer prognosis in need of other modalities (*e.g.*, palliative therapy) to improve upon outcomes and not necessarily OS. Also, our analysis does not distinguish across palliative therapy offered in the outpatient *vs* inpatient and early *vs* late referral settings whereby a difference in survival of the advanced stage patient is possible. Furthermore, palliative care entails a multidisciplinary approach to improve quality of life beyond palliative-intent therapies and our study does not account for referrals to palliative care. Additionally, in patients with incurable, end-stage esophageal cancer, survival may not be the appropriate outcome measure, whereas symptom burden, psychological distress, prognostic understanding, and quality of life may be more relevant.

CONCLUSION

In this retrospective analysis of 1493 patients with metastatic esophageal cancer who were not receiving chemotherapy, we identified a relatively high percentage of patients who did not receive any other palliative therapies. Several socioeconomic and clinicopathologic factors were predictive of OS and receipt of palliative therapies in these patients who did not receive chemotherapy. We found a numerical, but not statistically significant difference in OS associated with the receipt of palliative therapies when comparing patients with metastatic esophageal cancer not receiving chemotherapy. Collectively, our findings underscore that for populations at risk for worse survival outcomes, such as those with metastatic esophageal cancer, additional

research is needed to prospectively study the impact of palliative therapies on patient outcomes, including not just survival, but also symptom burden, psychological distress, prognostic understanding, and quality of life.

ARTICLE HIGHLIGHTS

Research background

Palliative chemotherapy has been associated with improved overall survival (OS) in metastatic esophageal cancer, but the role of other palliative therapies in this population is poorly understood.

Research motivation

Palliative therapies in patients with metastatic esophageal cancer who do not receive chemotherapy, defined as surgery, radiation therapy (RT), and/or other pain management therapy provided to prolong the patient's life by controlling symptoms, to alleviate pain, or to make the patient comfortable may offer an improvement in OS as well.

Research objectives

The objectives of this study were to investigate the patient and disease characteristics associated with receipt of other palliative therapies in metastatic esophageal cancer patients not receiving palliative chemotherapy. We also investigated the association of receiving other palliative therapies *vs* not receiving other palliative therapies with OS in these patients who did not receive chemotherapy.

Research methods

The National Cancer Database was used to identify patients between 2004-2015. Patients with M1 disease who did not receive chemotherapy but had been confirmed to receive other palliative therapies or not were included. Cases with unknown chemotherapy, RT, or nonprimary surgery status were excluded. Kaplan-Meier estimates of OS were calculated. Cox proportional hazards regression models were employed to examine factors influencing survival.

Research results

Out of 1493 patients who did not receive chemotherapy and had complete data, the majority (72.7%) did not receive other palliative therapies. There was no statistically significant difference in OS between those receiving other palliative therapies *vs* no palliative therapy. Several factors including treatment at an academic center, female sex, non-black, other race (compared to white race) were associated with improved OS, while South geographic region relative to West region and higher Charlson Comorbidity Index, histologic grade, and T-stage were associated with worse OS.

Research conclusions

Palliative therapies other than chemotherapy conferred a numerically higher, but not statistically significant difference in OS among patients with metastatic esophageal cancer not receiving chemotherapy. Several socioeconomic and clinicopathologic factors were predictive of OS and receipt of other palliative therapies in these patients who did not receive chemotherapy.

Research perspectives

Additional research is needed to prospectively study the impact of other palliative therapies on patient outcomes that OS may not capture in metastatic esophageal cancer. Quality of life metrics, inpatient status, and subgroup analyses are important for examining the role of palliative therapies other than chemotherapy in metastatic esophageal cancer and future studies are warranted.

ACKNOWLEDGEMENTS

The data used in the study are derived from a de-identified National Cancer Database file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed,

or the conclusions drawn from these data by the investigator.

REFERENCES

- 1 **Janmaat VT**, Steyerberg EW, van der Gaast A, Mathijssen RH, Bruno MJ, Peppelenbosch MP, Kuipers EJ, Spaander MC. Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer. *Cochrane Database Syst Rev* 2017; **11**: CD004063 [PMID: [29182797](#) DOI: [10.1002/14651858.CD004063.pub4](#)]
- 2 **Paul S**, Altorki N. Outcomes in the management of esophageal cancer. *J Surg Oncol* 2014; **110**: 599-610 [PMID: [25146593](#) DOI: [10.1002/jso.23759](#)]
- 3 **van Rossum PSN**, Mohammad NH, Vleggaar FP, van Hillegersberg R. Treatment for unresectable or metastatic oesophageal cancer: current evidence and trends. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 235-249 [PMID: [29235549](#) DOI: [10.1038/nrgastro.2017.162](#)]
- 4 **Smyth EC**, Lagergren J, Fitzgerald RC, Lordick F, Shah MA, Lagergren P, Cunningham D. Oesophageal cancer. *Nat Rev Dis Primers* 2017; **3**: 17048 [PMID: [28748917](#) DOI: [10.1038/nrdp.2017.48](#)]
- 5 **Haj Mohammad N**, Bernards N, van Putten M, Lemmens VEPP, van Oijen MGH, van Laarhoven HWM. Volume-outcome relation in palliative systemic treatment of metastatic oesophagogastric cancer. *Eur J Cancer* 2017; **78**: 28-36 [PMID: [28412586](#) DOI: [10.1016/j.ejca.2017.03.008](#)]
- 6 **Temel JS**, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA, Lynch TJ. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; **363**: 733-742 [PMID: [20818875](#) DOI: [10.1056/NEJMoa1000678](#)]
- 7 **Bakitas MA**, Tosteson TD, Li Z, Lyons KD, Hull JG, Li Z, Dionne-Odom JN, Frost J, Dragnev KH, Hegel MT, Azuero A, Ahles TA. Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial. *J Clin Oncol* 2015; **33**: 1438-1445 [PMID: [25800768](#) DOI: [10.1200/JCO.2014.58.6362](#)]
- 8 **Zimmermann C**, Swami N, Krzyzanowska M, Hannon B, Leigh N, Oza A, Moore M, Rydall A, Rodin G, Tannock I, Donner A, Lo C. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014; **383**: 1721-1730 [PMID: [24559581](#) DOI: [10.1016/S0140-6736\(13\)62416-2](#)]
- 9 **Greer JA**, Pirl WF, Jackson VA, Muzikansky A, Lennes IT, Heist RS, Gallagher ER, Temel JS. Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. *J Clin Oncol* 2012; **30**: 394-400 [PMID: [22203758](#) DOI: [10.1200/JCO.2011.35.7996](#)]
- 10 **Ferrell BR**, Temel JS, Temin S, Alesi ER, Balboni TA, Basch EM, Finn JI, Paice JA, Peppercorn JM, Phillips T, Stovall EL, Zimmermann C, Smith TJ. Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2017; **35**: 96-112 [PMID: [28034065](#) DOI: [10.1200/JCO.2016.70.1474](#)]
- 11 **Gupta V**, Coburn N, Kidane B, Hess KR, Compton C, Ringash J, Darling G, Mahar AL. Survival prediction tools for esophageal and gastroesophageal junction cancer: A systematic review. *J Thorac Cardiovasc Surg* 2018; **156**: 847-856 [PMID: [30011772](#) DOI: [10.1016/j.jtcvs.2018.03.146](#)]
- 12 **Opstelten JL**, de Wijkerslooth LR, Leenders M, Bac DJ, Brink MA, Loffeld BC, Meijnen-Bult MJ, Minderhoud IM, Verhagen MA, van Oijen MG, Siersema PD. Variation in palliative care of esophageal cancer in clinical practice: factors associated with treatment decisions. *Dis Esophagus* 2017; **30**: 1-7 [PMID: [26919349](#) DOI: [10.1111/dote.12478](#)]
- 13 **Abrams T**, Hess LM, Zhu YE, Schelman W, Liepa AM, Fuchs C. Predictors of heterogeneity in the first-line treatment of patients with advanced/metastatic gastric cancer in the U.S. *Gastric Cancer* 2018; **21**: 738-744 [PMID: [29392573](#) DOI: [10.1007/s10120-018-0802-5](#)]
- 14 **Deyo RA**, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45**: 613-619 [PMID: [1607900](#) DOI: [10.1016/0895-4356\(92\)90133-8](#)]
- 15 **Mnataganian G**, Ryan P, Norman PE, Hiller JE. Accuracy of hospital morbidity data and the performance of comorbidity scores as predictors of mortality. *J Clin Epidemiol* 2012; **65**: 107-115 [PMID: [21803545](#) DOI: [10.1016/j.jclinepi.2011.03.014](#)]
- 16 **Little R**. A test of missing completely at random for multivariate data with missing values. *J Am Stat Assoc* 1988; **83**: 1198-1202 [DOI: [10.2307/2290157](#)]
- 17 **van Buuren S**, Groothuis-Oudshoorn K. MICE: Multivariate Imputation by Chained Equations in R. *J Stat Softw* 2011; **45**: 1-67 [DOI: [10.18637/jss.v045.i03](#)]
- 18 **van Buuren S**. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res* 2007; **16**: 219-242 [PMID: [17621469](#) DOI: [10.1177/0962280206074463](#)]
- 19 **Rubin D**. Multiple imputation for nonresponse in surveys. New York: John Wiley Sons Inc., 1987: Chapter 3
- 20 **Schemper M**, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17**: 343-346 [PMID: [8889347](#) DOI: [10.1016/0197-2456\(96\)00075-x](#)]
- 21 **Kalbfleisch J**, Prentice R. The statistical analysis of failure time data. Wiley series in probability and mathematical statistics. New York: John Wiley Sons Inc., 1980
- 22 **Cox D**. Regression Models and Life Tables. *J Royal Stat Society* 1972; **B34**: 187-220
- 23 **Yamashita T**, Yamashita K, Kamimura R. A Stepwise AIC Method for Variable Selection in Linear Regression. *Commun Stat Theory Methods* 2007; **36**: 2395-2403 [DOI: [10.1080/03610920701215639](#)]
- 24 **Grambsch P**, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994; **81**: 515-526 [DOI: [10.2307/2337123](#)]
- 25 **Yamashita K**, Watanabe M, Mine S, Fukudome I, Okamura A, Yuda M, Hayami M, Imamura Y. The impact of the Charlson comorbidity index on the prognosis of esophageal cancer patients who underwent esophagectomy with curative intent. *Surg Today* 2018; **48**: 632-639 [PMID: [29383595](#) DOI: [10.1007/s00595-018-1630-2](#)]

- 26 **Baumgartner R**, Taghizadeh H, Jomrich G, Schoppmann SF, Preusser M, Ilhan-Mutlu A. Utilization and Efficacy of Palliative Chemotherapy for Locally Advanced or Metastatic Gastroesophageal Carcinoma. *Anticancer Res* 2020; **40**: 965-975 [PMID: [32014941](#) DOI: [10.21873/anticancer.14030](#)]
- 27 **Dijksterhuis WPM**, Verhoeven RHA, Slingerland M, Haj Mohammad N, de Vos-Geelen J, Beerepoot LV, van Voorthuizen T, Creemers GJ, van Oijen MGH, van Laarhoven HWM. Heterogeneity of first-line palliative systemic treatment in synchronous metastatic esophagogastric cancer patients: A real-world evidence study. *Int J Cancer* 2020; **146**: 1889-1901 [PMID: [31340065](#) DOI: [10.1002/ijc.32580](#)]
- 28 **Freeman RK**, Ascioti AJ, Mahidhara RJ. Palliative therapy for patients with unresectable esophageal carcinoma. *Surg Clin North Am* 2012; **92**: 1337-1351 [PMID: [23026285](#) DOI: [10.1016/j.suc.2012.07.004](#)]
- 29 **Merchant SJ**, Brogly SB, Booth CM, Goldie C, Nanji S, Patel SV, Lajkosz K, Baxter NN. Palliative Care and Symptom Burden in the Last Year of Life: A Population-Based Study of Patients with Gastrointestinal Cancer. *Ann Surg Oncol* 2019; **26**: 2336-2345 [PMID: [30969388](#) DOI: [10.1245/s10434-019-07320-z](#)]
- 30 **Lee A**, Khulusi S, Watson R. Gastroesophageal cancer patients need earlier palliative intervention - Using data to inform appropriate care. *Eur J Oncol Nurs* 2019; **40**: 126-130 [PMID: [31229202](#) DOI: [10.1016/j.ejon.2019.04.004](#)]
- 31 **Vermeulen BD**, Bruggeman L, Bac DJ, Schrauwen RWM, Epping LSM, Scheffer RCH, Tan ACITL, Groenen MJM, Verhoeven RHA, Siersema PD. Impact of multidisciplinary tumor board discussion on palliation of patients with esophageal or gastro-esophageal junction cancer: a population-based study. *Acta Oncol* 2020; **59**: 410-416 [PMID: [32067535](#) DOI: [10.1080/0284186X.2020.1725240](#)]
- 32 **Dy SM**, Isenberg SR, Al Hamayel NA. Palliative Care for Cancer Survivors. *Med Clin North Am* 2017; **101**: 1181-1196 [PMID: [28992862](#) DOI: [10.1016/j.mcna.2017.06.009](#)]
- 33 **Xie SH**, Lagergren J. Social group disparities in the incidence and prognosis of oesophageal cancer. *United European Gastroenterol J* 2018; **6**: 343-348 [PMID: [29774147](#) DOI: [10.1177/2050640617751254](#)]
- 34 **Khorana AA**, Tullio K, Elson P, Pennell NA, Grobmyer SR, Kalady MF, Raymond D, Abraham J, Klein EA, Walsh RM, Monteleone EE, Wei W, Hobbs B, Bolwell BJ. Time to initial cancer treatment in the United States and association with survival over time: An observational study. *PLoS One* 2019; **14**: e0213209 [PMID: [30822350](#) DOI: [10.1371/journal.pone.0213209](#)]



Observational Study

Predictive significance of cancer related-inflammatory markers in locally advanced rectal cancer

Kitinat Timudom, Thawatchai Akaraviputh, Vitoon Chinswangwatanakul, Ananya Pongpaibul, Pornpim Korpraphong, Janjira Petsuksiri, Suthinee Ithimakin, Atthaphorn Trakarnsanga

ORCID number: Kitinat Timudom 0000-0002-0848-2919; Thawatchai Akaraviputh 0000-0003-2969-2648; Vitoon Chinswangwatanakul 0000-0001-9662-1669; Ananya Pongpaibul 0000-0002-1950-0385; Pornpim Korpraphong 0000-0002-8435-1814; Janjira Petsuksiri 0000-0002-2334-4899; Suthinee Ithimakin 0000-0002-4205-6112; Atthaphorn Trakarnsanga 0000-0002-1980-7782.

Author contributions:

Trakarnsanga A was involved in the conceptualization, project administration, writing review and editing; Timudom K was involved in data curation, and writing the original draft; Akaraviputh T, Pongpaibul A, Korpraphong P, Petsuksiri J, Ithimakin S and Chinswangwatanakul V were involved in writing review and editing; all authors read and approved the final manuscript.

Institutional review board statement:

This study was approved by Siriraj's institutional review board committee and the committee's reference number is 335/2561(EC4).

Informed consent statement:

All patient information is de-identified.

Conflict-of-interest statement:

The

Kitinat Timudom, Thawatchai Akaraviputh, Vitoon Chinswangwatanakul, Atthaphorn Trakarnsanga, Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

Ananya Pongpaibul, Department of Pathology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

Pornpim Korpraphong, Janjira Petsuksiri, Department of Radiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

Suthinee Ithimakin, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

Corresponding author: Atthaphorn Trakarnsanga, MD, Associated Professor, Department of Surgery, Faculty of Medicine, Siriraj Hospital, 2 Prannok, Bangkoknoi, Bangkok 10700, Thailand. atthaphorn.tra@mahidol.ac.th

Abstract

BACKGROUND

Locally advanced rectal cancer is treated using neoadjuvant chemoradiation (nCRT), followed by total mesorectal excision (TME). Tumor regression and pathological post-treatment stage are prognostic for oncological outcomes. There is a significant correlation between markers representing cancer-related inflammation, including high neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) and unfavorable oncological outcomes. However, the predictive role of these markers on the effect of chemoradiation is unknown.

AIM

To evaluate the predictive roles of NLR, MLR, and PLR in patients with locally advanced rectal cancer receiving neoadjuvant chemoradiation.

METHODS

Patients ($n = 111$) with locally advanced rectal cancer who underwent nCRT followed by TME at the Minimally Invasive Surgery Unit, Siriraj Hospital between 2012 and 2018 were retrospectively analyzed. The associations between post-treatment pathological stages, neoadjuvant rectal (NAR) score and the

authors declare that they have no competing interests

Data sharing statement: The dataset utilized during the current study is available within the institutional collected data system which was used under Siriraj's institutional review board committee approval for this study. Data are available upon reasonable request with permission of Siriraj's institutional review board committee.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Thailand

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 27, 2020

Peer-review started: February 27, 2020

First decision: April 22, 2020

Revised: May 11, 2020

pretreatment ratios of markers of inflammation (NLR, MLR, and PLR) were analyzed.

RESULTS

Clinical stages determined using computed tomography, magnetic resonance imaging, or both were T4 ($n = 16$), T3 ($n = 94$), and T2 ($n = 1$). The NAR scores were categorized as high (score > 16) in 23.4%, intermediate (score 8-16) in 41.4%, and low (score < 8) in 35.2%. The mean values of the NLR, PLR, and MLR correlated with pathological tumor staging (ypT) and the NAR score. The values of NLR, PLR and MLR were higher in patients with advanced pathological stage and high NAR scores, but not statistically significant.

CONCLUSION

In patients with locally advanced rectal cancer, pretreatment NLR, MLR and PLR are higher in those with advanced pathological stage but the differences are not significantly different.

Key Words: Locally advanced rectal cancer; Cancer-related inflammatory markers; Neoadjuvant chemoradiation; Neutrophil-to-lymphocyte ratio; Monocyte-to-lymphocyte ratio; Platelet-to-lymphocyte ratio

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Previously, correlations between markers representing cancer-related inflammation, including high neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) and unfavorable oncological outcomes have been reported. The present study demonstrated the predictive role of these markers in patients with locally advanced rectal cancer. Pretreatment NLR, MLR, and PLR were higher in those with advanced pathological stage and high neoadjuvant rectal score, and represented a poor outcome.

Citation: Timudom K, Akaraviputh T, Chinswangwatanakul V, Pongpaibul A, Korpraphong P, Petsuksiri J, Ithimakin S, Trakarnsanga A. Predictive significance of cancer related-inflammatory markers in locally advanced rectal cancer. *World J Gastrointest Surg* 2020; 12(9): 390-396

URL: <https://www.wjgnet.com/1948-9366/full/v12/i9/390.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v12.i9.390>

INTRODUCTION

In Thailand, colorectal cancer is the third most common cancer, and approximately one-third of Thai patients with colorectal cancer have metastatic disease^[1]. Neoadjuvant chemoradiation (nCRT) followed by total mesorectal excision (TME) is the preferred treatment for locally advanced rectal cancer (clinical stage T3 or T4 or node-positive disease). This treatment regimen provides many benefits, including improved local control and reduced toxicity. Although a complete pathological response to this therapeutic regimen (ypT0N0) is a strong prognostic factor, we still lack precise preoperative prognostic and predictive factors for locally advanced rectal cancer. Therefore, surgical removal of the rectum remains the standard treatment and is essential in all patients.

Here we investigated the value of preoperative biochemical markers as prognostic factors and predictive markers for nCRT. Inflammation status correlates with the oncological outcomes of patients with rectal cancer^[2-5]. The immune system acts on cancer cells by producing numerous cytokines and mediators of inflammation. The neutrophil-to-lymphocyte ratio (NLR) serves as the primary prognostic marker of white blood cell status. Previous meta-analyses demonstrated the benefit of the NLR as a prognostic factor for worse oncological outcomes in various cancers including endometrial cancer, non-small cell lung cancer, hepatocellular carcinoma, gastric cancer, and colorectal cancer^[6,7]. Subsequently, the predictive roles of the monocyte-to-

Accepted: August 16, 2020**Article in press:** August 16, 2020**Published online:** September 27, 2020**P-Reviewer:** Burke DA**S-Editor:** Zhang H**L-Editor:** Webster JR**P-Editor:** Zhang YL

lymphocyte ratio (MLR) and the platelet-to-lymphocyte ratio (PLR) were established^[8]. Both pre- and post-chemoradiation NLR were prognostic of worse disease-free and overall survival among locally advanced cancer patients^[9,10]. However, the predictive role of these markers in patients receiving nCRT is still inconclusive. Here, we evaluate the predictive roles of pretreatment NLR, MLR, and PLR in patients with locally advanced rectal cancer receiving nCRT.

MATERIALS AND METHODS

The records of 111 patients with locally advanced rectal cancer who underwent nCRT followed by oncological surgical resection at the Minimally Invasive Surgery Unit, Siriraj Hospital between June 2012 and January 2018 were retrospectively analyzed. Thirty-six patients (32.4%) were diagnosed with mid-rectal cancer, defined as a tumor located 5–10 cm from the anal verge, and 75 patients (67.6%) were diagnosed with low-rectal cancer, defined as a tumor located within 5 cm from the anal verge. Clinical staging was performed using magnetic resonance imaging (MRI), computed tomography (CT) or both, with or without endorectal ultrasound (ERUS). Patients with evidence of distant metastasis on preoperative staging were excluded from the study. Demographic data collected included age, sex, clinical tumor and nodal stages, and location of tumors. A complete blood count examination was performed at baseline before starting nCRT in all patients. All patients received standard long-term nCRT comprising 45.0 to 50.4 Gy in twenty-eight fractions, infusion of 5-fluorouracil for five days during the first and fifth weeks of radiation, or continuous oral capecitabine therapy.

All patients underwent oncological resection after completing nCRT at intervals ranging from six to thirteen weeks depending on the clinical response, scheduling, and the surgeon's preference. High ligation of inferior mesenteric vessels and total mesorectal excision were performed. Pathologists specializing in gastroenterology examined the surgical specimens. Pathological tumor (ypT0-4) and nodal staging (ypN0-2) data were acquired. A pathological complete response was defined as no detectable viable tumor cells in the resected specimen (ypT0) and the resected node (ypN0). The neoadjuvant rectal (NAR) score was calculated according to the data generated using a Valentini nomogram for overall survival, using the clinical tumor stage (cT), pathological tumor stage (pT), and pathological nodal stage (pN)^[6,11]. The equation for calculating the NAR score is as follows: $NAR = [5ypN - 3(cT - ypT) + 12]^2 / 9.61$. NAR scores were categorized into the following levels: High (score > 16), intermediate (score 8–16) and low (score < 8)^[11,12]. High NAR scores correlated with poor oncological outcomes. Posttreatment pathological stages and ratios of markers of inflammation (pretreatment NLR, MLR, and PLR ratios) were compared.

Statistical analysis

Statistical analysis of all collected data was performed with SPSS version 19.0 (IBM Corporation, Armonk, NY, United States). All demographic data were analyzed using descriptive statistics. Numerical variables are expressed using frequency. Continuous variables were compared using independent samples Kruskal-Wallis (one-way ANOVA) test. A *P* value of < 0.05 was considered statistically significant.

RESULTS

Patient demographic data are shown in **Table 1**. Sixty-six patients were male and 45 were female with a median age of 61 years (range, 22–93 years). The clinical stages determined using CT, MRI, or both were as follows: T4 (*n* = 16), T3 (*n* = 94), and T2 (*n* = 1). Clinically positive lymph nodes were found in 16 patients (14.4%). The NAR scores were categorized as high (> 8), intermediate (8–16), and low (< 8) in 23.4%, 41.4% and 35.2%, respectively.

The mean values of the pretreatment NLR, PLR, and MLR correlated with pathologic tumor staging (ypT) and the NAR score. The mean values of the NLR of pathological stages 0, 1, 2, and 3 were 2.36, 2.42, 2.83 and 3.07, respectively (*P* = 0.40) (**Figure 1**). The mean values of the MLR of pathological stages 0, 1, 2 and 3 were 0.24, 0.27, 0.28, and 0.36, respectively (*P* = 0.18). The mean values of the PLR of pathological stages 0, 1, 2, and 3 were 10.15, 13.27, 14.20 and 15.56, respectively (*P* = 0.54). The mean values of the NLR were 2.52, 2.61, and 3.08 for low, intermediate, and high NAR

Table 1 Demographic data

	<i>n</i> (111)	%
Median age (yr)	61	
Sex		
Male	66	59.5
Female	45	40.5
Tumor location		
Middle rectum	36	32.4
Lower rectum	75	67.6
Clinical T staging		
cT2	1	1
cT3	94	84
cT4	16	15
Lymph node status		
Positive (cN+)	16	14.4
Negative (cN-)	95	85.6
NAR score		
Low	26	23.4
Intermediate	46	41.4
High	39	35.2

NAR: Neoadjuvant rectal.

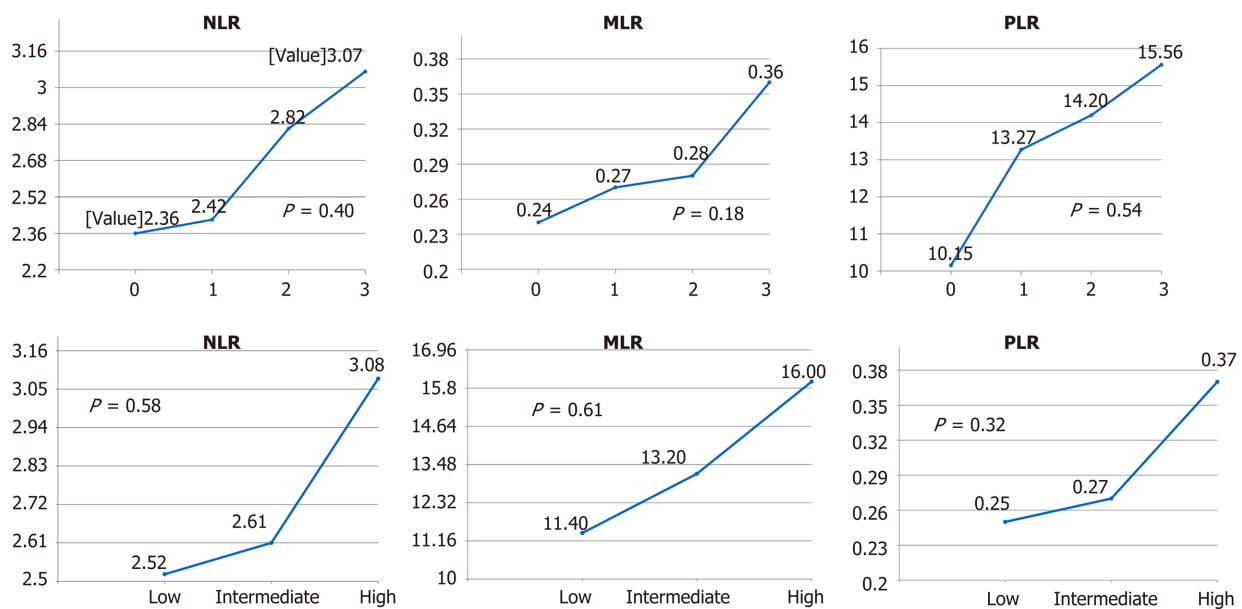


Figure 1 Mean values of the neutrophil-to-lymphocyte ratio, the monocyte-to-lymphocyte ratio and the platelet-to-lymphocyte ratio by stage. NLR: Neutrophil-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

scores, respectively ($P = 0.58$). The mean values of the MLR were 0.25, 0.27, and 0.37, respectively ($P = 0.32$). The mean values of the PLR were 11.40, 13.20, and 16.00, respectively ($P = 0.61$).

Twenty patients (76.9%) with low NARs experienced pathological complete responses. Furthermore, 34 patients (73.9%) with intermediate NAR scores and 37

patients (94.9%) with high NAR scores had pathological stages 2 and 3.

DISCUSSION

Our study demonstrated that the mean values of the NLR, PLR, and MLR correlated with pathological tumor staging and the NAR score. The ratios were higher in advanced pathological stages and high NAR scores. However, the differences were not statistically significant among the groups due to the small number of patients which is the main limitation of this study.

The systemic inflammatory response to cancer is increased in various cancers including lung cancer, ovarian cancer, tissue sarcoma, and colorectal cancer^[6]. The pathophysiology by which the inflammatory pathway might affect cancer is unknown. There is evidence to indicate an association between inflammation and impaired nutritional status. Inflammatory bowel disease serves as a good example, as colorectal cancer can develop in patients with chronic inflammatory bowel disease^[13].

The level of the systemic inflammatory response is determined by the concentration of C-reactive protein, which serves as a marker of acute phase protein stimulated by interleukin (IL)-6^[14-16]. The Glasgow prognostic score serves as a prognostic factor^[17]. However, these laboratory markers are not routinely measured during the preoperative evaluation of the majority of patients with rectal cancer, but complete blood counts are routinely examined.

T-cell lymphocytes play a major role in the antitumor immune response. The systemic inflammatory response is associated with lymphocytopenia and diminished lymphocyte function caused by the release of numerous proinflammatory cytokines such as IL-10 and transforming growth factor beta. Lymphocytopenia is the major contributor to high NLR, MLR, and PLR values. The low number of lymphocytes in the peripheral circulation may indicate a low antitumor response. CD8+ T lymphocytes play a major role in cancer immunity by killing cancer cells^[18]. Tumor-associated macrophages are associated with angiogenesis and tumor invasion^[19]. Thrombocytosis reflects cancer-induced inflammation. Furthermore, high concentrations of IL-1 and IL-6 were found in patients' plasma or cultured supernatants of tumor cells obtained from patients with thrombocytosis and tumors that produce colony-stimulating factor^[20]. A meta-analysis of 959 patients suggested that a high NLR is significantly associated with shorter overall survival, disease-free survival, and recurrence-free survival^[7].

The NAR score predicts the prognosis of patients with rectal cancer who receive nCRT. According to the NSABP R-04 trial, NAR scores were categorized as low, intermediate, and high, which were significantly associated with overall survival^[6]. In the present study, the mean values of pretreatment NLR, MLR, and PLR gradually increased as a function of the NAR score. These scores reflect an association between the levels of these markers and survival, although we did not demonstrate a significant association in the present study. However, in patients with high pretreatment NLR, MLR, and PLR, standard nCRT is warranted. We observed a restricted response to nCRT among patients with a high NAR score and high ratios of these inflammatory markers. Alternatively, upfront chemotherapy or a total neoadjuvant approach may play an important role in these patients.

The limitations of this study include its retrospective analysis of a small number of patients at a single center.

In summary, pretreatment NLR, MLR, and PLR in patients with locally advanced rectal cancer treated with nCRT were higher in patients with advanced pathological stages, although the differences were not statistically significant. Further studies with larger populations are required to evaluate the role of these inflammatory markers in predicting patient outcomes.

ARTICLE HIGHLIGHTS

Research background

The systemic inflammatory response is increased in cancer. The level of the systemic inflammatory response is indicated by the concentration of C-reactive protein or the Glasgow prognostic score. However, these laboratory markers are not routinely measured. The neutrophil-to-lymphocyte ratio (NLR), the monocyte-to-lymphocyte ratio (MLR) and the platelet-to-lymphocyte ratio (PLR) from the complete blood count

are prognostic for various cancers.

Research motivation

The NLR, MLR and PLR are associated with poor oncological outcomes in rectal cancer. However, the predictive role of these markers in patients receiving preoperative chemoradiation is inconclusive.

Research objectives

We evaluated the predictive roles of pretreatment NLR, MLR, and PLR in patients with locally advanced rectal cancer receiving neoadjuvant chemoradiation.

Research methods

The records of patients with locally advanced rectal cancer who underwent neoadjuvant chemoradiation followed by surgical resection at Siriraj Hospital between 2012 and 2018 were retrospectively analyzed. The associations between posttreatment pathological stages, neoadjuvant rectal (NAR) score and the pretreatment ratios of markers of inflammation (NLR, MLR, and PLR) were analyzed.

Research results

Among 111 patients, the clinical stages determined using computed tomography, magnetic resonance imaging, or both were as follows: T4 ($n = 16$), T3 ($n = 94$), and T2 ($n = 1$). The frequency of clinically positive lymph nodes was 14.4%. The NAR scores were categorized as high (> 8) in 23.4%, intermediate (8–16) in 41.4%, and low (< 8) in 35.2%. The mean values of the NLR of pathological stages 0, 1, 2, and 3 were 2.36, 2.42, 2.83 and 3.07, respectively ($P = 0.40$) (Figure 1). The mean values of the MLR of pathological stages 0, 1, 2 and 3 were 0.24, 0.27, 0.28, and 0.36, respectively ($P = 0.18$). The mean values of the PLR of pathological stages 0, 1, 2, and 3 were 10.15, 13.27, 14.20 and 15.56, respectively ($P = 0.54$). The mean values of the NLR were 2.52, 2.61, and 3.08 for low, intermediate, and high NAR scores, respectively ($P = 0.58$). The mean values of the MLR were 0.25, 0.27, and 0.37, respectively ($P = 0.32$). The mean values of the PLR were 11.40, 13.20, and 16.00, respectively ($P = 0.61$).

Research conclusions

The pretreatment NLR, MLR, and PLR of patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy followed by total mesorectal excision were higher in patients with advanced pathological stages, although the differences were not statistically significant.

Research perspectives

This study demonstrated the association between higher numbers of pretreatment inflammatory markers and higher advanced stages. Furthermore, higher numbers of pretreatment NLR, MLR, and PLR were associated with poorer response to neoadjuvant chemoradiation (high NAR score). Unfortunately, this is a retrospective analysis of a small number of patients at a single center. Therefore, there were no statistically significant results. Further studies of larger populations are required to evaluate the significance of these inflammatory markers in predicting the response.

ACKNOWLEDGEMENTS

We thank Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

REFERENCES

- 1 Techawathanawanna S, Nimmannit A, Akewanlop C. Clinical characteristics and disease outcome of UICC stages I-III colorectal cancer patients at Siriraj Hospital. *J Med Assoc Thai* 2012; **95** Suppl 2: S189-S198 [PMID: 22574549]
- 2 Dudani S, Marginean H, Tang PA, Monzon JG, Raissouni S, Asmis TR, Goodwin RA, Gotfrit J, Cheung WY, Vickers MM. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as predictive and prognostic markers in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiation. *BMC Cancer* 2019; **19**: 664 [PMID: 31277604 DOI: 10.1186/s12885-019-5892-x]
- 3 Braun LH, Baumann D, Zwirner K, Eipper E, Hauth F, Peter A, Zips D, Gani C. Neutrophil-to-Lymphocyte

- Ratio in Rectal Cancer-Novels Biomarker of Tumor Immunogenicity During Radiotherapy or Confounding Variable? *Int J Mol Sci* 2019; **20**: 2448 [PMID: [31108935](#) DOI: [10.3390/ijms20102448](#)]
- 4 **Nagasaki T**, Akiyoshi T, Fujimoto Y, Konishi T, Nagayama S, Fukunaga Y, Ueno M. Prognostic Impact of Neutrophil-to-Lymphocyte Ratio in Patients with Advanced Low Rectal Cancer Treated with Preoperative Chemoradiotherapy. *Dig Surg* 2015; **32**: 496-503 [PMID: [26544755](#) DOI: [10.1159/000441396](#)]
- 5 **Shen L**, Zhang H, Liang L, Li G, Fan M, Wu Y, Zhu J, Zhang Z. Baseline neutrophil-lymphocyte ratio (≥ 2.8) as a prognostic factor for patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation. *Radiat Oncol* 2014; **9**: 295 [PMID: [25518933](#) DOI: [10.1186/s13014-014-0295-2](#)]
- 6 **Templeton AJ**, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, Tannock IF, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014; **106**: dju124 [PMID: [24875653](#) DOI: [10.1093/jnci/dju124](#)]
- 7 **Dong YW**, Shi YQ, He LW, Su PZ. Prognostic significance of neutrophil-to-lymphocyte ratio in rectal cancer: a meta-analysis. *Onco Targets Ther* 2016; **9**: 3127-3134 [PMID: [27307753](#) DOI: [10.2147/OTT.S103031](#)]
- 8 **Lee IH**, Hwang S, Lee SJ, Kang BW, Baek D, Kim HJ, Park SY, Park JS, Choi GS, Kim JC, Cho SH, Kim JG. Systemic Inflammatory Response After Preoperative Chemoradiotherapy Can Affect Oncologic Outcomes in Locally Advanced Rectal Cancer. *Anticancer Res* 2017; **37**: 1459-1465 [PMID: [28314318](#) DOI: [10.21873/anticancer.11470](#)]
- 9 **Sung S**, Son SH, Park EY, Kay CS. Prognosis of locally advanced rectal cancer can be predicted more accurately using pre- and post-chemoradiotherapy neutrophil-lymphocyte ratios in patients who received preoperative chemoradiotherapy. *PLoS One* 2017; **12**: e0173955 [PMID: [28291841](#) DOI: [10.1371/journal.pone.0173955](#)]
- 10 **Cha YJ**, Park EJ, Baik SH, Lee KY, Kang J. Prognostic impact of persistent lower neutrophil-to-lymphocyte ratio during preoperative chemoradiotherapy in locally advanced rectal cancer patients: A propensity score matching analysis. *PLoS One* 2019; **14**: e0214415 [PMID: [30901357](#) DOI: [10.1371/journal.pone.0214415](#)]
- 11 **George TJ Jr**, Allegra CJ, Yothers G. Neoadjuvant Rectal (NAR) Score: a New Surrogate Endpoint in Rectal Cancer Clinical Trials. *Curr Colorectal Cancer Rep* 2015; **11**: 275-280 [PMID: [26321890](#) DOI: [10.1007/s11888-015-0285-2](#)]
- 12 **Fokas E**, Fietkau R, Hartmann A, Hohenberger W, Grützmann R, Ghadimi M, Liersch T, Ströbel P, Grabenbauer GG, Graeven U, Hofheinz RD, Köhne CH, Wittekind C, Sauer R, Kaufmann M, Hothorn T, Rödel C; German Rectal Cancer Study Group. Neoadjuvant rectal score as individual-level surrogate for disease-free survival in rectal cancer in the CAO/ARO/AIO-04 randomized phase III trial. *Ann Oncol* 2018; **29**: 1521-1527 [PMID: [29718095](#) DOI: [10.1093/annonc/mdy143](#)]
- 13 **Kim ER**, Chang DK. Colorectal cancer in inflammatory bowel disease: the risk, pathogenesis, prevention and diagnosis. *World J Gastroenterol* 2014; **20**: 9872-9881 [PMID: [25110418](#) DOI: [10.3748/wjg.v20.i29.9872](#)]
- 14 **Pathak S**, Nunes QM, Daniels IR, Smart NJ. Is C-reactive protein useful in prognostication for colorectal cancer? A systematic review. *Colorectal Dis* 2014; **16**: 769-776 [PMID: [25039573](#) DOI: [10.1111/codi.12700](#)]
- 15 **Kersten C**, Louhimo J, Ålgars A, Lahdesmaki A, Cvancerova M, Stenstedt K, Haglund C, Gunnarsson U. Increased C-reactive protein implies a poorer stage-specific prognosis in colon cancer. *Acta Oncol* 2013; **52**: 1691-1698 [PMID: [24102179](#) DOI: [10.3109/0284186X.2013.835494](#)]
- 16 **Guthrie GJ**, Roxburgh CS, Richards CH, Horgan PG, McMillan DC. Circulating IL-6 concentrations link tumour necrosis and systemic and local inflammatory responses in patients undergoing resection for colorectal cancer. *Br J Cancer* 2013; **109**: 131-137 [PMID: [23756867](#) DOI: [10.1038/bjc.2013.291](#)]
- 17 **McMillan DC**. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat Rev* 2013; **39**: 534-540 [PMID: [22995477](#) DOI: [10.1016/j.ctrv.2012.08.003](#)]
- 18 **Hoffmann TK**, Dworacki G, Tsukihiro T, Meidenbauer N, Gooding W, Johnson JT, Whiteside TL. Spontaneous apoptosis of circulating T lymphocytes in patients with head and neck cancer and its clinical importance. *Clin Cancer Res* 2002; **8**: 2553-2562 [PMID: [12171883](#)]
- 19 **Pollard JW**. Trophic macrophages in development and disease. *Nat Rev Immunol* 2009; **9**: 259-270 [PMID: [19282852](#) DOI: [10.1038/nri2528](#)]
- 20 **Suzuki A**, Takahashi T, Nakamura K, Tsuyuka R, Okuno Y, Enomoto T, Fukumoto M, Imura H. Thrombocytosis in patients with tumors producing colony-stimulating factor. *Blood* 1992; **80**: 2052-2059 [PMID: [1382717](#)]

Distal gastric tube resection with vascular preservation for gastric tube cancer: A case report and review of literature

Masahiro Yura, Kazuo Koyanagi, Kiyohiko Adachi, Asuka Hara, Keita Hayashi, Yuki Tajima, Yasushi Kaneko, Hiroto Fujisaki, Akira Hirata, Kiminori Takano, Kumiko Hongo, Kikuo Yo, Kimiyasu Yoneyama, Reiko Dehari, Motohito Nakagawa

ORCID number: Masahiro Yura 0000-0003-4150-2085; Kazuo Koyanagi 0000-0002-8010-8630; Kiyohiko Adachi 0000-0002-7952-6616; Asuka Hara 0000-0002-3295-9094; Keita Hayashi 0000-0002-4022-7627; Yuki Tajima 0000-0002-9121-0227; Yasushi Kaneko 0000-0003-4854-7673; Hiroto Fujisaki 0000-0002-3719-4924; Akira Hirata 0000-0001-6836-1177; Kiminori Takano 0000-0003-0366-8367; Kumiko Hongo 0000-0001-5150-7838; Kikuo Yo 0000-0002-1971-0390; Kimiyasu Yoneyama 0000-0001-5715-7365; Reiko Dehari 0000-0003-0812-9549; Motohito Nakagawa 0000-0003-0507-444X.

Author contributions: Yura M and Koyanagi K performed the surgery and wrote the paper; Nakagawa M reviewed the manuscript; Dehari R contributed to pathological diagnosis; All other authors equally contributed to medical treatment; All authors were responsible for the revision of the manuscript and final approval for submission.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement:

Masahiro Yura, Kiyohiko Adachi, Asuka Hara, Keita Hayashi, Yuki Tajima, Yasushi Kaneko, Hiroto Fujisaki, Akira Hirata, Kiminori Takano, Kumiko Hongo, Kikuo Yo, Kimiyasu Yoneyama, Motohito Nakagawa, Department of Surgery, Hiratsuka City Hospital, Kanagawa 2540065, Japan

Kazuo Koyanagi, Department of Gastroenterological Surgery, Tokai University School of Medicine, Isehara 2591193, Japan

Reiko Dehari, Department of Surgical Pathology, Hiratsuka City Hospital, Kanagawa 2540065, Japan

Corresponding author: Masahiro Yura, MD, Doctor, Surgeon, Department of Surgery, Hiratsuka City Hospital, 1-19-1, Minamihara, Hiratsuka-shi, Kanagawa 2540065, Japan. myura@ncc.go.jp

Abstract

BACKGROUND

Survival rates in patients with esophageal cancer undergoing esophagectomy have improved, but the prevalence of gastric tube cancer (GTC) has also increased. Total resection of the gastric tube with lymph node dissection is considered a radical treatment, but GTC surgery is more invasive and involves a higher risk of severe complications or death, particularly in elderly patients.

CASE SUMMARY

We report an elderly patient with early GTC that had invaded the duodenum who was successfully treated with resection of the distal gastric tube and Roux-en-Y (R-Y) reconstruction. The tumor was a type 0-IIc lesion with ulcer scars surrounding the pyloric ring. Endoscopic submucosal resection was not indicated because the primary lesion was submucosally invasive, was undifferentiated type, surrounded the pyloric ring, and had invaded the duodenum. Resection of distal gastric tube with R-Y reconstruction was safely performed, with preservation of the right gastroepiploic artery (RGEA) and right gastric artery (RGA).

CONCLUSION

Distal resection of the gastric tube with preservation of the RGEA and RGA is a good treatment option for elderly patients with cT1bN0 GTC in the lower part of the gastric tube.

None of the authors declare any conflict of interest.

CARE Checklist (2016) statement:

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: June 15, 2020

Peer-review started: June 15, 2020

First decision: July 21, 2020

Revised: August 1, 2020

Accepted: August 31, 2020

Article in press: August 31, 2020

Published online: September 27, 2020

P-Reviewer: Han JG, Yu PF

S-Editor: Huang P

L-Editor: Filipodia

P-Editor: Zhang YL



Key Words: Gastric tube cancer; Distal resection; Preservation of right gastroepiploic artery and right gastric artery; Elderly patients; Duodenal invasion; Case report; Posterior mediastinal reconstruction

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Surgical removal of the reconstructed gastric tube is invasive and carries a relatively high risk of postoperative morbidity and mortality, especially for elderly patients. We present the case of an 82-year-old man who underwent successful resection of distal gastric tube for early gastric tube cancer with duodenal invasion. The interesting features of this case include the advanced age of the patient, distal resection of a gastric tube reconstructed *via* the posterior mediastinal route, and preservation of the right gastroepiploic artery and right gastric artery. None of these features have been described in previous reports.

Citation: Yura M, Koyanagi K, Adachi K, Hara A, Hayashi K, Tajima Y, Kaneko Y, Fujisaki H, Hirata A, Takano K, Hongo K, Yo K, Yoneyama K, Dehari R, Nakagawa M. Distal gastric tube resection with vascular preservation for gastric tube cancer: A case report and review of literature. *World J Gastrointest Surg* 2020; 12(9): 397-406

URL: <https://www.wjgnet.com/1948-9366/full/v12/i9/397.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v12.i9.397>

INTRODUCTION

Gastric and head and neck cancers are the most frequent malignancies co-occurring with esophageal cancer^[1]. Recent advances in the diagnosis and treatment of esophageal cancer have improved prognosis after esophagectomy but have also led to an increasing occurrence of gastric tube cancer (GTC). While the use of endoscopic resection for early GTC without lymph node (LN) metastasis has increased^[2-4], total resection of the gastric tube with LN dissection is considered the standard radical treatment for GTC when endoscopic submucosal dissection (ESD) is not indicated. Surgical removal of a reconstructed gastric tube is an invasive procedure that involves a higher risk of postoperative morbidity and mortality^[5]. In particular, the possibility of LN metastasis and operative mortality must be carefully considered in choosing the surgery. Less invasive surgery should be considered for elderly and other high-risk patients even if there is a risk of LN metastasis. Distal resection is one of the less invasive procedures for patients with early GTC located on the distal side of the gastric tube. Moreover, preservation of the main trunk of the right gastroepiploic artery (RGEA) and the right gastric artery (RGA) would retain the main blood supply to the reconstructed gastric tube, given that the other gastric vessels were divided during the previous surgery. Several reports have described successful partial resection for early GTC^[6,7]. Here, we present a successful case of surgical treatment for GTC and provide details of the surgical procedure. The noteworthy features of this case include the advanced age of the patient (82 years; older than in any previous surgical reports), GTC invading the duodenum, previous reconstruction *via* the posterior mediastinum, and resection of the distal gastric tube while preserving the RGEA and RGA.

CASE PRESENTATION

Chief complaints

An 82-year-old man presented to the Department of Surgery of the Hiratsuka City Hospital (Japan). He had no complaints and had continued to visit the hospital for routine postoperative follow-up examinations after esophagectomy for esophageal cancer.

History of present illness

The patient had undergone subtotal esophagectomy with gastric tube reconstruction *via* the posterior mediastinal route for esophageal cancer 13 years earlier. No recurrence was detected, but gastric tube cancer was found during a routine follow-up 13 years after the original subtotal esophagectomy.

History of past illness

The patient had hypertension, chronic renal disease, and a history of subtotal esophagectomy with posterior mediastinal reconstruction for esophageal cancer 13 years earlier. Pathological examination of the resected esophageal cancer revealed a basaloid carcinoma with invasion of the submucosa, diagnosed as pT1bN0M0, p-stage I according to the Union for International Cancer Control Tumor Node Metastasis Classification of Malignant Tumors, 8th edition^[8].

Physical examination

No noticeable physical findings other than the previous surgical incision were observed.

Laboratory examinations

A blood analysis revealed mild anemia (hemoglobin; 12.3 g/dL) with normal white blood cell and platelet counts. Prothrombin and partial thromboplastin times were normal. Blood biochemistry revealed chronic renal disease (creatinine, 1.09 mg/dL; Creatinine clearance, 46.7 mL/min) and increased brain natriuretic peptide 128.5 pg/mL (normal range: < 18.0 pg/mL).

An electrocardiogram showed ST-T abnormalities on leads II, III, aVf, and V4-6. Echocardiography revealed almost normal cardiac function with mild aortic stenosis. A pulmonary function examination revealed the following: Vital capacity, 72.6% of predicted; and forced expiratory volume in 1 s, 67.7% of predicted (1.57 L). A chest X-ray showed the reconstructed gastric tube in the mediastinum.

Imaging examinations

Endoscopic examination revealed a type 0-IIc tumor with an ulcer scar surrounding the pyloric ring and invading the duodenum. The lesion was not stained by indigo carmine (Figure 1A and B). Computed tomography was unable to detect the primary tumor, and no obvious nodal metastasis was observed (Figure 2A-D).

FINAL DIAGNOSIS

Pathological examination of the resected specimen revealed a moderately to poorly differentiated adenocarcinoma with submucosal invasion and ulcerative scars (UL-IIs-IIIs) without lymphovascular invasion (Figure 3A and B). The cancer had invaded the duodenum. The horizontal and vertical surgical margins were negative, and the #6LN was negative for metastasis. The pathological diagnosis was pT1bN0M0 pStage IA.

TREATMENT

Biopsies were taken, and the histological examination led to a diagnosis of a moderately to poorly differentiated adenocarcinoma. The preoperative GTC stage was LD circ cT1bN0M0 cStage I according to the Japanese Classification of Gastric Carcinoma, 15th edition^[9].

ESD was not indicated for the GTC based on guidelines for treating gastric cancer^[10] because the lesion was diagnosed as an undifferentiated type with submucosal invasion. Additionally, the lesion surrounded the pyloric ring and had invaded the duodenum, so ESD would have been technically difficult. Surgical risk factors for this patient included his advanced age (82 years), poor pulmonary function, chronic renal disorder, hypertension, and history of subtotal esophagectomy with posterior mediastinal reconstruction and mild aortic stenosis. The therapeutic strategy was explained to the patient, who opted to undergo surgery.

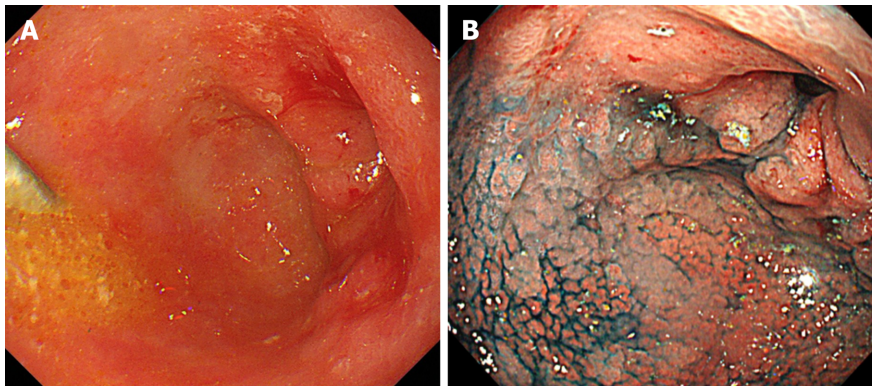


Figure 1 Endoscopic findings. A: Esophagogastroduodenoscopy revealed a 0-IIc primary tumor with ulcerations surrounding the pyloric ring; B: The lesion was unstained by indigo carmine.

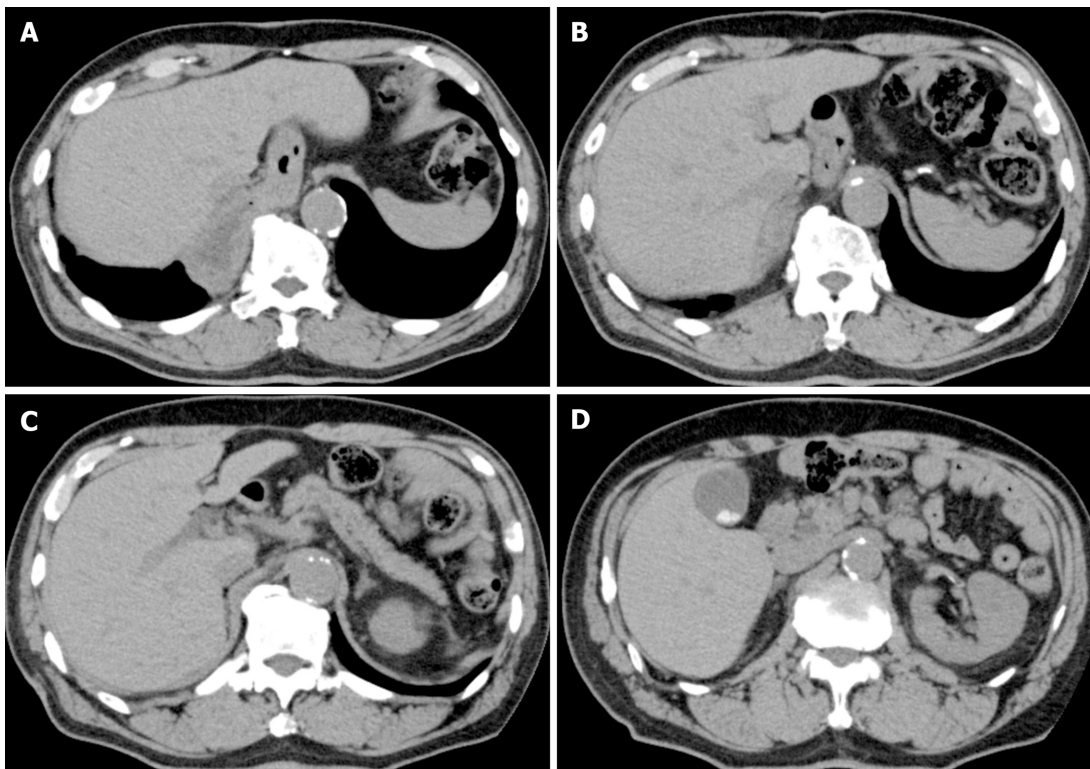


Figure 2 Computed tomography findings. A-D: Computed tomography was unable to detect the primary tumor, and no obvious nodal metastasis was observed.

Resection of the distal gastric tube and Roux-en-Y reconstruction preserving the main trunk of the RGEA and RGA

Delamination was performed between the omentum and abdominal wall along the previous surgical wound. The gastric tube was then mobilized by separating the anterior and posterior lobes of the mesocolon up to the vicinity of the root of the right gastroepiploic vein. After a Kocher mobilization, the RGA, RGEA, and infrapyloric artery supplying blood to the gastric tube were identified. To preserve the main trunks of the arteries, peripheral branches to the stomach wall were cut according to the area to be resected (Figure 4A and B). We also performed #6LN sampling because of swelling, but the sample was not submitted for an intraoperative pathological examination. The duodenum was cut as distally as possible to maintain an adequate surgical margin, using a 60-mm Endo GIA Reinforced Reload with Tri-Staple stapler (Covidien, Mansfield, MA, United States). Esophagogastroduodenoscopy was performed during surgery to determine the proximal cutting location line. The gastric tube was cut in the abdominal cavity using a 60-mm stapler. Gastrojejunostomy (GJ) was performed with the stapler, and the antecolic R-Y reconstruction was completed.

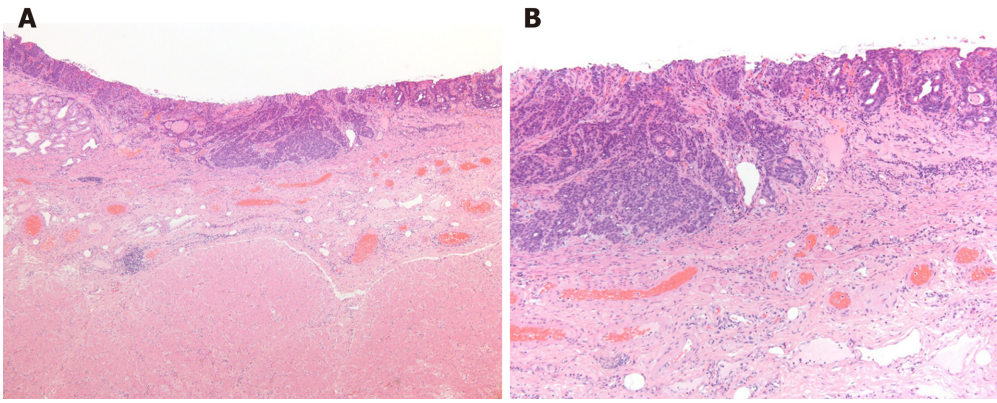


Figure 3 Pathological findings. Pathological examination of the resected material revealed a moderately to poorly differentiated adenocarcinoma with submucosal invasion and ulcerative scars, but without lymphovascular invasion. A: Hematoxylin and eosin staining results, $\times 4$; B: Hematoxylin and eosin staining results, $\times 10$.

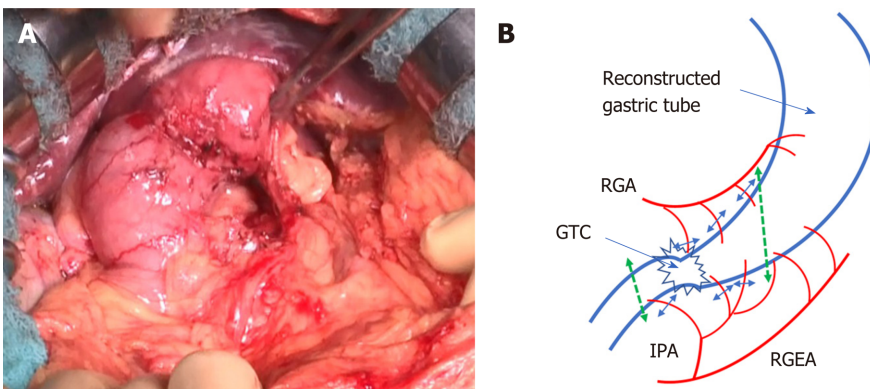


Figure 4 Tumor location. The peripheral branches to the stomach wall were cut according to the area to be resected, to preserve the main trunks of the right gastric artery and right gastroepiploic artery. Photograph taken during surgery showing the resected branches of the infrapyloric artery. Schematic of the dissection line. GTC: Gastric tube cancer; IPA: Infrapyloric artery; RGA: Right gastric artery; RGEA: Right gastroepiploic artery.

GJ was performed on the anterior wall of the greater curvature to avoid vessel injury (Figure 5A and B). Resection of the distal gastric tube was successful, and the proximal side was preserved without the need for thoracotomy. Sufficient surgical margins were confirmed in the resected material. The total operation time was 4 h 48 min, and total blood loss was < 10 mL.

OUTCOME AND FOLLOW-UP

Postoperative course

The patient was able to drink water on postoperative day 1, resumed eating on postoperative day 2, and was discharged on postoperative day 12 without any surgical complications (Clavien-Dindo grade > 3)^[11]. The patient's diet and activities of daily living were the same as before surgery.

DISCUSSION

We present the case of an 82-year-old man who underwent successful resection of distal gastric tube for early GTC with duodenal invasion. The interesting features of this case include the advanced age of the patient, distal resection of a gastric tube reconstructed *via* the posterior mediastinal route, and preservation of the RGEA and RGA. None of these features have been described in previous reports. In general, total resection of the gastric tube with LN dissection is considered the standard radical treatment for GTC for which ESD is not indicated. However, surgical removal of the

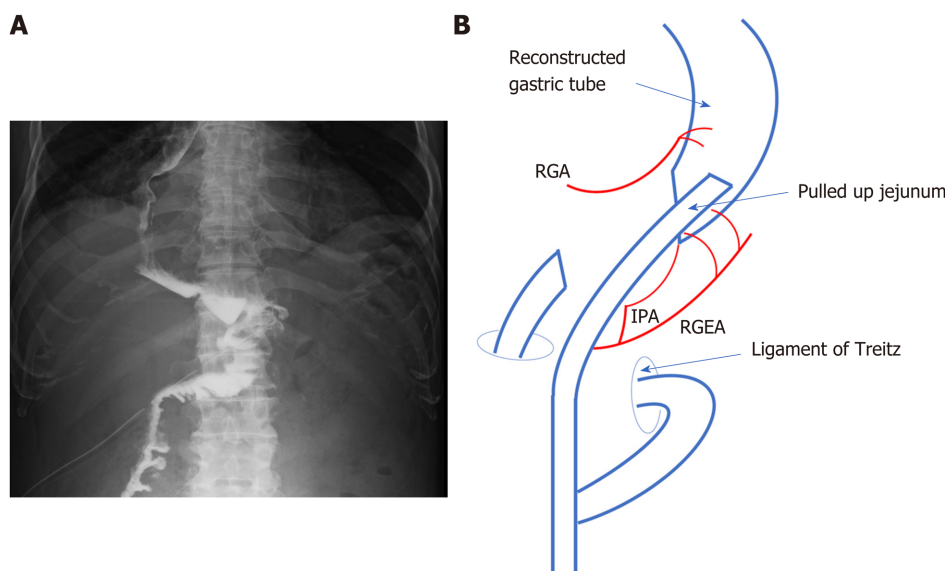


Figure 5 Roux-en-Y reconstruction. Barium swallow test with antecolic Roux-en-Y reconstruction. Schematic of gastrojejunostomy with antecolic Roux-en-Y reconstruction. IPA: Infrapyloric artery; RGA: Right gastric artery; RGEA: Right gastroepiploic artery.

reconstructed gastric tube is invasive and carries a relatively high risk of postoperative morbidity and mortality^[5]. Furthermore, this procedure is complicated when the reconstruction route selected at the original esophagectomy was *via* the posterior mediastinum, because the gastric tube is surrounded by vital organs, including the heart, lungs, and aorta. We previously reported that the level of difficulty of the surgical procedure differs according to the route of reconstruction, and accounts for differences in the resection rate (50%, 77%, and 93% for the posterior mediastinal, retrosternal, and ante-thoracic routes, respectively)^[12]. Because a gastric tube pulled up *via* the posterior mediastinal route exists in the deepest part of the abdomen, even partial resection will be difficult unless the lesion is located near the pyloric ring, as in the present case. However, in elderly and high-risk patients with early GTC without LN metastasis, distal resection of the gastric tube is considered to be a safer surgical technique than complete resection of the gastric tube.

Due to recent advances in the diagnosis and treatment of esophageal cancer, surgical outcomes have improved and the prevalence of GTC after esophagectomy has increased to 2.1%-3.5%^[2,13]. The characteristics and treatments of 224 GTC patients reported in 29 studies (12 retrospective studies and 17 case reports) between 1998 and 2020 (Table 1)^[3-6,12,14-37] showed that the mean age of patients at the time of GTC treatment was 67.2 years (range: 43-85 years), and 202 patients (90.2%) were male. According to the available data of these studies, the majority of GTCs were the differentiated type (77.3%; $n = 160$), followed by the undifferentiated type (19.8%; $n = 41$), and others (mixed type, neuroendocrine carcinoma, squamous cell carcinoma; $n = 7$). The majority of the lesions were located in the lower part of the gastric tube (59.4%; $n = 107$), while the middle third was the second most common location (32.2%; $n = 58$). Endoscopic mucosal resection and ESD were the most frequently used treatments ($n = 138$), followed by total or subtotal resection ($n = 44$), partial resection ($n = 31$), chemotherapy/chemoradiotherapy/palliative treatment ($n = 19$), and distal resection or antrectomy of the gastric tube ($n = 5$). The mean time from the original esophageal cancer to GTC was 60.9 mo (range: 4-236 mo).

In our patient, GTC was detected 13 years after esophagectomy. Thus, long-term follow-up (> 5 years) is necessary to detect GTC in the early stage after esophagectomy. Early detection allows less invasive and curative treatment *via* ESD, partial resection, or resection of the gastric tube, without the need for total gastric tube resection. The efficacy and safety of endoscopic resection for GTC have been demonstrated in several studies^[2,4,33]. Hirayama *et al*^[4] reported an 85% (28/33) curative resection rate using ESD for early GTC, and the 2- and 5-year overall survival rates were 73.3% and 64.1%, respectively. Nonaka *et al*^[2] reported that the disease-specific 5-year survival rate in non-curative patients after ESD was 72.7%. Additional surgery was not performed in 15 of 16 (94%) non-curative resection patients at risk of LN metastasis. These survival rates were considered acceptable in the present case, because the 5-year survival rate of a general 82-year-old male cohort in Japan is

Table 1 Studies included in the review

Ref.	Publication year	Journal	Study type	Number of patients
Horie <i>et al</i> ^[36]	2020	<i>Asian J Endosc Surg</i>	Case report	1
Yamana <i>et al</i> ^[35]	2020	<i>Int J Surg Case Rep</i>	Case report	1
Hara <i>et al</i> ^[34]	2020	<i>Surg Case Rep</i>	Case report	1
Hirayama <i>et al</i> ^[4]	2019	<i>Esophagus</i>	Retrospective study	29
Shirakawa <i>et al</i> ^[6]	2018	<i>Esophagus</i>	Retrospective study	30
Mukasa <i>et al</i> ^[33]	2015	<i>World J Gastroenterol</i>	Retrospective study	11
Lee <i>et al</i> ^[32]	2014	<i>Eur J Cardiothorac Surg</i>	Retrospective study	18
Tawaraya <i>et al</i> ^[3]	2014	<i>Gastrointest Endosc</i>	Retrospective study	15
Ho <i>et al</i> ^[31]	2014	<i>Dis Esophagus</i>	Case report	4
Kim <i>et al</i> ^[30]	2012	<i>Korean J Thorac Cardiovasc Surg</i>	Case report	1
Saito <i>et al</i> ^[29]	2012	<i>J Surg Oncol</i>	Case report	2
Jabłoński <i>et al</i> ^[28]	2012	<i>World J Surg Oncol</i>	Case report	1
Shiozaki <i>et al</i> ^[27]	2012	<i>Surg Today</i>	Case report	1
Oki <i>et al</i> ^[26]	2011	<i>Surg Today</i>	Retrospective study	10
Yoon <i>et al</i> ^[25]	2011	<i>Eur J Cardiothorac Surg</i>	Retrospective study	10
Bamba <i>et al</i> ^[24]	2010	<i>Surg Endosc</i>	Retrospective study	25
Zygoń <i>et al</i> ^[37]	2010	<i>BMJ Case Rep</i>	Case report	1
Osumi <i>et al</i> ^[23]	2009	<i>Endoscopy</i>	Retrospective study	7
Motoyama <i>et al</i> ^[22]	2006	<i>Ann Thorac Surg</i>	Case report	2
Yamashita <i>et al</i> ^[21]	2006	<i>Dig Liver Dis</i>	Case report	1
Atmani <i>et al</i> ^[20]	2006	<i>Dis Esophagus</i>	Case report	2
Okamoto <i>et al</i> ^[19]	2004	<i>Ann Thorac Surg</i>	Retrospective study	8
Akita <i>et al</i> ^[18]	2004	<i>J Surg Oncol</i>	Retrospective study	5
Ikeda <i>et al</i> ^[17]	2003	<i>J Thorac Cardiovasc Surg</i>	Case report	1
Lamblin <i>et al</i> ^[16]	2003	<i>Dis Esophagus</i>	Case report	3
Sugiura <i>et al</i> ^[5]	2002	<i>J Am Coll Surg</i>	Retrospective study	26
Shigemitsu <i>et al</i> ^[15]	2002	<i>Jpn J Clin Oncol</i>	Case report	5
Ben-nun <i>et al</i> ^[14]	2000	<i>Dis Esophagus</i>	Case report	1
Koyanagi <i>et al</i> ^[12]	1998	<i>J Gastroenterol Hepatol</i>	Case report	2

66.4%^[38]. Nonetheless, even at an early stage of GTC, endoscopic resection is difficult when the lesion is located on the staple line or pyloric ring, as was the case in our patient, and it may require a surgical approach with a higher risk of postoperative complications. Suzuki *et al*^[39] reported a high mortality rate (33%) for total resection of a reconstructed gastric tube after esophagectomy. Nonaka *et al*^[2] also reported a high mortality rate (23.8%) even in a high-volume Japanese cancer center.

A previous study reported that the frequency of nodal metastasis in GTC was 0% for intramucosal tumors and 10% for submucosal tumors^[24], such that LN dissection may be unnecessary for the vast majority of patients with early GTC. Generally, surgical gastrectomy with LN dissection is the standard treatment for early gastric cancer because there is a 1%-10% possibility of concurrent LN metastasis^[40]. However, elderly people are at higher risk of surgery-related death than are non-elderly patients, and the benefits of minimizing the risk of recurrence and metastasis in this group may be less profound. Therefore, if the estimated LN metastasis rate is lower than the 5-year mortality rate of a general cohort of the same age, surgery without LN dissection should be considered. In the present case, the swollen #6LN was resected but not checked by intraoperative pathological examination, because we had no plans to

perform radical LN dissection to prevent fatal complications (such as necrosis of the gastric tube) considering the status of the patient. Yagi *et al*^[7] reported that sentinel node biopsy could help avoid unnecessary LN dissection. However, it cannot be performed at every institution, nor has the accuracy of sentinel node biopsy been confirmed in patients undergoing gastrointestinal tract reconstruction including the gastric tube.

Preserving the blood supply of the remnant gastric tube is necessary for any partial resection of reconstructed gastric tube. LN dissection with resection of the distal gastric tube requires ligation of the RGEA and RGA, which can injure these vessels and cause ischemia in the lower and middle parts of the gastric tube. Yoshida *et al*^[40] reported two cases of resection of the distal part of the gastric tube, with dissection of the RGEA and RGEV, that required vascular reconstruction. Saito *et al*^[29] also reported two cases of subtotal gastric tube resection in which the RGEA and RGA were sacrificed based on an intraoperative indocyanine green evaluation of blood flow. In those cases, blood supply was re-established from the cervical esophagus for 5 cm until the proximal region of the gastric tube. However, vascular charge was needed during GJ. Additionally, operation time and blood loss were 538-783 min and 1490-2855 mL, both of which are considered highly invasive in elderly and/or high-risk patients. Therefore, the RGEA and RGA should be preserved during resection of the distal gastric tube in older or high-risk patients to prevent invasive surgery and fatal complications.

Some limitations of this study should be discussed. First, the observation period after the surgery was only 5 mo, although we continued to check for recurrence during additional follow-up visits. Thus, only the feasibility of the procedure could be demonstrated in this report. Second, the acceptable morbidity and mortality rates for prophylactic LN dissection are not clear but will vary depending on the patient's age, condition and attitudes about life and death, which will complicate surgical decision-making.

CONCLUSION

We suggest that resection of the distal gastric tube with preservation of the main trunk of the RGEA and RGA can serve as a safe surgical treatment for cT1bN0 GTC in elderly patients.

REFERENCES

- 1 Nagasawa S, Onda M, Sasajima K, Takubo K, Miyashita M. Multiple primary malignant neoplasms in patients with esophageal cancer. *Dis Esophagus* 2000; **13**: 226-230 [PMID: 11206637 DOI: 10.1046/j.1442-2050.2000.00116.x]
- 2 Nonaka S, Oda I, Sato C, Abe S, Suzuki H, Yoshinaga S, Hokamura N, Igaki H, Tachimori Y, Taniguchi H, Kushima R, Saito Y. Endoscopic submucosal dissection for gastric tube cancer after esophagectomy. *Gastrointest Endosc* 2014; **79**: 260-270 [PMID: 24060521 DOI: 10.1016/j.gie.2013.07.059]
- 3 Tawarayama S, Jin M, Matsuhashi T, Suzuki Y, Sawaguchi M, Watanabe N, Onochi K, Koizumi S, Hatakeyama N, Ohba R, Mashima H, Ohnishi H. Advanced feasibility of endoscopic submucosal dissection for the treatment of gastric tube cancer after esophagectomy. *Gastrointest Endosc* 2014; **79**: 525-530 [PMID: 24246794 DOI: 10.1016/j.gie.2013.10.007]
- 4 Hirayama Y, Fujisaki J, Yoshimizu S, Horiuchi Y, Yoshio T, Ishiyama A, Hirasawa T, Imamura Y, Mine S, Watanabe M, Tsuchida T. Efficacy and safety of endoscopic resection for gastric tube cancer after surgical resection of esophageal squamous cell carcinoma. *Esophagus* 2019; **16**: 194-200 [PMID: 30600485 DOI: 10.1007/s10388-018-00653-w]
- 5 Sugiura T, Kato H, Tachimori Y, Igaki H, Yamaguchi H, Nakanishi Y. Second primary carcinoma in the gastric tube constructed as an esophageal substitute after esophagectomy. *J Am Coll Surg* 2002; **194**: 578-583 [PMID: 12022598 DOI: 10.1016/s1072-7515(02)01135-3]
- 6 Shirakawa Y, Noma K, Maeda N, Ninomiya T, Tanabe S, Kikuchi S, Kuroda S, Nishizaki M, Kagawa S, Kawahara Y, Okada H, Fujiwara T. Clinical characteristics and management of gastric tube cancer after esophagectomy. *Esophagus* 2018; **15**: 180-189 [PMID: 29951985 DOI: 10.1007/s10388-018-0611-2]
- 7 Yagi Y, Ii T, Tanaka S, Oguri H. Resection of distal gastric tube cancer with sentinel node biopsy: a case report and review of the literature. *World J Surg Oncol* 2015; **13**: 10 [PMID: 25627444 DOI: 10.1186/s12957-014-0421-5]
- 8 Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors: International union against cancer. 8th ed. Oxford: Wiley; 2017
- 9 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, 15th ed. Tokyo: Kanehara Publisher, 2017
- 10 Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2020 [PMID: 32060757 DOI: 10.1007/s10120-020-01042-y]

- 11 **Clavien PA**, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; **250**: 187-196 [PMID: 19638912 DOI: 10.1097/SLA.0b013e3181b13ca2]
- 12 **Koyanagi K**, Ozawa S, Ando N, Shih CH, Nakamura E, Takeuchi H, Hayashi K, Kitajima M. Case report: Metachronous early gastric carcinoma in a reconstructed gastric tube after radical operation for oesophageal carcinoma. *J Gastroenterol Hepatol* 1998; **13**: 311-315 [PMID: 9570246 DOI: 10.1111/j.1440-1746.1998.01561.x]
- 13 **Motoyama S**, Saito R, Kitamura M, Suzuki H, Nakamura M, Okuyama M, Imano H, Inoue Y, Ogawa J. Prospective endoscopic follow-up results of reconstructed gastric tube. *Hepatogastroenterology* 2003; **50**: 666-669 [PMID: 12828056]
- 14 **Ben-nun A**, Soudack M, Best LA. Gastric tube gastrectomy. *Dis Esophagus* 2000; **13**: 243-244 [PMID: 11206641 DOI: 10.1046/j.1442-2050.2000.00119.x]
- 15 **Shigemitsu K**, Naomoto Y, Shirakawa Y, Haisa M, Gunduz M, Tanaka N. Five cases of early gastric cancer in the reconstructed gastric tube after radical resection for esophageal cancer. *Jpn J Clin Oncol* 2002; **32**: 425-429 [PMID: 12451041 DOI: 10.1093/jjco/hyf083]
- 16 **Lamblin A**, Mariette C, Triboulet JP. Adenocarcinoma in a gastric tube after esophagectomy for esophageal carcinoma. *Dis Esophagus* 2003; **16**: 158-159 [PMID: 12823220 DOI: 10.1046/j.1442-2050.2003.00317.x]
- 17 **Ikeda Y**, Tobari S, Niimi M, Kodaira S, Okinaga K. Second primary double carcinomas of the residual cervical esophagus and the gastric tube after thoracic esophagectomy. *J Thorac Cardiovasc Surg* 2003; **125**: 1561-1562 [PMID: 12830090 DOI: 10.1016/s0022-5223(03)00052-7]
- 18 **Akita H**, Doki Y, Ishikawa O, Takachi K, Miyashiro I, Sasaki Y, Ohigashi H, Murata K, Noura S, Yamada T, Eguchi H, Imaoka S. Total removal of the posterior mediastinal gastric conduit due to gastric cancer after esophagectomy. *J Surg Oncol* 2004; **85**: 204-208 [PMID: 14991878 DOI: 10.1002/jso.20017]
- 19 **Okamoto N**, Ozawa S, Kitagawa Y, Shimizu Y, Kitajima M. Metachronous gastric carcinoma from a gastric tube after radical surgery for esophageal carcinoma. *Ann Thorac Surg* 2004; **77**: 1189-1192 [PMID: 15063232 DOI: 10.1016/j.athoracsur.2003.09.071]
- 20 **Atmani A**, Topart P, Vandenbroucke F, Louzi A, Ferrand L, Lozac'h P. Metachronous cancer of gastropasty after esophagectomy. *Dis Esophagus* 2006; **19**: 512-515 [PMID: 17069598 DOI: 10.1111/j.1442-2050.2006.00623.x]
- 21 **Yamashita H**, Kitayama J, Ishigami H, Yamaguchi H, Souma D, Nagano R, Nagawa H. Multiple gastric tube carcinomas after curative oesophagectomy. *Dig Liver Dis* 2006; **38**: 214-215 [PMID: 16314151 DOI: 10.1016/j.dld.2005.10.003]
- 22 **Motoyama S**, Saito R, Okuyama M, Maruyama K, Ogawa J. Treating gastric tube cancer with distal gastrectomy preserving the gastroepiploic artery. *Ann Thorac Surg* 2006; **81**: 751-753 [PMID: 16427900 DOI: 10.1016/j.athoracsur.2004.11.011]
- 23 **Osumi W**, Fujita Y, Hiramatsu M, Kawai M, Sumiyoshi K, Umegaki E, Tokioka S, Yoda Y, Egashira Y, Abe S, Higuchi K, Tanigawa N. Endoscopic submucosal dissection allows less-invasive curative resection for gastric tube cancer after esophagectomy - a case series. *Endoscopy* 2009; **41**: 777-780 [PMID: 19746318 DOI: 10.1055/s-0029-1215024]
- 24 **Bamba T**, Kosugi S, Takeuchi M, Kobayashi M, Kanda T, Matsuki A, Hatakeyama K. Surveillance and treatment for second primary cancer in the gastric tube after radical esophagectomy. *Surg Endosc* 2010; **24**: 1310-1317 [PMID: 19997933 DOI: 10.1007/s00464-009-0766-y]
- 25 **Yoon YS**, Kim HK, Choi YS, Kim K, Kim J, Shim YM. Primary gastric cancer in an oesophageal gastric graft after oesophagectomy. *Eur J Cardiothorac Surg* 2011; **40**: 1181-1184 [PMID: 21868245 DOI: 10.1016/j.ejcts.2011.02.061]
- 26 **Okai E**, Morita M, Toh Y, Kimura Y, Ohgaki K, Sadanaga N, Egashira A, Kakeji Y, Tsujitani S, Maehara Y. Gastric cancer in the reconstructed gastric tube after radical esophagectomy: a single-center experience. *Surg Today* 2011; **41**: 966-969 [PMID: 21748613 DOI: 10.1007/s00595-010-4402-1]
- 27 **Shiozaki A**, Fujiwara H, Ichikawa D, Okamoto K, Komatsu S, Murayama Y, Ikoma H, Kuriu Y, Nakanishi M, Ochiai T, Kokuba Y, Sonoyama T, Otsuji E. Video-assisted surgery for gastric carcinoma arising in a gastric tube reconstructed retrosternally. *Surg Today* 2012; **42**: 209-213 [PMID: 22075659 DOI: 10.1007/s00595-011-0029-0]
- 28 **Jabłoński S**, Piskorz L, Wawrzycki M. Gastric tube resection due to metachronic cancer and a recurrence in anastomosis after Ivor-Lewis esophagectomy--case report. *World J Surg Oncol* 2012; **10**: 83 [PMID: 22591456 DOI: 10.1186/1477-7819-10-83]
- 29 **Saito T**, Yano M, Motoori M, Kishi K, Fujiwara Y, Shingai T, Noura S, Ohue M, Ohigashi H, Ishikawa O. Subtotal gastrectomy for gastric tube cancer after esophagectomy: a safe procedure preserving the proximal part of gastric tube based on intraoperative ICG blood flow evaluation. *J Surg Oncol* 2012; **106**: 107-110 [PMID: 22331794 DOI: 10.1002/jso.23050]
- 30 **Kim JJ**, Park JK, Wang YP, Sung SW, Park HJ, Lee SI. Total gastrectomy in gastric conduit cancer. *Korean J Thorac Cardiovasc Surg* 2012; **45**: 53-55 [PMID: 22363910 DOI: 10.5090/kjcts.2012.45.1.53]
- 31 **Ho C**, Tong DK, Tsang JS, Law SY. Post-esophagectomy gastric conduit cancers: treatment experiences and literature review. *Dis Esophagus* 2014; **27**: 141-145 [PMID: 23551754 DOI: 10.1111/dote.12070]
- 32 **Lee GD**, Kim YH, Choi SH, Kim HR, Kim DK, Park SI. Gastric conduit cancer after oesophagectomy for oesophageal cancer: incidence and clinical implications. *Eur J Cardiothorac Surg* 2014; **45**: 899-903 [PMID: 24157484 DOI: 10.1093/ejcts/ezt497]
- 33 **Mukasa M**, Takedatsu H, Matsuo K, Sumie H, Yoshida H, Hinosaka A, Watanabe Y, Tsuruta O, Torimura T. Clinical characteristics and management of gastric tube cancer with endoscopic submucosal dissection. *World J Gastroenterol* 2015; **21**: 919-925 [PMID: 25624726 DOI: 10.3748/wjg.v21.i3.919]
- 34 **Hara K**, Matsunaga T, Fukumoto Y, Miyauchi W, Kono Y, Shishido Y, Hanaki T, Miyatani K, Watanabe J, Kihara K, Yamamoto M, Tokuyasu N, Takano S, Sakamoto T, Honjo S, Fujiwara Y. Successful preservation of the proximal stomach tube by evaluating blood flow using indocyanine green for gastric tube cancer: a case report. *Surg Case Rep* 2020; **6**: 85 [PMID: 32337608 DOI: 10.1186/s40792-020-00848-3]
- 35 **Yamana I**, Murakami T, Ryu S, Ichikawa J, Shin Y, Koreeda N, Sannomiya H, Sato K, Okamoto T,

- Sakamoto Y, Yoshida Y, Yanagisawa J, Noritomi T, Hasegawa S. Subtotal gastrectomy for gastric tube cancer using intraoperative indocyanine green fluorescence method. *Int J Surg Case Rep* 2020; **71**: 290-293 [PMID: 32480340 DOI: 10.1016/j.ijscr.2020.04.049]
- 36 **Horie K**, Oshikiri T, Kitamura Y, Shimizu M, Yamazaki Y, Sakamoto H, Ishida S, Koterazawa Y, Ikeda T, Yamamoto M, Kanaji S, Matsuda Y, Yamashita K, Matsuda T, Nakamura T, Suzuki S, Kakeji Y. Thoracoscopic retrosternal gastric conduit resection in the supine position for gastric tube cancer. *Asian J Endosc Surg* 2020; **13**: 461-464 [PMID: 31583826 DOI: 10.1111/ases.12757]
- 37 **Zygoń JI**, Skokowski J, Zieliński J, Drucis K, Golabek-Dropiewska K. Metachronous adenocarcinoma in a gastric tube after radical surgery for oesophageal cancer. *BMJ Case Rep* 2010; **2010** [PMID: 22408648 DOI: 10.1136/bcr.07.2009.2116]
- 38 **National Cancer Center Japan**. Center for Cancer Control and Information Services. Cohort Survival https://ganjoho.jp/reg_stat/statistics/qa_words/cohort01.html
- 39 **Suzuki H**, Kitamura M, Saito R, Motoyama S, Ogawa J. Cancer of the gastric tube reconstructed through the posterior mediastinal route after radical surgery for esophageal cancer. *Jpn J Thorac Cardiovasc Surg* 2001; **49**: 466-469 [PMID: 11517585 DOI: 10.1007/bf02913915]
- 40 **Yoshida T**, Nagahama T, Maruyama M, Ebuchi M. Endoscopic comparison of two cases: distal resection of reconstructed gastric tube. *Hepatogastroenterology* 2002; **49**: 371-374 [PMID: 11995453]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

