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The Role of Personalized Preoperative Prehabilitation in Patients Undergoing Surgery for Gastric Cancer

DOCTORAL DISSERTATION

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Personalizuotos priešoperacinės reabilitacijos reikšmė pacientų sergančių skrandžio vėžiu gydyme

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CONTENT

ABBREVIATIONS

5-FU: 5- fluorouracil	IBD: inflammatory bowel diseases
6-MWT: 6-minute walk test	IMT: inspiratory muscle training
95% CI: 95% confidence interval	IPAQ: International Physical Activity Questionnaire score
AGC: advanced gastric cancer	LE: lower esophagus
CCI: Charlson Comorbidity Index	LN: lymph node
CRC: colorectal cancer	lnNR: lymph node non-responders
CRF: case report forms	NAC: neoadjuvant chemotherapy
DFS: disease-free survival	nCRT: neoadjuvant chemoradiotherapy
ECF: epirubicin, cisplatin, and fluorouracil	NRS2002: Nutritional Risk Score-2002 questionnaire score
ECX: chemotherapy regimen of epirubicin, cisplatin, capecitabine	OR: odds ratio
EGC: Esophagogastric cancer	OS: 5-year overall
EGJ: esophagogastric junction	R1-2: microscopically or macroscopically positive margin
5-FU: 5- fluorouracil	RCT: randomized control trial
6-MWT: 6-minute walk test	RR: risk ratio
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core-30	SD: standard deviation
EORTC QLQ-STO22: European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core-30 and STO-22	SGB2: Subtotal gastrectomy with Billroth II reconstruction
EOX: chemotherapy regimen of epirubicin, oxaliplatin, capecitabine	SIBO: small intestinal bacterial overgrowth
FEV1: Forced Expiratory Volume in the first second	TRG: tumor regression grade
FLOT: chemotherapy regimen of fluorouracil, folinic acid, oxaliplatin, and docetaxel	RKT: randomizuotas kontrolinis tyrimas

FOLFOX: chemotherapy regimen of fluorouracil, folinic acid, and oxaliplatin	SKV: Skrandžio vėžys
FVC: Forced Vital Capacity	SSGK: su sveikata susijusiai gyvenimo kokybei
GI: gastrointestinal	
HADS: Hospital anxiety and depression scale score	
HR: hazard ratios	
HRQOL: health-related quality of life	

The Ph.D. theses are submitted for defense as a set of research articles and some parts have been quoted verbatim from the previously published articles listed below:

1. **Bausys A,** Mazeikaite M, Bickaite K, Bausys B, Bausys R, Strupas K. The Role of Prehabilitation in Modern Esophagogastric Cancer Surgery: A Comprehensive Review. Cancers (Basel). 2022 Apr 22;14(9):2096. doi: 10.3390/cancers14092096. PMID: 35565226; PMCID: PMC9102916.

2. Maksimaityte V, **Bausys A**, Kryzauskas M, Luksta M, Stundiene I, Bickaite K, Bausys B, Poskus T, Bausys R, Strupas K. Gastrectomy impact on the gut microbiome in patients with gastric cancer: A comprehensive review. World J Gastrointest Surg. 2021 Jul 27;13(7):678-688. doi: 10.4240/wjgs.v13.i7.678. PMID: 34354801; PMCID: PMC8316847.

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Some of the results shown in these theses has been communicated to the society in national and international meetings:

1. **Augustinas Bausys**, Angela Horvath, Rasa Sabaliauskaite, Eugenijus Stratilatovas, Sonata Jarmalaite, Burkhard Schuetz, Philipp Stiegler, Rimantas Bausys, Vanessa Stadlbauer, Kestutis Strupas. Subtotal gastrectomy with Billroth II anastomosis is associated with oralization of the gut microbiome and intestinal inflammation. Presented as oral presentation at ESSR 55th congress on 2020.12.10-11, Inssbruck, Austria (virtual)
2. **Augustinas Bausys**, Toomas Umarik, Martynas Luksta, Arvo Reinsoo, Rokas Rackauskas, Giedre Anglickiene, Marius Kryzauskas, Kristina Tonismae, Veslava Senina, Dmitrij Seinin, Rimantas Bausys, and Kestutis Strupas. Time interval between neoadjuvant chemotherapy and gastrectomy impact on short- and long-term outcomes in patients with advanced gastric cancer. Presented as oral presentation at BAS 2021 congress on 2021.06.03-04, Riga, Latvia (virtual)
3. **Augustinas Bausys**, Veslava Senina, Martynas Luksta, Bernardas Bausys, Klaudija Bickaite, Andrius Rybakovas, Arvydas Laurinavicius, Tomas Poskus, Dmitrij Seinin, Rimantas Bausys, Kestutis Strupas. Histologic lymph nodes regression after preoperative chemotherapy as

prognostic factor in non-metastatic advanced gastric adenocarcinoma. Presented as oral presentation at BAS 2021 congress on 2021.06.03-04, Riga, Latvia (virtual)

4. **Augustinas Bausys**, Angela Horvath, Rasa Sabaliauskaite, Sonata Jarmalaite, Burkhard Schuetz, Philipp Stiegler, Rimantas Bausys, Vanessa Stadlbauer, Kestutis Strupas. Intestinal dysbiosis after subtotal gastrectomy with Billroth II anastomosis for gastric cancer. Presented as poster presentation at ESSO 40 on 2021.11.8-10, Lisboa, Portugal
5. **Augustinas Bausys**, Toomas Ümarik, Martynas Luksta, Arvo Reinsoo, Rokas Rackauskas, Marius Kryzauskas, Kristina Tõnismäe, Veslava Senina, Dmitrij Seinin, Rimantas Bausys, Kestutis Strupas. The optimal timing for gastrectomy after neoadjuvant chemotherapy. Presented as poster presentation at ESSO 40 on 2021.11.8-10, Lisboa, Portugal.
6. **A.Bausys**, M.Luksta. Vilniaus skrandžio vėžio konsorciumas - klinikiniai tyrimai 2022. Šiuolaikinis chirurgo vaidmuo: nuo paruošimo operacijai iki metastatinės ligos gydymo. Presented as oral presentation at Lietuvos chirurgų asociacijos organizuojama konferencija: Chirurgija – tarp pareigos ir inovacijų, teisės bei finansų on 2022.10.14-15, Vilnius, Lietuva.
7. **A.Baušys (prenešėjas)**, Martynas Luksta, Rimantas Bausys, Kestutis Strupas. Personalized trimodal prehabilitation for gastrectomy: interim analysis of randomized control trial (PREFOG study). 22nd EAA Congress-15th ISGA COngress-5th International Conference of Evolutionary Medicine. Data:2022.08.24-27. Vieta: Vilnius, Lietuva.
8. **A.Baušys.** Personalized, Multimodal, Home-based Prehabilitation before gastrectomy: results of a randomized Clinical Trial. Presented at “Current treatment strategies in treatment of gastrointestinal cancers” meeting on, 2023.04, Kiev, Ukraine (virtual).
9. **A.Baušys.** Personalized home-based trimodal prehabilitation. Multi-center, open-label randomized control trial. Presented as oral presentation at BAS 2023 congress on 2021.10, Talinn, Estonia.

CHAPTER 1: GENERAL INTRODUCTION AND AIMS OF THIS THESIS

Gastric cancer

Gastric cancer (GC) is the fifth common malignancy worldwide with over 1 million new cases and more than 750 thousand deaths annually (1). Similarly, in Lithuania, it is also the fifth most common cancer with more than 800 cases each year (data from Lithuania cancer registry). GC is commonly thought of as a single type of cancer, but it can actually be divided into two categories based on anatomical location: cardia GC arising in the proximal area of the stomach and noncardia GC arising in more distal regions (2). These categories have distinct risk factors, causes, and patterns of occurrence. Noncardia GC is mostly caused by chronic *Helicobacter pylori* infection, which infects roughly half of the world's population but only leads to cancer in a small percentage of cases due to genetic and environmental factors. Other risk factors for noncardia GC include alcohol and tobacco use, high consumption of processed meat and grilled/barbecued meat and fish, and low fruit intake. On the other hand, cardia GC is not typically associated with *H. pylori* infection and may be linked to excess body weight and gastroesophageal reflux disease (1,3,4). In most populations, the incidence and mortality rates of noncardia GC have been steadily declining over the past few decades. This positive trend can be attributed to successful prevention efforts, including a decrease in *H. pylori* prevalence and improvements in food preservation and storage techniques. Contrary, the incidence rates of cardia GC increased from the 1960s to the 1980s in the Western countries, but seems to have stabilized nowadays (1,5). Recent noteworthy findings indicate an increase in the incidence of GC (both cardia and noncardia) among young adults (<50 years old). Previous studies in the United States focusing on noncardia gastric cancer found that the increases among young individuals were mainly observed in non-Hispanic Whites and those residing in wealthier counties. It has been hypothesized that the rising prevalence of autoimmune gastritis and disruptions in the gastric microbiome, possibly associated with increased use of antibiotics and acid-suppressing medications, may have contributed to the paradoxical rise in stomach cancer among younger generations (1,5). Despite that global incidence of GC is declining it remains major oncologic problem worldwide.

Surgery for gastric cancer

Surgery remains the main and only potentially curative treatment option for GC (6). The aims of GC surgery are to remove the tumor with an adequate resection margin and to perform appropriate lymhanodectomy. The extent of surgical resection necessary to achieve clear margins without cancer cells (R0) varies based on factors such as tumor size, location, and histological type. While ongoing discussions exist regarding the optimal proximal resection margin, the current Japanese Gastric Cancer Treatment Guidelines recommend a proximal margin of at least 3 cm for T2 or deeper tumors with an expansive growth pattern and 5 cm for those with an infiltrative growth pattern (7). In cases of tumors invading the esophagus, a resection margin greater than 5 cm is not necessarily required. However, it is preferable to perform a frozen section examination of the resection line to ensure an R0 resection(7). Subtotal gastrectomy is favored over total gastrectomy due to reduced postoperative morbidity, thus it is preferred in all cases when sufficient proximal margin can be ensured (8).

The extent of lymphadenectomy for GC is categorized according to the D-level criteria as D1, D1+, or D2. In brief, D1 level involves the removal of perigastric lymph nodes, while D2 includes second-tier nodes along the hepatic artery, celiac trunk, and splenic artery. The specific lymph node stations to be removed depend on the type of gastrectomy being performed. D1 lymphadenectomy is appropriate for very early GC, whereas D2 is the standard for all potentially curable cT2-4 tumors, including cases where lymph node metastases are suspected (7). The benefits of D2 lymphadenectomy have been clearly demonstrated in a large-scale randomized control trial (RCT) conducted in the Netherlands. After a 15-year follow-up, D2 lymphadenectomy was found to reduce locoregional recurrence and gastric cancer-related mortality rates (9). It should be noted that D2 procedure in this study was associated with higher postoperative mortality and morbidity. It should be noted that the D2 procedure in this study was associated with higher postoperative mortality and morbidity. However, currently available spleen-preserving D2 resection techniques are known to be much safer. Therefore, D2 lymphadenectomy is recommended for all patients with resectable locally advanced gastric cancer (9).

In line with many surgical fields, minimally invasive surgery has been proposed and implemented in select centers as an alternative to open resections for GC. Several RCTs conducted in Eastern countries have examined the acceptability of minimally invasive gastrectomy for GC. These studies have not raised concerns regarding the oncological quality of the surgery and have even suggested reduced postoperative morbidity, although long-term outcomes are still pending(10–15). Few RCTs on this topic has been performed in the West

as well. Despite similar oncological outcomes, both RCTs did not show that minimally invasive surgery results in reduced postoperative morbidity and long-term outcomes are yet not reported (16,17).

Overall, despite recent progress in surgical and anesthetic techniques surgery for GC remains extremely challenging for patients and surgeons, because it is associated with significant postoperative morbidity and mortality, that can exceed 50 % and 5 %, respectively (18–20). The most common complications include postoperative infections (pneumonia, surgical site infections, urinary tract infections and others), duodenal stump and anastomotic leakages, postoperative ileus, pulmonary embolism, postoperative bleeding and deterioration of underlying chronic diseases, such as heart failure, renal insufficiency and others (8,21). Consequently, there is a need for novel strategies to improve GC surgery outcomes.

Neoadjuvant chemotherapy for gastric cancer

In cases where patients have ≥cT2N0 disease that is potentially resectable, it is generally recommended to administer neoadjuvant/perioperative therapy instead of opting for immediate surgery followed by adjuvant therapy. Although there is a lack of randomized trials directly comparing these strategies, the former approach offers a higher probability of delivering maximum systemic therapy. Moreover, neoadjuvant chemotherapy can lead to downstaging of the disease, cure occult micrometastases, and improve R0 resection rates. All these potential benefits of neoadjuvant chemotherapy approach are known to translate to improves long-term outcomes of GC patients (22).

The MAGIC RCT was the groundbreaking study, that demonstrated the survival advantage of combining perioperative chemotherapy with surgery compared to surgery alone in patients diagnosed with operable gastroesophageal adenocarcinoma (with a 5-year survival of 36% versus 23%) (23). The perioperative chemotherapy regimen utilized in the RCT was a 3-drug combination of epirubicin, cisplatin, and fluorouracil (ECF). Similar benefit of neoadjuvant chemotherapy has been confirmed by another large scale RCT from France, which showed that perioperative chemotherapy with cisplatin and fluorouracil improves 5-year overall (OS) survival rate to 38 % compared to 24 % in surgery alone group (24). Moreover, recent phase 2/3 FLOT4-AIO RCT, showed that neoadjuvant chemotherapy benefit may be further increased by modern FLOT (fluorouracil plus leucovorin, oxaliplatin, and docetaxel) chemotherapy regimen. FLOT increased 5-year OS rates 36 % to 45 % when compared to ECF (or ECX, where X refers to capecitabine) (25).

There are some concerns and skepticism surrounding the neoadjuvant chemotherapy approach. Firstly, the largest RCTs examining neoadjuvant chemotherapy have faced criticism for the poor quality of surgery, particularly the lack of proper extended lymphadenectomy. Secondly, these studies included not only GC patients but also those with esophageal adenocarcinoma, making it possible that a proper radical surgery such as gastrectomy with D2 lymphadenectomy could eliminate the survival benefit observed after incomplete surgery. Additionally, the location of the tumor outside the stomach, such as at the esophagogastric junction (EGJ) or lower esophagus (LE), may amplify the response to preoperative treatment (26). Due to these factors, neoadjuvant chemotherapy is the standard approach in Western countries but is less commonly used in the East, where surgery with D2 lymphadenectomy has been the historical standard of care. Furthermore, most studies have primarily focused on the impact of chemotherapy on the primary GC tumor, and there is limited data on how it affects lymph node metastases (27). Additionally, neoadjuvant cytotoxic treatment can have negative effects on patients' physical and nutritional status, leading to sarcopenia and reduced physiological reserve, thereby increasing the risks associated with surgery (6,28–30). To mitigate these risks, current practice schedules surgery for patients at least 4-8 weeks after completing the last cycle of neoadjuvant chemotherapy. This timeframe is considered necessary to allow recovery from the short-term side effects of chemotherapy, particularly hematologic toxicity (31). However, there is a lack of evidence regarding the optimal timing for gastrectomy in this context.

Quality of life after radical treatment for gastric cancer

Surgery for GC has a notable impact on the health-related quality of life (HRQOL) of long-term survivors. The most significant decline in HRQOL occurs in the months following surgery, but it gradually recovers and reaches levels similar to baseline within the subsequent 6-12 months (32,33). However, many gastrectomized patients continue to experience various gastrointestinal symptoms. One of the most common issues among long-term survivors is intermittent or persistent chronic diarrhea, affecting up to 40% of patients (34–38). Additionally, abdominal pain, constipation, indigestion, and reflux are frequently reported gastrointestinal symptoms (38,39). Currently, there is limited understanding of the underlying mechanisms responsible for the development of these symptoms, resulting in a lack of effective treatment options. It has been suggested that surgery-induced dysbiosis plays a significant role in the pathogenesis, but further high-quality evidence is needed to confirm or refute this hypothesis.

Structure of this thesis

Study hypotheses, tasks, and methods

This thesis describes several projects all aimed to improve outcomes for patients undergoing surgery for GC by testing several hypotheses:

1) Multimodal prehabilitation improves GC patients‘ physical fitness, increase adherence to neoadjuvant treatment, reduce postoperative morbidity and enhance HRQOL.
2) Neoadjuvant chemotherapy induced histologic GC tumor and lymph node metastases regression is associated with improved long-term outcomes.
3) Optimal time after the completion of neoadjuvant chemotherapy maximizes the rate of major pathologic response for patients with GC;
4) GC surgery-induced dysbiosis is associated with gastrointestinal symptoms.

To test the hypotheses, address the scientific questions and fill the gaps in current knowledge a series of tasks was performed. Task and methods used to answer the scientific questions are summarized in Table 1.

Table 1. Study tasks (scientific question) and methods used to answer the scientific questions

Task (scientific question)	***Method***
1. To overview and summarize current evidence for prehabilitation in modern esophagogastric cancer surgery.	Comprehensive literature review was conducted, and the findings are presented in ***Part I*** of **Chapter 2.**
2. To address the existing gaps of current knowledge and examine hypothesis No. 1.	To accomplish this task, a RCT protocol was devised (***Part II,*** **Chapter 2***)*. Subsequently, the study was carried out, and the results of the RCT are presented (***Part III,*** **Chapter 2***)*
3. To examine whether neoadjuvant chemotherapy-induced histologic GC tumor and lymph node metastases regression is linked to improved long-term outcomes.	To accomplish this, a retrospective study was performed, and the findings are presented in ***Part 1*** of **Chapter 3**.
4. To explore the optimal interval between the completion of neoadjuvant chemotherapy and surgery to maximize the rate of	To address this scientific inquiry, an international cohort study was conducted, and the findings are presented in ***Part 2*** of **Chapter 3.**

Task (scientific question)	*Method*
major pathologic response in patients with GC.	
5. To examine the association between GC surgery-induced dysbiosis and gastrointestinal symptoms.	To address this scientific inquiry, a comprehensive literature review on gastrectomy impact on the gut microbiome in patients with gastric cancer was conducted (***Part 1,*** **Chapter 5**). Further, a cross-sectional proof-of-concept study was carried out, and the results are presented in ***Part 2*** of **Chapter 5**.

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CHAPTER 2: PREHABILITATION FOR GASTRIC CANCER SURGERY

PART 1: The Role of Prehabilitation in Modern Esophagogastric Cancer Surgery: A Comprehensive Review

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Review

The Role of Prehabilitation in Modern Esophagogastric Cancer Surgery: A Comprehensive Review

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Simple Summary: Surgery is the only potentially curative treatment option for esophagogastric cancer. Although esophagectomy/gastrectomy remains associated with major surgical trauma and significant morbidity. Prehabilitation has emerged as a novel strategy to improve postoperative outcomes by preparing patients for a surgery-associated physiological challenge. We discuss current knowledge and the results of studies on the role of prehabilitation in esophagogastric cancer surgery.

Abstract: Esophagogastric cancer is among the most common malignancies worldwide. Surgery with or without neoadjuvant therapy is the only potentially curative treatment option. Although esophagogastric resections remain associated with major surgical trauma and significant postoperative morbidity. Prehabilitation has emerged as a novel strategy to improve clinical outcomes by optimizing physical and psychological status before major surgery through exercise and nutritional and psychological interventions. Current prehabilitation programs may be unimodal, including only one intervention, or multimodal, combining the benefits of different types of interventions. However, it still is an investigational treatment option mostly limited to clinical trials. In this comprehensive review, we summarize the current evidence for the role of prehabilitation in modern esophagogastric cancer surgery. The available studies are very heterogeneous in design, type of interventions, and measured outcomes. Yet, all of them confirm at least some positive effects of prehabilitation in terms of improved physical performance, nutritional status, quality of life, or even reduced postoperative morbidity. However, the optimal interventions for prehabilitation remain unclear; thus, they cannot be standardized and widely adopted. Future studies on multimodal prehabilitation are necessary to develop optimal programs for patients with esophagogastric cancer.

Keywords: esophageal cancer; gastric cancer; esophagectomy; gastrectomy; prehabilitation; exercise

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1. Introduction

Esophagogastric cancer (esophageal and gastric cancer; EGC) is among the most common malignancies worldwide, with over 1.6 million new cases and 1.2 million deaths annually [1–3]. Surgery is the main and only curative treatment option [4,5]. However, gastric and esophageal resections remain associated with high postoperative morbidity and mortality rates [4–6]. Current evidence indicates the benefits of neoadjuvant chemo(radio)therapy [7–9]. Preoperative cytotoxic treatment improves oncological outcomes, but impairs patients' physical and nutritional status, promotes sarcopenia, and decreases physiological reserve, thus further increasing the surgery-related risk [4,10–12]. Consequently, there is a need for novel strategies to improve EGC surgery outcomes.

Recently, prehabilitation has emerged as a way to prepare a patient for major surgery. As it is a relatively new concept in surgical oncology, definitions of prehabilitation still vary. They consistently state that it is a pre-emptive preparation of a patient to reduce risks and enhance recovery after a stressful event. Prehabilitation has significantly reduced postoperative morbidity in some high-risk patients undergoing major abdominal surgery [13]. Additionally, it reduces systemic inflammation [14], attenuates chemotherapy-induced toxicity [15], modulates several host- and tumor-related pathways during standard chemotherapy [15], and may even promote tumor regression following neoadjuvant therapy [16]. Current studies on prehabilitation are very heterogenous in a perioperative care pathway and measured outcomes. Moreover, some studies show controversial results, as prehabilitation has no benefit in frail patients undergoing minimally invasive colorectal cancer surgery [17]. Therefore, the role of prehabilitation in modern EGC surgery remains unclear. This review aims to comprehensively overview the current evidence for prehabilitation in patients undergoing major esophagogastric resections for cancer.

2. Literature Search Strategy

A comprehensive literature search was conducted using the PubMed database last on 1 December 2021. The search term we used was 'prehabilitation' OR 'exercise' OR 'nutritional support' OR 'psychological support' AND 'esophageal cancer' OR 'gastric cancer". Time restrictions for publications were not used. Only manuscripts published in the English language were reviewed. Two independent reviewers (A.B. and K.B.) reviewed all titles and abstracts to identify clinical studies investigating prehabilitation in EGC patients. Full-text articles were retrieved if relevant abstracts were identified (Figure 1). An additional manual search of the reference lists was performed to ensure the comprehensive literature search procedure. The quality of evidence provided by each study was evaluated using the Jadad [18] and the Newcastle–Ottawa [19] scales for randomized and non-randomized studies, respectively.

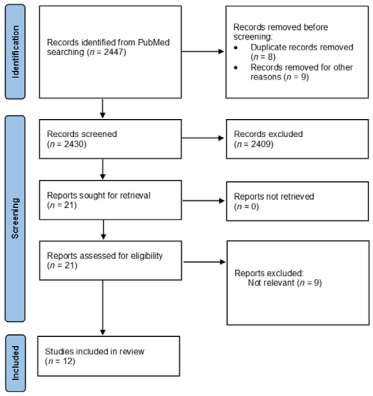

Figure 1. Literature search flow diagram.

3. The Current Concept of Prehabilitation in Esophagogastric Cancer Surgery

Current definitions of prehabilitation vary but consistently state that it is a pre-emptive preparation of a patient to reduce risks and enhance recovery after a stressful event. EGC surgery is an ideal example of a stressor because of extensive surgical trauma, physiological consequences of previous cytotoxic treatments, and psychological distress. These factors interact with the burden of cancer, which includes impaired nutritional and physiological

reserves due to cachexia, malnutrition, and sarcopenia. The preoperative period constitutes a unique opportunity to prepare the patient for these challenges because most are highly motivated to change behavior for perioperative benefits [20]. Contemporary prehabilitation programs may include one (unimodal) or several (multimodal) interventions aiming to correct modifiable risk factors, promote a patient's physical activity, optimize nutritional status, and intervene in psychological wellbeing. There is no consensus on the optimal design of a prehabilitation program; thus, different approaches have been investigated (Table 1).

Table 1. Characteristics of studies investigating prehabilitation for esophagogastric cancer surgery.

Author; Year	Design	Description and Number of Participants; (n)	Measured Outcomes	N–O Score	Jadad Score
Allen et al. [21]; 2021	RCT	Esophagogastric cancer patients scheduled for surgery after neoadjuvant chemotherapy; (n = 54)	Primary outcome: • Change in AT by CPET. Secondary outcomes: • Change in peak VO2 by CPET; • Sarcopenia measured by computed tomography; • HGS; • Health-related quality of life by EORTC QLQ-C30 questionnaire, Beck Anxiety Inventory, and Beck Depression score; • Full adherence to the planned neoadjuvant chemotherapy and its toxicity; • Weekly step count; • Postoperative morbidity; • 30-day hospital readmission rate; • 3-year mortality rate.	N/A	3
Minnella et al. [22]; 2018	RCT	Esophagogastric cancer patients scheduled for surgery ± neoadjuvant treatment; (n = 68)	Primary outcome: • Change in functional capacity over time by 6MWD. Secondary outcomes: • Postoperative morbidity at 30 days; • Length of hospital stay; • 30-day hospital visits; • 30-day readmission rates; • 30-day death rates; • Full adherence to the planned neoadjuvant chemotherapy; • Compliance with prehabilitation program.	N/A	3
Valkenet et al. [23]; 2018	RCT	Esophageal cancer patients scheduled for surgery ± neoadjuvant treatment; (n = 270)	Primary outcome: • Postoperative pneumonia rate. Secondary outcomes: • Respiratory muscle function: maximum inspiratory pressure and inspiratory muscle endurance; • Pulmonary function: expiratory volume in 1 s and FVC; • Postoperative complication rate; • Duration of mechanical bowel ventilation; • Length of hospital stay; • Quality of life by EuroQol-5D and SF-12 questionnaires; • Physical activity by SQUASH questionnaire; • Fatigue by MFI-20 questionnaire.	N/A	3

Table 1. *Cont.*

Author; Year	Design	Description and Number of Participants; (n)	Measured Outcomes	N–O Score	Jadad Score
van Adrichem et al. [24]; 2014	RCT	Esophageal cancer patients scheduled for surgery ± neoadjuvant CRT; (n = 45)	Primary outcome: • Postoperative pulmonary complications rate. Secondary outcomes: • Length of stay; • Stay in ICU; • Number of reintubations; • Maximal inspiratory pressure before and after training; • Lung functions (FVC, FEV1, FEV1/FVC, and PIF); • Feasibility by the number of IMT-related adverse events, compliance to training, and a self-estimated load of participation.	N/A	3
Xu et al. [25]; 2015	Pilot study (RCT)	Esophageal cancer patients scheduled for neoadjuvant CRT and surgery; (n = 59)	Primary outcomes: • Functional walking capacity by 6MWD and strength by HGS; • Nutritional status by BW and fat-free lean mass by bioelectrical impedance. Secondary outcome: • Treatment tolerance by interruptions in chemotherapy or radiotherapy; unplanned hospital admission; grade > 2 neutropenia; fever > 38.5 °C; intravenous nutritional support and wheelchair use.	N/A	3
Yamana et al. [26]; 2015	RCT	Esophageal cancer patients scheduled for surgery ± neoadjuvant treatment; (n = 63)	Primary outcome: • Postoperative pulmonary complication rate. Secondary outcomes: • Respiratory function by FVC, FEV1, FEV1%, and PEF.	N/A	3
Christensen et al. [27]; 2018	Non-randomized control trial	Patients with GOJ adenocarcinoma scheduled for neoadjuvant treatment and surgery; (n = 50)	Primary outcome: • Frequency of serious adverse events (defined as events that prevented surgery). Secondary outcomes: • Neoadjuvant treatment tolerability; • Postoperative complication rate; • Postoperative hospital stay; • Patient-reported tolerability to neoadjuvant treatment by FACT-E questionnaire; • Response to treatment by infiltration of the resection margin and immunoscore, tumor regression grade by Mandard, and pathological tumor stage (pTNM).	8	N/A
Dettling et al. [28]; 2013	Non-randomized controlled trial	Patients scheduled for esophagectomy ± neoadjuvant treatment; (n = 83)	Primary outcomes: • Feasibility by the occurrence of adverse effects, patients' satisfaction; • Initial effectiveness by pre-operative improvement in respiratory function. Secondary outcomes: • Postoperative pneumonia rate; • Length of hospital stay; • Duration of mechanical ventilation; • Reintubation rate; • Length of stay in the ICU; • Postoperative morbidity rate.	8	N/A

Table 1. *Cont.*

Author; Year	Design	Description and Number of Participants; (n)	Measured Outcomes	N–O Score	Jadad Score
Argudo et al. [29]; 2020	Pilot study (prospective interventional study)	Esophagogastric cancer patients scheduled for neoadjuvant treatment and surgery; (n = 40)	• Feasibility by TELOS components; • Tolerability; • Exercise capacity by cardiopulmonary exercise testing; • Pulmonary and muscle function; • Peripheral muscle function; • Health-related quality of life by EORTC QLQ-C30 questionnaire.	6	N/A
Piraux et al. [30]; 2020	Pilot study (prospective interventional study)	Esophagogastric cancer patients scheduled for surgery ± neoadjuvant treatment; (n = 23)	Primary outcome • Feasibility (recruitment, retention and attendance rates, adverse events, and patient satisfaction). Secondary outcomes • Functional exercise capacity by 6MWD; • CRF by FACIT-F scale; • Quality of life by FACT-G questionnaire; • Anxiety and depression by HADS questionnaire.	6	N/A
Yamamoto et al. [31]; 2016	Pilot study (prospective interventional study)	Gastric cancer patients aged ≥ 65 years with a diagnosis of sarcopenia scheduled for gastrectomy; (n = 22)	• Nutritional intake (total number of calories and protein daily intake); • Body composition (body mass, fat mass, lean body mass); • Sarcopenia parameters (handgrip strength, gait speed, and skeletal muscle mass index).	6	N/A
Cho et al. [32]; 2014	Matched pair analysis	Patients with clinical stage I gastric cancer and metabolic syndrome scheduled for gastrectomy; (n = 72)	Primary outcome: • Postoperative complications rate. Secondary outcomes: • The operative time; • Intraoperative blood loss; • Hospital stay; • Visceral fat and body weight.	7	N/A

RCT: randomized controlled trial; CRT: chemoradiotherapy; N/A: not applicable; GOJ: gastroesophageal junction; AT: anaerobic threshold; CPET: cardiopulmonary exercise testing; 6MWD: six minute walking distance; HGS: hand-grip strength; BW: body weight; FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; FEV1%: forced expiratory volume in the first second predicted; PEF: peak expiratory flow.

Among them, there are 5 randomized control trials (RCTs) [21–24,26], 4 pilot studies [25,29–31], 2 non-randomized control trials [27,28], and 1 matched-pair analysis [32]. Despite the fact that all studies focused on prehabilitation for EGC surgery, they are heterogeneous in applied interventions and measured outcomes. Tables 2 and 3 show the structure of prehabilitation programs and their impact on clinical outcomes.

Table 2. Structure of interventions in prehabilitation programs for esophagogastric cancer surgery.

Author; Year	Prehabilitation Group			Control Group
	Type of Prehabilitation (Unimodal vs. Multimodal)	Timing of Prehabilitation	Interventions Used for Prehabilitation	
Allen et al. [21]; 2021	Multimodal	Prehabilitation was initiated for 15 preoperative weeks.	• Exercise intervention: supervised aerobic, resistance, and flexibility training twice a week and home-based exercise training three times per week; • Nutritional intervention: needs-based nutritional interventions with frequent, tailored dietetic input from specialist dieticians, increasing calorie and protein intake where appropriate depending on assessments and physical activity levels; • Psychological intervention: six sessions of medical coaching, which included discussion of health status, strength recognition, resilience profiling and development, social and support systems, emotional management, and goal setting.	• Standard of care
Minnella et al. [17]; 2018	Multimodal	Prehabilitation was initiated before the initial surgery or at the time of neoadjuvant therapy.	• Exercise intervention: individualized, home-based exercise training program including aerobic and strengthening exercise; • Nutritional intervention: metabolic requirement was adjusted to meet the increased nutritional demand. Food-based dietary advice was given, and a whey protein supplement was prescribed to guarantee a daily protein intake.	• Standard of care
Valkenet et al. [18]; 2018	Unimodal	Prehabilitation was initiated for 2 weeks or longer. When neoadjuvant therapy was administered, prehabilitation started afterward.	• Exercise intervention: inspiratory muscle training.	• Standard of care
van Adrichem et al. [19]; 2014	Unimodal	Prehabilitation was initiated for 3 weeks. When neoadjuvant therapy was administered, prehabilitation started afterward.	• Exercise intervention: high-intensity inspiratory muscle training.	• Exercise intervention: endurance inspiratory muscle training
Xu et al. [24]; 2015	Multimodal	Prehabilitation was initiated for 4–5 weeks during the neoadjuvant chemoradiotherapy.	• Exercise intervention: nurse-supervised walking; • Nutritional intervention: nutritional advice.	• Standard of care
Yamana et al. [20]; 2015	Unimodal	Prehabilitation was initiated for ≥7 days before the surgery.	• Exercise intervention: respiratory muscle training; muscle strengthening exercises for the lower limbs and abdominal muscles; biking on an ergometer.	• Standard of care
Christensen et al. [25]; 2018	Unimodal	Prehabilitation was initiated at the time of neoadjuvant treatment.	• Exercise intervention: supervised high-intensity aerobic and resistance exercise.	• Standard of care
Dettling et al. [26]; 2013	Unimodal	Prehabilitation was initiated for 2 weeks or longer.	• Exercise intervention: inspiratory muscle training.	• Standard of care

Table 2. *Cont.*

Author; Year	Prehabilitation Group			Control Group
	Type of Prehabilitation (Unimodal vs. Multimodal)	Timing of Prehabilitation	Interventions Used for Prehabilitation	
Argudo et al. [21]; 2020	Multimodal	Prehabilitation was initiated after neoadjuvant chemotherapy for 5 weeks.	• Exercise intervention: high-intensity interval training on the ergometric bicycle; respiratory muscle training using a respiratory muscle trainer. • Nutritional intervention: individualized nutritional therapy based on nutritional status and ability to fulfill caloric-protein requirements.	• N/A
Piraux et al. [22]; 2020	Unimodal	Prehabilitation was initiated for 2–4 weeks before the surgery.	• Exercise intervention: aerobic, resistance, and respiratory muscle training using an online tele-prehabilitation platform.	• N/A
Yamamoto et al. [23]; 2016	Multimodal	Prehabilitation was initiated for 3 weeks, although the actual duration differed depending on the surgery date.	• Exercise intervention: handgrip training, walking, and resistance training; • Nutritional intervention: nutritional advice and 2.4 g daily oral supplementation with leucine metabolite b-hydroxy-b-methylbutyrate (HMB).	• N/A
Cho et al. [27]; 2014	Unimodal	Prehabilitation was initiated for 4 weeks.	• Exercise intervention: aerobic exercise, resistance training, and stretching.	• Standard of care

CRT: chemoradiotherapy; N/A: not applicable.

Table 3. Outcomes of included studies evaluating prehabilitation for esophagogastric cancer surgery.

Author; Year	Prehabilitation Impact on Physical Status	Prehabilitation Impact on Postoperative Outcomes	Other Effects of Prehabilitation
Allen et al. [21]; 2021	Prehabilitation attenuated peak VO2 decrease and skeletal muscle loss following neoadjuvant therapy. Additionally, HGS was better retained in the prehabilitation group, and patients in this group were more physically active by higher weekly step count.	Prehabilitation had no impact on the number and severity of complications, length of hospital stay, 30-day readmission rates, and 3-year cancer-related mortality.	Prehabilitation improved QoL by global health status after 2 cycles of neoadjuvant chemotherapy and at 2 weeks, 6 weeks, and 6 months postoperatively. Additionally, prehabilitation resulted in better BAI and DBI II scores preoperatively and 6 weeks and 6 months postoperatively. A higher proportion of patients in the prehabilitation group received neoadjuvant chemotherapy at full dose.
Minnella et al. [17]; 2018	Prehabilitation improved functional capacity before and after surgery by increasing 6MWD.	Prehabilitation had no impact on the number and severity of complications, length of hospital stay, emergency department visits, and readmission rates.	N/A
Valkenet et al. [18]; 2018	Prehabilitation resulted in a higher increase in inspiratory muscle strength and endurance.	Prehabilitation did not affect postoperative pneumonia and other postoperative complication rates.	Prehabilitation did not affect the quality of life, fatigue, and physical activity levels.

Table 3. *Cont.*

Author; Year	Prehabilitation Impact on Physical Status	Prehabilitation Impact on Postoperative Outcomes	Other Effects of Prehabilitation
van Adrichem et al. [19]; 2014	The increase in maximal inspiratory pressure was similar between the groups which received preoperative inspiratory muscle training.	The incidence of postoperative pulmonary complications, length of stay, and the number of reintubations were lower in the high-intensity inspiratory muscle training group.	N/A
Xu et al. [24]; 2015	Prehabilitation ameliorated decline in 6MWD and hand-grip strength.	N/A	Prehabilitation ameliorated weight and lean muscle mass loss. Additionally, patients in the prehabilitation group had a significantly lower need for intravenous nutritional support and wheelchair use.
Yamana et al. [20]; 2015	Prehabilitation did not affect respiratory function representing parameters (FVC, FEV1, FEV1%, and PEF).	Prehabilitation ameliorated the severity of postoperative complications (by lower Clavien–Dindo score) and postoperative pneumonia (by lower Utrecht Pneumonia Scoring System score).	N/A
Christensen et al. [25]; 2018	Prehabilitation resulted in improved fitness and muscle strength.	Prehabilitation did not affect the postoperative complication rate.	Prehabilitation resulted in improved quality of life by FACT-E score.
Dettling et al. [26]; 2013	Prehabilitation increased inspiratory muscle strength and endurance.	Prehabilitation did not affect postoperative pneumonia and other complication rates.	N/A
Argudo et al. [21]; 2020	Prehabilitation improved exercise capacity in terms of VO2 peak and workload and distance improvement in the 6MWD and inspiratory and expiratory muscle strength.	N/A	Prehabilitation resulted in the improvement of some domains of health-related quality of life (social and role functions).
Piraux et al. [22]; 2020	N/A	N/A	Prehabilitation improved fatigue, quality of life, physical well-being, emotional well-being, and anxiety.
Yamamoto et al. [23]; 2016	Prehabilitation significantly increased handgrip strength.	N/A	Prehabilitation improved nutritional uptake by increasing calorie and protein intake.
Cho et al. [27]; 2014	N/A	Prehabilitation decreased hospital stay and the number of severe postoperative complications (anastomotic leakage, pancreatic fistula, intra-abdominal abscess, and other severe abdominal complications).	Prehabilitation significantly decreased BMI, bodyweight, abdominal circumference, and visceral fat.

6MWD: six minute walking distance; N/A: not applicable; FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; FEV1%: forced expiratory volume in the first second predicted; PEF: peak expiratory flow.

3.1. Exercise Interventions in Unimodal and Multimodal Prehabilitation Programs

Exercise has obvious and indisputable benefits on individuals' health, including those who have cancer. Physical activity increases fitness levels and physical functioning. It

also decreases cancer-related fatigue and improves quality of life [33,34]. A preoperative exercise intervention improves patients' functional capacity and thus may reduce perioperative morbidity [13]. These benefits make exercise interventions the backbone of current prehabilitation programs. The exact benefit of exercise depends on its type. There is no consensus on the optimal exercise regimen, which most likely explains the diversity of interventions seen throughout the literature.

Most available studies on EGC patients investigated unimodal prehabilitation consisting of exercise interventions only [23,24,26–28,30,32]. It is not surprising that the majority focused on preoperative inspiratory muscle training (IMT) because pulmonary complications are the most common after EGC surgery, affecting up to 20–40% of patients [35,36]. Pulmonary morbidity contributes to a prolonged hospital stay, increased treatment costs, mortality, and long-term impaired outcomes [9,37,38]. Thus, even the slightest improvement in these complication rates may significantly improve EGC treatment outcomes [9]. Studies by Dettling et al. [28], Valkenet et al. [23], and Argudo et al. [29] investigated IMT for 2–5 weeks using specialized inspiratory-threshold loading devices. These studies consistently showed the feasibility and safety of such prehabilitation [23,28,29]. Preoperative IMT improved inspiratory muscle function [23,28,29], but had no impact on postoperative morbidity [23,28]. However, the effectiveness of preoperative IMT with a special device may depend on the type of exercise. Adrichem et al. compared two different exercise protocols—high intensity and endurance IMT using Respifit S and Threshold-IMT devices, respectively. Both training protocols significantly increased maximal inspiratory pressure, representing an inspiratory function, but only high-intensity training decreased postoperative pulmonary morbidity [24]. Alternatively, preoperative respiratory rehabilitation can be conducted without any special equipment [26]. Yamana et al. demonstrated that even a short (>7 days) but intensive and complex supervised respiratory prehabilitation program consisting of different exercises for respiratory muscles together with aerobic exercise effectively reduces postoperative pulmonary morbidity in esophageal cancer patients [26].

Other types of exercise interventions investigated in unimodal prehabilitation studies were aerobic and resistance training with or without exercises for IMT and stretching [27,30,32]. Such a combination has a strong rationale because different exercises have different benefits. Aerobic exercises improve physical fitness and cardiac, respiratory, and musculoskeletal function even after a short training time (2–3 weeks) [39]. Resistance training promotes skeletal muscles hypertrophy, increases muscle mass, strength and function, and thus counteracts sarcopenia [40,41]. Resistance training is important in all age groups, including elderly and frail patients [40,41], who are at the highest risk for postoperative complications after EGC resections [42,43]. Unimodal exercise prehabilitation consisting of aerobic and resistance training is safe and feasible. It positively impacts fitness level, strength, and quality of life in EGC patients [30,44]. Moreover, a small matched-pair study from Japan suggested that such prehabilitation reduces the overall postoperative morbidity rate in high-risk patients undergoing gastrectomy [32]. Aerobic and/or resistance training is also the core intervention of multimodal prehabilitation programs [21,22,25,31]. Xu et al. showed that even the simplest aerobic exercise, such as walking, has a positive effect [25]. Only 25 min of nurse-supervised walking three times a week attenuates neoadjuvant chemoradiotherapy-induced decline in physical fitness and increases walking distance and hand-grip strength [25]. Similar benefits of aerobic and resistance training have been shown in other studies [21,22,31,32]. Despite notable differences between exercise protocols, all studies consistently showed positive effects by improved physical fitness levels [22,31], muscle mass [31], cardiorespiratory function [21], and reduced number of postoperative complications [32].

3.2. Nutritional and Psychological Interventions as Components of Multimodal Prehabilitation

Malnutrition affects about 80% of EGC patients and greatly negatively impacts treatment outcomes [45–47]. It increases the risk of systemic treatment-related toxicity, poor treatment adherence, postoperative morbidity, and mortality [48–51]. The etiology of mal-

nutrition and the reasons for such a high incidence are multifactorial. It includes a variety of mechanisms related to cancer itself, the host response to the disease, and treatment [52]. First, tumors within the esophagus or stomach may simply cause a mechanical obstruction that prevents the passage of food through the gastrointestinal tract [48]. Second, cancer induces metabolic disturbances, immune system response, and CNS alterations that result in taste change, food aversion, and inhibition of absorption/digestion of nutrients [52,53]. Third, psychological stress, a common fear, depression, and anxiety, may also negatively impact appetite and food intake [52]. These changes result in insufficient caloric intake and promote depletion of micro-and macro-nutrients reserves in the body [53]. Moreover, cancer induces catabolic activities that lead to nutritional overconsumption and ultimately clinically relevant malnutrition [53]. Malnutrition is a modifiable risk factor, which can be efficiently adjusted if diagnosed early [54]. Well-timed nutritional interventions before major gastrointestinal surgery effectively improve nutritional status and quality of life and even reduce postoperative morbidity [55–57]. Thus, nutritional interventions seem like a necessary component of multimodal prehabilitation programs in EGC patients.

Currently, 5 studies investigated the effect of nutritional interventions that included food-based dietary advice ± oral nutritional supplements or enteral nutrition via feeding tubes if necessary [21,22,25,29,31]. Three of these studies showed an obvious positive effect of nutritional support by increased protein intake and a higher number of consumed calories [31]. Additionally, nutritional support attenuated neoadjuvant treatment-induced weight and muscle mass loss [21,25]. The other two studies did not measure outcomes that would directly represent nutritional interventions' effect. Although, these studies showed that multimodal prehabilitation that includes nutritional support effectively improves the functional capacity and quality of life of EGC patients [22,29].

Besides physiological challenges, such as previously mentioned physical and nutritional issues, many EGC patients suffer from psychological and emotional distress [58–62]. Depression and anxiety impair compliance to cancer treatment and quality of life [58,63] and promote the development and progression of the disease. The proposed molecular mechanism for depression-induced carcinogenesis includes disease-related overproduction of reactive oxygen species leading to oxidative stress that promotes activation of different proto-oncogenes contributing to subsequent cancer development [62,64]. Therefore, it is not surprising that psychological distress is related to impaired long-term outcomes in cancer patients [58,65]. Psychological prehabilitation is suggested as a strategy to alleviate psychological distress and improve treatment outcomes. The systematic review by Tsimopoulou et al. summarized evidence from seven studies investigating psychological interventions before surgery for the breast, prostate, and colorectal cancer patients [66]. These interventions did not improve traditional surgical outcomes (postoperative morbidity and mortality or hospitalization time). Still, they positively affected patients' reported outcomes, including psychological well-being, quality of life, and somatic symptoms [66]. In a cohort of EGC patients, only Allen et al. investigated psychological intervention as a part of multimodal prehabilitation [21]. The intervention consisted of six sessions of medical coaching to discuss health status, strength recognition, resilience profiling and development, social and support systems, emotional management, and goal setting [21]. The authors discuss that it may have contributed to higher neoadjuvant therapy completion rates by increasing patients' resilience to their neoadjuvant journey. Nonetheless, it is difficult to reliably evaluate the impact of psychological support because the study had no clear endpoints for it [21].

4. Important Questions for the Wider Implementation of Prehabilitation Programs in Modern Esophagogastric Cancer Surgery and Gaps in Current Knowledge

This review summarized the current evidence for prehabilitation in modern EGC surgery. The available studies are very heterogeneous in design, type of interventions, and measured outcomes. All of them confirmed at least some positive effects of prehabilitation in terms of improved physical performance, nutritional status, quality of life, or even

reduced number of postoperative complications [22–32]. Despite extensive evidence that supports the concept of prehabilitation, the heterogeneity of available studies prevents the standardization and wide adoption of the strategy. Clinicians willing to implement prehabilitation for EGC surgery will face several important questions, although not all can be answered yet.

4.1. Question 1: Multimodal or Unimodal Prehabilitation?

The most optimal regimen of prehabilitation remains unknown. Currently, multimodal and unimodal prehabilitation programs are available [67], with a similar level of evidence for effectiveness. Considering that EGC patients face physical, nutritional, and psychological challenges [68–70], multimodal prehabilitation may have greater benefits [67]. Multimodal prehabilitation requires more resources from healthcare professionals to train appropriate exercise interventions and provide nutritional and psychological support. Several ongoing trials investigating multimodal prehabilitation before EGC resection will elucidate the current unclarities in the topic [4,71,72].

4.2. Question 2: Supervised or Home-Based Prehabilitation?

Prehabilitation can be utilized in a hospital under the supervision of healthcare professionals or at home after initial training. Both strategies have advantages and disadvantages. On the one hand, supervised prehabilitation allows strict monitoring of the adherence to the program, and necessary adjustments are easy to make. Some conflicting evidence shows better outcomes of supervised training in patients with chronic low back pain [73], intermittent claudication [74], recent myocardial infarction [75], or after anterior cruciate ligament reconstruction [76]. However, the need for regular visits to treatment centers may preclude prehabilitation in patients who suffer logistical challenges. Additionally, additional visits to the hospital may be undesired by patients, especially in light of the ongoing COVID-19 pandemic. Tele-prehabilitation may be an alternative to supervised prehabilitation without traveling [30]. However, it remains unclear if supervised prehabilitation has any benefits over home-based prehabilitation [77,78]. Current literature indicates that the patient's preferred method is home-based intervention; thus, a high level of adherence can be expected [79]. It seems that home-based unsupervised or semisupervised prehabilitation may be the most reasonable option for the majority of EGC patients.

4.3. Question 3: How to Ensure Adherence to Prehabilitation Program?

Insufficient adherence is among the biggest challenges limiting the effectiveness of prehabilitation [80]. Thus, there is a need for tools that would overcome the issue. Direct supervision by healthcare professionals could enhance a patient's motivation and willpower to participate [81]. However, as mentioned previously, supervised prehabilitation has some major disadvantages. Incorporating behavioral science professionals' support may improve patients' motivation for interventions and adherence to prehabilitation [82]. However, only one [21] included psychological support among the available studies. Thus, stronger evidence is necessary, and future studies should elucidate the role of these specialists. Additionally, there is a need for studies to identify exact reasons precluding adherence to prehabilitation. Identification of barriers will let us create strategies to overcome them.

4.4. Question 4: At Which Stage of Treatment Should Prehabilitation Be Initiated?

The time frame between diagnosis and surgery is relatively short; thus, prehabilitation should be initiated as early as possible in patients undergoing surgery first. However, it is trickier with patients who need neoadjuvant therapy. One window for prehabilitation is the time between the completion of neoadjuvant therapy and surgery, which typically lasts at least 4–6 weeks [8]. Alternatively, prehabilitation may be initiated earlier, even at the time of diagnosis, and utilized throughout the neoadjuvant therapy. The feasibility of prehabilitation interventions in EGC patients undergoing cytotoxic neoadjuvant treatment has already been shown [21,25]. Early initiated prehabilitation may counteract some negative impacts

of neoadjuvant treatment, including a decline in cardiorespiratory function and physical capacity [41,83]. These are major risk factors for morbidity in EGC surgery [84]; thus, it seems rational to schedule patients for prehabilitation at an early phase of the treatment.

4.5. Question 5: What Benefits of Prehabilitation Could Be Expected in Esophagogastric Cancer Patients?

4.5.1. Prehabilitation's Impact on Postoperative Morbidity

Three of seven studies investigating the impact of prehabilitation on postoperative morbidity after EGC resections showed a significant positive impact [21–23,26,28,39]. Two studies demonstrated that respiratory prehabilitation could reduce postoperative pulmonary complication rates [24,26]. One study showed aerobic- and resistance training-based prehabilitation significantly reduces postoperative morbidity after gastrectomy in high-risk patients with metabolic syndrome [32].

4.5.2. Prehabilitation's Impact on Adherence to Neoadjuvant Treatment Protocol

Two studies evaluated multimodal prehabilitation's impact on adherence to all planned neoadjuvant treatments and showed conflicting results [21,22]. A randomized control study by Minella et al. showed a similar low (8%) non-compliance rate in the control and prehabilitation groups [22], while a slightly larger study by Allen et al. showed very different results [21]. A much higher non-compliance rate of 54% was observed in the control group, and prehabilitation significantly decreased it to 25% [21].

4.5.3. Prehabilitation Impact on Quality of Life

Five studies investigated prehabilitation's impact on quality of life [21,23,27,29,30]. Valkenet et al. showed that isolated inspiratory muscle training has no impact on quality of life-related outcomes [23]. In contrast, four studies that used complex exercise interventions demonstrated the positive effect of prehabilitation on social role functions [29], physical and emotional well-being [27,30], fatigue [29,30], anxiety and depression [30], and other quality of life-related outcomes [21,27,29,30].

4.5.4. Prehabilitation Impact on Long-Term Outcomes

There is evidence that prehabilitation improves long-term outcomes in colorectal cancer patients [85]. However, its impact on long-term outcomes in EGC patients remains unknown. Future studies are necessary to address this question.

5. Conclusions

Prehabilitation has emerged as a novel strategy to optimize a patient's status before major surgery. In this comprehensive review, we summarized the current evidence for the role of prehabilitation in modern EGC surgery. Despite the heterogeneity of the studies' designs, all of them confirmed at least some positive effects of prehabilitation. The benefits included improved physical performance, nutritional status, quality of life, and even fewer postoperative complications. Future studies are necessary to determine the most optimal design of prehabilitation programs for esophagogastric resection.

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PART 2: Personalized trimodal prehabilitation for gastrectomy

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Personalized trimodal prehabilitation for gastrectomy

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Abstract

Background: Surgery is the only potentially curative treatment for gastric cancer, however, it bears a high postoperative morbidity and mortality rate. A recent randomized control trial proposed prehabilitation to reduce the postoperative morbidity in patients undergoing major abdominal surgery. Currently, there is a lack of evidence of using prehabilitation for patients undergoing gastrectomy for gastric cancer. The aim of our study is to demonstrate that home-based prehabilitation can reduce postoperative morbidity after gastrectomy for gastric cancer.

Methods: PREFOG is a multi-center, open-label randomized control trial comparing 90-days postoperative morbidity rate after gastrectomy for gastric cancer between patients with or without prehabilitation. One-hundred twenty-eight patients will be randomized into an intervention or control group. The intervention arm will receive trimodal home-based prehabilitation including nutritional, psychological and exercise interventions. Secondary outcomes of the study will include physical and nutritional status, anxiety and depression level, quality of life, postoperative mortality rates and full completion of the oncological treatment as determined by the multidisciplinary tumor board.

Discussion: PREFOG study will show if home-based trimodal prehabilitation is effective to reduce postoperative morbidity after gastrectomy for gastric cancer. Moreover, this study will allow us to determine whether prehabilitation can improve physical fitness and activity levels, nutritional status and quality of life as well as reducing anxiety and depression levels after gastrectomy for gastric cancer.

Trial registration: ClinicalTrials.gov NCT04223401 (First posted: 10 January 2020).

Abbreviations: AT = anaerobic threshold, *CBC* = common blood count, CRF = case report form, CRP = C-reactive protein, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30, EORTC QLQ-STO-22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire STO-22, GC = gastric cancer, HADS = Hospital anxiety and depression scale score, IPAQ = International Physical Activity Questionnaire, NRS2002 = Nutritional Risk Score-2002 questionnaire score, RCT = randomized control trial.

Keywords: gastric cancer, home-based, prehabilitation, randomized control trial

1. Introduction

Surgery is the main and only curative treatment option for gastric cancer (GC).[1] Despite the progress in surgical and anesthetic techniques, gastrectomy remains associated with high postoperative morbidity (~50%) and mortality (~5%) rates.[2–4] Furthermore, patients suffering postoperative complications are less likely to receive adjuvant therapy or must delay the initiation of it[5,6] and it impairs the long-term outcomes.[7] Therefore, there is a great need for novel strategies to reduce the postoperative morbidity after gastrectomy for GC.

The authors report no conflicts of interest.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Poor physical condition (determined by cardiopulmonary exercise testing), sarcopenia, and preoperative malnutrition often accompanies GC and represents decreased physiological reserve, predicting postoperative complications.[4,8,9] Moreover, the majority of patients with resectable GC are considered for perioperative chemotherapy which improves oncological outcomes but impairs patients' physical fitness before the surgery.[10,11] Some patients' risk factors are modifiable and may be improved within several weeks before surgery by a short multimodal prehabilitation consisting of physical training, nutritional adjustments and psychological support.[12–14] Besides improved physical and nutritional status attributed to prehabilitation, a recent randomized control trial (RCT) showed a 51% reduction of postoperative complications after major abdominal surgery.[15] Given the high morbidity rate, poor initial physical and nutritional status and the need for preoperative chemotherapy, GC patients would be ideal candidates to receive prehabilitation. To date, several studies already investigated the role of prehabilitation in esophagogastric surgery.[16] However, most of these focused on patients receiving esophagectomy, with limited data for gastrectomy.[16] A match pair analysis study showed reduced postoperative morbidity following prehabilitation in patients with GC and metabolic syndrome,[17] while a small pilot study found increased physical status in elderly sarcopenic GC patients.[18] However, these studies were rather small and inconclusive. There is a need for an RCT to address the role of prehabilitation in GC surgery.

The aim of this study is to demonstrate reduced postoperative morbidity after gastrectomy for GC in patients who undergo home-based prehabilitation.

2. Methods

2.1. Study setting and trial design

This multicenter study is designed as a prospective, parallel-group, 1:1 randomized control, open-label trial. The study will be conducted at two major gastrointestinal cancer treatment centers of Lithuania: National Cancer Institute and Vilnius University hospital Santaros Klinikos. A study flowchart is provided in Figure 1. Data collection and follow-up schedules are shown in Table 1.

2.2. Eligibility criteria

The study will include gastric cancer patients scheduled for elective total or subtotal gastrectomy at multidisciplinary team meetings. Patients scheduled for gastrectomy first and gastrectomy after neoadjuvant chemotherapy are eligible. Participants will be included after screening for eligibility and obtaining written informed consent. To participate in the study candidates must meet the following inclusion criteria:

1. Age $\geq$ 18 years.
2. Patient agrees to participate in a clinical study.
3. Patient requires surgical treatment for gastric cancer.

Patients will be excluded if they meet the following criteria:

1. Patient requires surgical treatment for gastric cancer recurrence.
2. Patient condition not allowing to postpone surgery for at least 4 weeks.
3. Patients' physical or mental condition that does not allow the patient to participate in the prehabilitation program.

2.3. Interventions

2.3.1. Control group. The control (standard of care) group will receive routine care from their gastric cancer diagnosis to surgical treatment. These patients will receive no specific advice for prehabilitation before surgery except a recommendation for nutritional supplements by high-energy drinks on the decision of the surgeon.

2.3.2. Prehabilitation group. The prehabilitation (intervention) group will receive home-based trimodal prehabilitation before the gastrectomy. The prehabilitation will consist of:

1) *Exercise intervention:* Patients will be consulted by physical medicine and rehabilitation physicians and physiotherapists to develop personalized home-based exercise program according to a physical performance examination and results of spiroergometry. All patients will undergo three supervised training sessions where they will be trained in correct exercise techniques and self-control in training intensity. Additionally, each patient will receive a written exercise program with detailed description of it. The home-based program will consist of 4 types of exercises:

- Endurance training for 10 to 30 minutes daily by walking/stair climbing/dancing/water exercises/biking. The type of exercise will depend on the patient's choice. The target intensity is 40% to 65% of the heart rate reserve.
- Respiratory muscles training for 5 to 10 minutes daily.
- Resistance training to improve muscular strength for 10 to 20 minutes 3 times per week.
- Stretching exercises for 5 to 10 minutes 3 times per week.

In total daily training sessions will not exceed 60 minutes.

2) *Nutritional support:* A dietician will perform a physical examination and bioimpedance to evaluate the nutritional status of each patient and will provide personalized recommendations for the prevention or correction of malnutrition. The energy and protein requirements will be estimated with 25 to 30 kcal/kg and 1.5 g/kg of ideal body weight respectively. If necessary, patients will be prescribed to consume oral nutritional supplements to increase the consumption of calories and proteins.

3) *Psychological support:* Patients will undergo consultation by specialized onco-psychologist. The anxiety and depression level will be evaluated by the HAD score and patients will be trained to perform relaxation techniques to reduce and manage anxiety at home.

The total length of the prehabilitation program will depend on the gastric cancer treatment pathway. Patients scheduled for the gastrectomy first will undergo prehabilitation for 4 weeks before surgery. Patients scheduled for neoadjuvant chemotherapy first will receive prehabilitation through the entire time of neoadjuvant treatment. The length of the prehabilitation will depend on the neoadjuvant chemotherapy scheme, which is chosen by medical oncologists irrespective of participation in the study.

2.4. Strategies to improve adherence to interventions

To increase compliance with the prehabilitation program patients will be asked to fill a diary to record their daily prehabilitation practice. Also, the study staff will contact the patient to inquire about the adherence to the study protocol weekly by the phone call.

2.5. Study outcomes

2.5.1. Primary endpoint. The primary outcome of the study is the postoperative morbidity rate by the Clavien-Dindo classification at 90 days postoperatively. All postoperative complica-

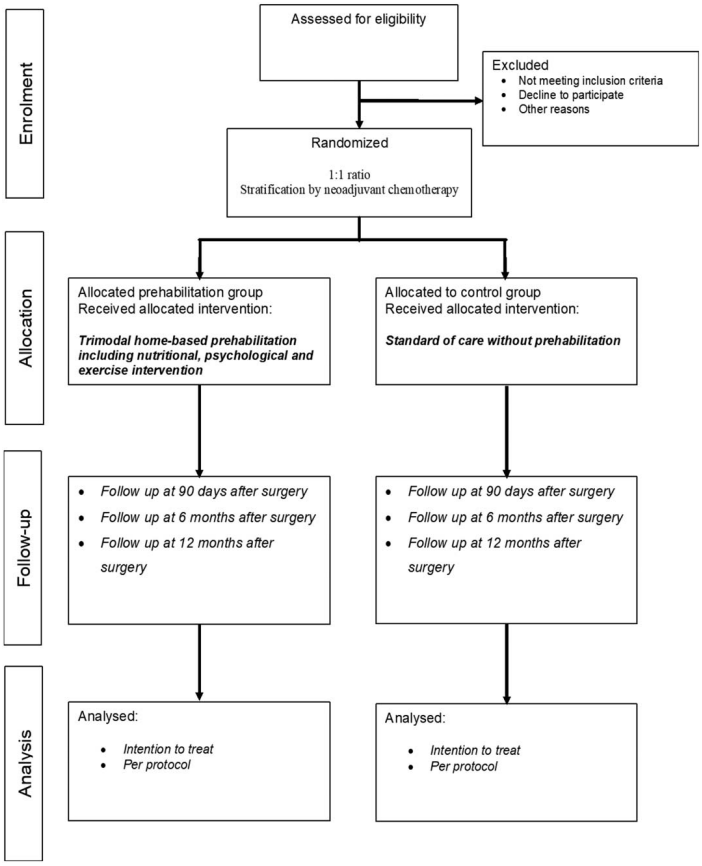

Figure 1. Consort diagram: flow chart.

tions will be recorded at the time of discharge and the surgeon will document any events after discharge at the outpatient appointment 90 days postoperatively. All complications will be classified by the Clavien-Dindo classification.

2.5.2. Secondary endpoints. The secondary endpoints include:

1) Postoperative intrahospital and 90-day mortality rate
2) Postoperative intrahospital and 30-day morbidity rate
3) Physical status of the patient at baseline, pre-surgery, at discharge and 12 months after surgery by:
   - Six-minute walk test
   - Spiroergometry (VO_2, VO_{2max}, AT)
   - Grip strength test
   - Sit to stand test
   - Timed up and go test
   - Thoracic excursion test
   - International Physical Activity Questionnaire (IPAQ) score.
4) Nutritional status at baseline, pre-surgery, 3, 6 and 12 months after surgery by:
   - Blood albumin level
   - Bioimpedance
   - Nutritional Risk Score-2002 questionnaire score (NRS2002)
5) Quality of Life at baseline, pre-surgery, 3, 6, and 12 months after surgery by:
   - EORTC QLQ-C30 and STO-22 questionnaires scores
6) Anxiety and depression level at baseline, pre-surgery, 3, 6 and 12 months after surgery by:
   - Hospital anxiety and depression scale (HADS) score
7) The proportion of patients completing the oncological treatment fixed in a multidisciplinary tumor board (including

Table 1

Standard protocol items: recommendations for interventional trials (SPIRIT) figure. Flowchart of the PREhabilitation FOr Gastrectomy (PREFOG) trial.

			Study Period					
			Post-allocation					Close-out
Timepoint**	**Enrolment** $-t_1$	**Allocation** 0	***Baseline***	***Day before surgery***	***Discharge***	***90 days after surgery***	***6 months after surgery***	***12 months after surgery***
Enrolment:								
Eligibility screen	X							
Informed consent	X							
Screening log	X							
Allocation		X						
Interventions:								
Prehabilitation								
ASSESSMENTS:								
Demographic questionnaire	X	X	X	X	X	X	X	X
CBC			X	X	X	X	X	X
CRP, total protein, albumin			X	X	X	X	X	X
EORTC QLQ-C30 and STO-22 questionnaires			X	X	X	X	X	X
HADS			X	X	X	X	X	X
IPAQ			X	X	X	X	X	X
NRS2002			X	X	X	X	X	X
Spiroergometry			X	X*				
6 MWT			X	X	X			X
Bioimpedance			X	X*				X
10-meter walk test; sit-to-stand test; timed up&go test; grip strength test, thoracic excursion test			X	X*				X
ASA classification				X				
ICU care					X			
Type of Surgery					X			
TNM classification					X			
Tumor regression grade by Becker					X			
Tumor characteristics					X			
Postoperative morbidity/mortality					X	X	X	X
Length of hospital stay					X			
Preoperative chemotherapy			X					
Postoperative chemotherapy/radiotherapy								X
Serious adverse events			Throughout the study period					

CBC = common blood count, CRP = C-reactive protein, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30, EORTC QLQ-STO-22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire STO-22, HADS = Hospital anxiety and depression scale score, IPAQ = International Physical Activity Questionnaire, NRS2002 = Nutritional Risk Score-2002 questionnaire score.

* measurements are re-assessed preoperatively if patients receive preoperative chemotherapy.

preoperative chemotherapy, surgery, and postoperative chemotherapy) at 12 months after treatment initiation

2.5.3. Other objectives and supplementary data collected.

Additionally, we will collect data regarding patient demographics, clinical variables (i.e., age and gender, smoking, alcohol usage), surgical and anesthetic details (i.e., intensive care unit and hospital length of stay, type and length of surgery, blood loss, intraoperative complications, t. protein and CRP levels) and disease-related parameters (i.e., stage of disease by TNM classification, tumor regression grade by Becker classification). Study data will be collected and managed using case report forms (CRF).

2.6. Biobanking

Additional informed consent may be taken from patients for the biobanking of blood, urine and tissue samples as a part of daily practice in the study institutions. These samples may be used for future laboratory, genetic or molecular analysis.

2.7. Data collection and management

All the data will be recorded in CRFs, to maintain the confidentiality all personal data will be coded. Data will be collected at baseline, preoperatively, during the intrahospital period (preoperatively and postoperatively) and after discharge (up until 12 months after surgery).

2.8. Recruitment

All gastric cancer patients discussed at the multidisciplinary tumor board meetings in the participating institutions are screened for eligibility for the study. Potentially eligible patients are approached with written informed consent at the outpatient visit to the surgeon. Patient recruitment started at February 2020. Twenty-two months are planned for the recruitment and 300 patients are anticipated to undergo gastrectomy at the study institutions within this time. Therefore, the recruitment of 128 patients seems to be feasible.

2.9. Assignment of interventions: allocation

2.9.1. Sequence generation. Participants will be randomly assigned to either control or experimental group with a 1:1 allocation as per a computer-generated randomization schedule stratified by neoadjuvant treatment using random permuted blocks of 4 and 6. The randomization sequence was created using an online available free tool (https://www.sealedenvelope.com/).

2.9.2. Concealment mechanism and implementation. The researcher assistant will prepare sequentially numbered, opaque, sealed envelopes containing randomization sheets. To distinguish patients receiving perioperative chemotherapy, the envelopes will be additionally marked. The randomization sheet will report the randomization code and assigned treatment (standard of care or prehabilitation). The prepared and sealed envelopes will be split into equal piles and delivered to the dedicated place in both study centers. At the time of randomization, the investigator (surgeon consulting the patient) will choose an envelope with the lowest number and will write the name and date of birth of the participant before opening to prevent subversion of the allocation sequence. After opening, the randomization information will be given to the patient, the baseline condition of the patient will be assessed and the case report form (CRF) will be filled in.

2.9.3. Blinding. The study cannot be blinded because participation in a prehabilitation program cannot be hidden from neither patients nor practitioners.

2.10. Sample size

The sample size calculation was done using G*Power 3.1.9.4 software using the reduction of 90 days postoperative complication rates as the primary outcome. Based on the assumption that the percentage of patients developing postoperative complications after gastrectomy is approximately 50% for the control group (based on our centers historical experience and results from RCTs)[2,3] and can be reduced to 25% in the prehabilitation group (based on results of recent RCT showing 50% reduction of postoperative complications by prehabilitation),[15] a group sample size of 58 patients is needed to achieve 80% power in detecting this difference in 90-days postoperative morbidity at a two-sided level of significance of 5%. Under the assumption of a drop-out rate of up to 10%, a total of 128 patients (64 per group) needs to be enrolled in the study.

2.11. Statistical analysis

All clinical data will be analyzed on an intention to treat basis but will also be described on 'as treated' basis. Initially, all the clinical data will be analyzed using descriptive statistic methods. The primary outcome analysis will be based on a Chi-Square test. For secondary endpoint analysis, Chi-Square or Fisher Exact test, T-Test or Mann-Whitney test will be used where appropriate. Other statistical methods will be used if there will be a need.

2.12. Criteria for discontinuing or modifying allocated intervention

The study can be terminated for individual patients due to:

(a) a severe adverse event;
(b) significant protocol violations;
(c) withdrawal of consent;
(d) loss to follow-up;
(e) any other situation that leads to the decision to terminate the study.

The whole trial can be stopped by the investigator if adverse events occur or other unforeseeable events might influence the safety or well-being of the study participants. After termination, all study patients will be followed up according to the standard follow-up policy of our institution for gastric cancer.

2.13. Ethics

The study protocol has been approved by the Vilnius University Regional Bioethics committee (Nr.2020/1-1185-675) and registered with clinicaltrials.gov (NCT04223401). Written informed consent will be obtained from the patients before participation in the study. The trial will be performed guided by the World Medical Association's Declaration of Helsinki, Guideline for Good Clinical Practice, and regulatory laws in Lithuania.

3. Discussion

Surgical resection remains the cornerstone of treatment with curative intent for GC. However, postoperative complications after gastrectomy are a significant problem resulting in increased treatment costs, prolonged hospital stay, delayed adjuvant therapy and impaired long-term outcomes.[19–22] The physical, nutritional and emotional capacity of the individual patients predicts the postoperative outcomes.[23–26] Some of the interventions, such as intensive intraoperative monitoring, well-timed admission to intensive care unit and enhanced recovery through ERAS protocols are proposed in the early perioperative period to improve the postoperative outcomes.[27] Although, the ideal timeframe for prehabilitation intervention is the preoperative period, as the decline in physical and emotional status is to be expected after major surgery. An intensive postoperative program would be more detrimental to patient recovery and would fail to better prepare patients for surgery. It is rational to expect, that increasing patients' physiological fitness before surgical trauma will preserve a higher level of functional capacity over the entire perioperative period and would hopefully extend postoperatively. The process of improving patients' physical, nutritional, and emotional capacity before surgery has been termed multimodal prehabilitation. The goal centers on wholesome preparation of the patient to withstand the physical and emotional stress of surgery.[28]*Promising results of prehabilitation have been reported including reduced* postoperative complication rates[15] and earlier recovery of physical function after major abdominal surgery.[29] Although the current evidence from randomized studies remains weak and inconsistent, it suggests a potential strategy to reduce postoperative mortality rates.[30,31] Only a few studies focused on prehabilitation for gastrectomy and none of them investigated the real multimodal prehabilitation approach in a randomized control trial.[16,17] The matched-pair analysis by Cho et al[17] showed the benefit of isolated exercise intervention for GC patients with a high body mass index (>25 kg/m^2) and metabolic syndrome, while the pilot study by Yamamoto et al[18] demonstrated the potency of exercise and nutritional intervention for sarcopenic and elderly GC patients. Despite this promising potential to improve postoperative outcomes by prehabilitation, the evidence level is low and further investigation is necessary. Currently, multimodal prehabilitation including exercise,

nutritional and psychological interventions is under investigation in the ongoing PREHAB study.[32] However, this study employs supervised exercise interventions, which require repeated clinical appointments. It becomes a geographical challenge when the cancer centers cover a large area with a widely spread population. The need for routine visits limits patients' recruitment and adherence. To overcome such logistic issues, home-based prehabilitation was considered as an alternative, especially as recent data support the effectiveness of such programs for patients with lung and pancreatic cancer.[33,34] Thus, our study was designed to investigate the trimodal prehabilitation in a home-based setting to limit participant visits, improve recruitment and reduce participant burden. Naturally, the compliance to the prehabilitation program in a home-based setting may be challenging. Therefore, the first three exercise trainings are supervised by a physiotherapist to ensure appropriate techniques and provide detailed written instructions for further personalized training at home. To assure compliance to the program we will use a self-reported diary and will implement a weekly phone call to assess patient adherence. The PREFOG study presented here will demonstrate whether home-based personalized prehabilitation will decrease the postoperative morbidity after gastrectomy for gastric cancer. Moreover, this study will allow us to determine whether prehabilitation can improve physical fitness and activity levels, nutritional status and quality of life, as well as reduce anxiety and depression levels after gastrectomy for gastric cancer.

4. Declarations

We declare that this study is funded by Vilnius University. The individual data of the patients will remain confidential. The results of this study may be presented at national and international conferences and published. The study is a part of doctoral thesis of A.B. at the Faculty of Medicine Vilnius University. All the authors declare that they have no additional conflict of interest.

Protocol date and version and study status: Protocol version 2, dated 2020-01-29. Currently study is recruiting patients.

Author contributions

All listed authors contributed contributed to the conception and design of the work. KS, RB, SL, EG JC contributed to the provision of resources; AB, ML, JK, GA, VM, LG, IJ, AC, DV and GK contributes to the acquisition of data. AB prepared the manuscript. RB and KS revised the manuscript. All authors read and approved the final manuscript.

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PART 3: Effect of Personalized, Multimodal, Home-based Prehabilitation on Postoperative Complications after Surgery for Gastric Cancer: Results of a Randomized Clinical Trial

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Randomized Clinical Trial

Effect of home-based prehabilitation on postoperative complications after surgery for gastric cancer: randomized clinical trial

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Abstract

Background: Recent studies have demonstrated that prehabilitation improves patients' physical fitness but its impact on postoperative morbidity remains unclear. This study aimed to assess the effect of personalized, multimodal, semisupervised, home-based prehabilitation on postoperative complications after surgery for gastric cancer.

Methods: This RCT was conducted at two centres in Lithuania. Patients (aged at least18 years) with gastric cancer scheduled to undergo elective primary surgery or surgery after neoadjuvant chemotherapy for gastric cancer were randomized (1 : 1) to prehabilitation or standard care. Prehabilitation included exercise interventions focused on endurance, respiratory muscle strength, stretching, and resistance training as well as nutritional and psychological support. The primary outcome was the proportion of patients with postoperative complications within 90 days after surgery. Secondary outcomes included 90-day mortality rate, physical condition, fitness level, nutritional status, quality of life, anxiety and depression level, and proportion of patients completing neoadjuvant chemotherapy.

Results: Between February 2020 and September 2022, 128 participants were randomized to prehabilitation (64) or standard care (64), and 122 (prehabilitation 61, control 61) were analysed. The prehabilitation group had increased physical capacity before the operation compared with baseline (mean 6-min walk test change +31 (95 per cent c.i. 14 to 48) m; $P = 0.001$). The prehabilitation group had a decreased rate of non-compliance with neoadjuvant treatment (risk ratio (RR) 0.20, 95 per cent c.i. 0.20 to 0.56), a 60 per cent reduction in the number of patients with postoperative complications at 90 days after surgery (RR 0.40, 0.24 to 0.66), and improved quality of life compared with the control group.

Conclusion: Prehabilitation reduced morbidity in patients who underwent gastrectomy for gastric cancer.

Registration number: NCT04223401 (http://www.clinicaltrials.gov).

Introduction

Gastric cancer is the fifth most common cancer and the fourth deadliest worldwide, resulting in over 1 million new cases and approximately 769 000 deaths annually[1]. Surgery is the only potentially curative treatment for advanced gastric cancer[2]. However, postoperative morbidity and mortality are significant[2]. Current evidence supports the use of perioperative chemotherapy for advanced gastric cancer[3,4]. Although preoperative systemic cytotoxic treatment improves oncological outcomes, it also impairs patients' physical fitness, and may lead to malnutrition and sarcopenia thereby increasing surgical risk[5,6].

Prehabilitation focuses on patient optimization before major surgery, with the goal of reducing operative risks and enhancing subsequent recovery. Prehabilitation typically involves physiotherapy with or without nutritional and psychological support. Increasing evidence suggests that prehabilitation improves physical function in patients requiring major intra-abdominal cancer surgery[7–10], and may have a protective effect against postoperative complications in high-risk patients[8,11]. However, RCTs[9,10,12,13] have shown conflicting results, including studies of patients with gastric cancer[9,10].

To address this gap, an RCT was designed to investigate the impact of personalized, multimodal, semisupervised, home-based

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prehabilitation on 90-day postoperative morbidity in patients scheduled for elective gastric cancer surgery.

Methods

Study design

This open-label RCT was conducted at two major gastrointestinal cancer treatment centres in Lithuania: the National Cancer Institute and Vilnius University Hospital Santaros Klinikos. The study commenced after the protocol had received approval from the Vilnius University Regional Bioethics Committee (2020/1-1185-675). The study was registered at ClinicalTrials.gov (NCT04223401). This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975 and reported according to the CONSORT statement. The study protocol has been published previously[14]. All the patients provided written informed consent before participating in the study.

Participants

Patients aged 18 years or more who were scheduled to undergo elective gastric cancer surgery or surgery after neoadjuvant chemotherapy, as determined by multidisciplinary team (MDT) meetings at both study centres, were eligible for the study. Exclusion criteria were: surgery required for gastric cancer recurrence, patient condition that did not allow surgery to be postponed for at least 4 weeks, and inability to participate in the prehabilitation programme owing to the patient's physical or mental condition. Participants were screened for eligibility at the MDT and informed about the study by one of the investigators at the outpatient visit.

Randomization and masking

The study participants were assigned randomly to one of the two groups: standard preoperative care (control group) or standard preoperative care with prehabilitation (prehabilitation group). Allocation in a 1 : 1 ratio was determined by a computer-generated randomization schedule stratified by neoadjuvant treatment using random permuted blocks of 4 and 6. The randomization sequence was created using a free online tool (https://www.sealedenvelope.com/). The allocation designation was sequentially numbered and placed in opaque, sealed envelopes that were opened by the investigator at the time of randomization. Owing to the nature of the intervention, neither the participants nor personnel were blinded to the group allocation. The medical staff providing care for the patient were not actively informed about the allocation. Data collection and analyses were performed in a blinded manner with respect to the group allocation.

Intervention

All patients underwent a baseline assessment within 1 week of inclusion in the study, which included a physical performance examination and bicycle spiroergometry. Patients randomized to the prehabilitation group received a personalized, multimodal, semisupervised, home-based prehabilitation programme, which consisted of exercise, nutritional, and psychological support. For the exercise intervention, patients were evaluated by a physical medicine and rehabilitation physician and physiotherapist, and a personalized home-based exercise programme was developed based on the results of the physical performance examination and bicycle spiroergometry. The exercise programme included four types of exercise: endurance training for 10–30 min daily by walking, stair climbing, dancing, water exercises, or cycling, the type being determined by the patient's preference, with target intensity 40–65 per cent of heart rate reserve; respiratory muscle training for 5–10 min daily; resistance training to improve muscular strength for 10–20 min three times per week; and stretching exercises for 5–10 min three times per week. The daily training sessions did not exceed 60 min. Patients underwent three supervised training sessions to learn correct exercise techniques and self-control of the training intensity. Afterwards, each patient received a written exercise programme with a detailed description.

Nutritional support involved consultation with a physician nutrition specialist, with personalized recommendations for the prevention or correction of malnutrition. The energy and protein requirements were estimated at 25–30 kcal per kg and 1.5 g per kg ideal bodyweight respectively. If necessary, patients were prescribed oral nutritional supplements to increase the consumption of calories and protein. Finally, all patients received 250 ml oral nutritional supplements at least once a day (Nutridrink Protein®; Nutricia Advanced Medical Nutrition, part of the Danone company, Hoofddorp, the Netherlands) for 10 days before operation; these were donated by a local dealer.

Psychological support was provided by an oncopsychologist. Anxiety and depression were assessed by means of the Hospital Anxiety and Depression Scale (HADS) score, and patients were trained in relaxation techniques to reduce and manage anxiety at home.

The duration of the prehabilitation programme varied depending on the gastric cancer treatment pathway. Patients scheduled for upfront gastrectomy underwent prehabilitation for 4 weeks before surgery, and those who were scheduled for neoadjuvant chemotherapy received prehabilitation throughout the duration of neoadjuvant treatment and until the operation. To increase compliance, patients were asked to fill out a prehabilitation practice diary, and were routinely contacted and interviewed about adherence to interventions via telephone calls from study staff.

Patients in the control group did not receive advice on prehabilitation-related interventions, apart from some who were recommended to use high-energy nutritional supplements for 10–14 days before surgery.

Outcomes

The primary outcome of the study was the number of patients with at least one complication within 90 days after surgery. Complications were graded according to the Clavien–Dindo classification[15,16]. Secondary outcomes were: postoperative 90-day mortality rate; changes in physical condition, fitness level and nutritional status between baseline and preoperative time points; quality of life and anxiety and depression level; and proportion of patients who completed the full oncological treatment protocol at 12 months after treatment initiation (only proportion of patients completing neoadjuvant chemotherapy is reported in this article).

The impact of prehabilitation on physical condition and fitness level was determined by changes in: 6-min walk test (6-MWT)[17]; maximal oxygen consumption, anaerobic threshold (AT), forced vital capacity, and forced expiratory volume in the first second during bicycle spiroergometry; hand-grip strength[18]; 30-s sit-to-stand test[19]; 10-m sprint test[20]; and timed up-and-go test[21]. All patients were assessed by physical performance examination and bicycle spiroergometry at baseline and reassessed within 1 week before the operation.

The impact of prehabilitation on nutritional status and quality of life was determined by the change in serum albumin level, BMI,

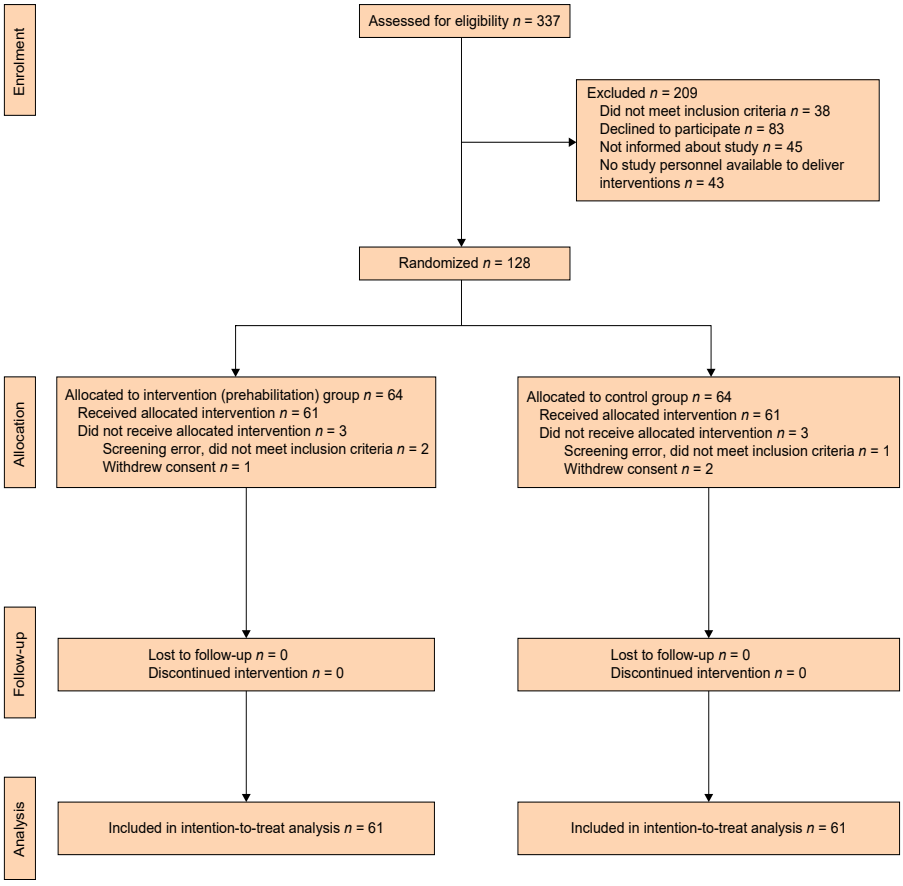

Fig. 1 Flow chart for the study

and scores on European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 and STO-22 respectively[22]. Anxiety and depression were determined using the HADS score[23]. Non-adherence with neoadjuvant chemotherapy was defined as any deviation from per-protocol treatment, including dose reduction, treatment interruption, and early discontinuation of treatment.

Statistical analysis

The sample size calculation was done using G*Power 3.1.9.4 software, with reduction in 90-day postoperative complication rates as the primary outcome. The percentage of patients developing postoperative complications after gastrectomy was estimated at 50 per cent for the control group, based on historical experience at the authors' centres and results from previous RCTs[24,25]. Based on the results of a recent RCT[8], a 50 per cent reduction in complications (to achieve a 25 per cent complication rate) was predicted for the prehabilitation group. Hence, a group sample size of 58 patients was needed to achieve 80 per cent power in detecting a difference with a two-sided level of significance of 5 per cent. Assuming a drop-out rate of up to 10 per cent, a total of 128 patients (64 per group) were needed to be enrolled in the study.

Continuous variables are presented as mean(s.d.) and categorical variables as numbers with percentages. Differences between the two groups were compared using χ^2 or Fisher's exact tests for categorical variables, and Student's *t* test or Mann–Whitney *U* test, depending on the distribution of the variables, for continuous data. Parameters representing physical condition, nutritional status, quality of life, and psychological status were compared between the baseline and preoperative time points in the study groups using a paired-samples *t* test. The intention-to-treat method was used and the analysis included all

Table 1 Baseline characteristics

	Prehabilitation ($n = 61$)	Control ($n = 61$)
Age (years), mean(s.d.)	61(11)	64(10)
Sex ratio (M : F)	35 : 26	42 : 19
BMI (kg/m^2), mean(s.d.)	25.5(5.4)	27.1(4.9)
Charlson Co-morbidity Index score		
≤ 5	48 (78.7)	49 (80.3)
> 5	13 (21.3)	12 (19.7)
Active smoker	13 (21.3)	11 (18.0)
Clinical disease stage		
I	5 (8.2)	5 (8.2)
II	33 (54.1)	34 (55.7)
III	18 (29.5)	19 (31.1)
IV	5 (8.2)	3 (5.0)
Scheduled for neoadjuvant chemotherapy	52 (85.2)	51 (83.6)
Received surgery	59 (96.7)	59 (96.7)
Type of surgery		
Total gastrectomy	21 (35.6)	20 (33.9)
Subtotal gastrectomy	33 (55.9)	31 (52.5)
Oesophagectomy	3 (5.1)	5 (8.5)
Palliative procedure	2 (3.4)	3 (5.1)
Surgical approach		
Open	38 (64.4)	40 (67.8)
Laparoscopic	20 (33.9)	17 (28.8)
Conversion	1 (1.7)	2 (3.4)
Multiorgan surgery	7 (11.9)	5 (8.5)
Duration of surgery (min), mean(s.d.)	198(95)	198(101)
No. of retrieved lymph nodes, mean(s.d.)	25(9)	29(11)
Completeness of resection		
R0	55 (93.2)	56 (94.9)
R1–2	4 (6.8)	3 (5.1)

Values are *n* (%) unless otherwise indicated.

patients who started the allocated intervention. Subgroup analyses for baseline characteristics (age, sex, neoadjuvant therapy, preoperative serum albumin level) and surgical approach (minimally invasive or open) were undertaken. For sensitivity analysis, the primary outcome was redefined as the mean comprehensive complication index (CCI) score[26] or the mean number of complications at 90 days after surgery. The listwise deletion method was used for missing data. All statistical analyses were conducted using SPSS® version 25.0 (IBM, Armonk, NY, USA).

Results

Patients

Between 6 February 2020 and 22 September 2022, 128 participants were randomized to prehabilitation (64) or control (64) groups. After randomization, three patients (5 per cent) in each group were excluded. Eventually, 122 participants (prehabilitation group 61, control group 61) were included in the intention-to-treat analysis (*Fig. 1*). *Table 1* shows patient and disease characteristics for the prehabilitation and control groups. All patients diagnosed with stage IV gastric cancer had positive peritoneal cytology and no evidence of other distant metastases.

Following the start of allocated interventions, two patients (3.3 per cent) in each group did not undergo the planned surgery and were therefore unable to undergo reassessment for secondary outcomes. In the prehabilitation group, one patient (1.6 per cent) died before surgery from a sudden cardiac arrest, and another patient (1.6 per cent) was deemed unfit for surgery because of a decline in physical status. In the control group, two patients (3.3 per cent) were unfit for surgery.

Prehabilitation and its impact on adherence to neoadjuvant treatment, physical condition, nutritional status, and quality of life

There were no adverse events related to the prehabilitation. The mean(s.d.) interval between the baseline assessment and surgery was 92(33) days in the prehabilitation group, and 90(54) days in the control group. Neoadjuvant chemotherapy was scheduled for 52 of 61 patients (85.2 per cent) and 51 of 61 patients (83.6 per cent) in the prehabilitation and control groups respectively ($P = 0.999$). Characteristics of neoadjuvant chemotherapy are shown in *Table S1*. The rate of non-adherence to the neoadjuvant treatment protocol was lower in the prehabilitation group (7.7 *versus* 37.3 per cent, $P = 0.001$; risk ratio (RR) 0.20, 95 per cent c.i. 0.20 to 0.56), including a lower proportion of patients requiring chemotherapy drug dose reduction (5.7 *versus* 23.5 per cent, $P = 0.012$; RR 0.24, 0.07 to 0.81) and early discontinuation of chemotherapy (1.9 *versus* 13.7 per cent, $P = 0.031$; RR 0.14, 0.01 to 1.09). Following premature discontinuation of chemotherapy, the patient in the prehabilitation group did not proceed with surgery, whereas all patients in the control group underwent operations as planned.

After the intervention, patients in the prehabilitation group demonstrated significant improvement in 6-MWT results, with an increase of 7.1 per cent (+31 (95 per cent c.i. 14 to 48) m; $P = 0.001$). They also showed a 13 (95 per cent c.i. 4 to 21)-point increase ($P = 0.005$) in EORTC QLQ-C30 global health status score and a 13 (2 to 24)-point increase ($P = 0.022$) in emotional functioning score. These patients also exhibited improvements in symptom scale scores (*Table S2*).

Table 2 Postoperative outcomes

	Prehabilitation (*n* = 59)	Control (*n* = 59)	P‡
Duration of hospital stay (days), mean(s.d.)	11(7)	13(9)	0.083§
No. of patients with 90-day postoperative complications	14 (23.7)	35 (59.3)	0.001
Severity of 90-day complications*			0.001
I	0 (0)	9 (15.3)	
II	4 (6.8)	16 (27.1)	
IIIa	8 (13.6)	6 (10.2)	
IIIb	0 (0)	1 (1.7)	
IVa	1 (1.7)	1 (1.7)	
IVb	0 (0)	0 (0)	
V	1 (1.7)	3 (5.1)	
CCI score, mean(s.d.)	7.8(17.1)	16.7(23.1)	0.019§
Type of complication			
Pulmonary	2 (3.4)	8 (13.6)	0.094
Infections of uncertain source	2 (3.4)	8 (13.6)	0.094
Wound infection	1 (1.7)	6 (10.2)	0.114
Anaemia requiring haemotransfusions	4 (6.8)	3 (5.1)	0.999
Anastomotic insufficiency	1 (1.7)	4 (6.8)	0.364
Postoperative bleeding	3 (5.1)	1 (1.7)	0.619
Intra-abdominal abscess	1 (1.7)	2 (3.4)	0.999
Pancreatitis or pancreatic fistula	2 (3.4)	1 (1.7)	0.999
Cardiovascular	1 (1.7)	2 (3.4)	0.999
Neurological	1 (1.7)	2 (3.4)	0.999
Nausea/vomiting	0 (0)	3 (5.1)	0.224
Duodenal stump leakage	1 (1.7)	1 (1.7)	0.999
Anastomotic stenosis	0 (0)	1 (1.7)	0.999
Urinary tract infections	0 (0)	1 (1.7)	0.999
Other†	0 (0)	8 (13.6)	0.006
90-day readmission rate	2 (3.4)	7 (11.9)	0.163

Values are *n* (%) unless otherwise indicated. *According to Clavien–Dindo classification. †Transverse colonic ischaemia requiring surgical intervention, lymphorrhoea, urinary retention, renal insufficiency, sudden cardiac arrest, and death. CCI, comprehensive complication index. ‡χ^2 or Fisher's exact test, except §Student's *t* test.

Postoperative outcomes

The 90-day postoperative morbidity rate was lower in the prehabilitation group than in the control group (23.7 *versus* 59.3 per cent; $P = 0.001$) (*Table 2*). Accordingly, the estimated RR showed that prehabilitation had a protective effect against 90-day postoperative complications (RR 0.40, 95 per cent c.i. 0.24 to 0.66). Complication severity analysis showed that minor complications (Clavien–Dindo grade I–II) were significantly less common in the prehabilitation group (6.8 *versus* 42.4 per cent, $P = 0.001$; RR 0.16, 0.05 to 0.43), but the rate of severe complications (Clavien–Dindo grade III or higher) was similar in the two groups (16.9 *versus* 18.6 per cent, $P = 0.810$; RR 0.90, 0.41 to 1.97). There was no statistically significant difference between the groups in duration of hospital stay, 90-day mortality, or 90-day readmission rates.

The sensitivity analysis showed that the mean(s.d.) CCI score was lower in the prehabilitation group than the control group (7.8(17.1) *versus* 16.7(23.1), $P = 0.019$; mean difference −8.8, 95 per cent c.i. −1.4 to −16.3) and this group had a lower mean number of 90-day postoperative complications (0.3(0.6) *versus* 0.9(1.4) respectively, $P = 0.006$; mean difference −0.57, −0.98 to −0.16). Subgroup analysis for the primary outcome, 90-day postoperative morbidity, is shown in *Fig. 2*.

Discussion

In this study, personalized, multimodal, semisupervised, home-based prehabilitation improved the physical status of the patient and led to a 60 per cent reduction in 90-day postoperative morbidity. Furthermore, prehabilitation improved adherence to neoadjuvant treatment protocols and enhanced the quality of life for patients with gastric cancer.

Evidence for the efficacy of prehabilitation before major abdominal surgery is controversial and has so far been insufficient to support widespread implementation. An RCT[8] demonstrated that personalized prehabilitation can reduce the rate of postoperative complications by 51 per cent after abdominal surgery . However, that study included only high-risk patients (aged over 70 years and/or ASA fitness grade III–IV and Duke Activity Status Index score 46 or less), some of whom had

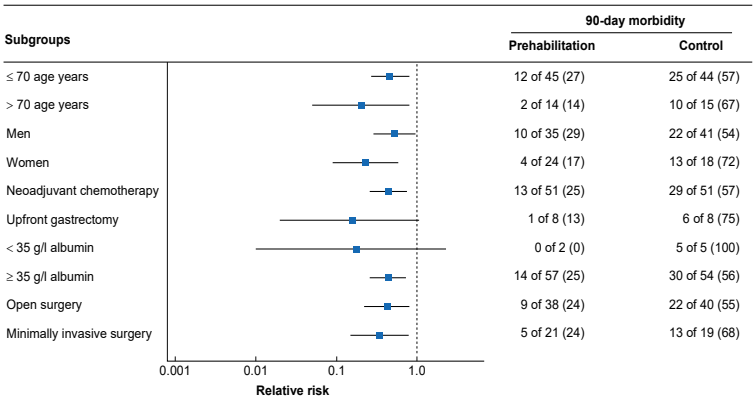

Fig. 2 Subgroup analysis of effect of prehabilitation on 90-day postoperative complication rate

Values in parentheses are percentages.

benign pathology. An RCT by Carli *et al.*[12] did not show a reduction in postoperative morbidity in frail patients undergoing colorectal cancer surgery. Recent systematic[27] and narrative[28] reviews focusing on prehabilitation in patients with oesophagogastric cancer were inconclusive because of the heterogeneity of included studies, small sample sizes, and a limited number of RCTs. The two largest available RCTs[9,10] investigating multimodal prehabilitation before oesophagogastric resections demonstrated its positive effect on patients' physical fitness, but failed to show its impact on the number and severity of postoperative complications. Minella *et al.*[10] demonstrated that multimodal prehabilitation increased patients' functional capacity, measured as the distance covered in a 6-MWT, by a mean(s.d.) of 36.9(51.4) m. A comparable improvement was observed in the present study, where prehabilitation increased 6-MWT results by +31 (95 per cent c.i. 14 to 48) m ($P = 0.001$). This increase was clinically significant, as previous studies have shown that every additional 20-m improvement is associated with a reduced risk of postoperative complications after abdominal cancer resections[29]. However, previous RCTs[9,10] were designed primarily to assess physical fitness outcomes and did not provide information on postoperative morbidity. The present RCT has shown a relationship between prehabilitation-induced improvement in patients' functional capacity and reduced 90-day morbidity. Prehabilitation had no effect on the AT, and this parameter declined from baseline to the preoperative phase in both groups. The decrease in AT was anticipated in the control group as the majority of participants received neoadjuvant chemotherapy which is known to reduce AT[30]. However, prehabilitation used in the present study lacked efficacy in mitigating this decline, suggesting the need for alternative exercise interventions. Furthermore, a previous RCT[9] that investigated a multimodal prehabilitation approach, encompassing aerobic, resistance, and flexibility training, also failed to demonstrate efficacy in preventing the decline in AT.

Sensitivity analyses confirmed the effect of prehabilitation on intrahospital morbidity and its beneficial role in reducing the mean number of postoperative complications at 90 days. Subgroup analyses also confirmed the effectiveness of prehabilitation across the subgroups including both sexes, elderly patients aged over 70 years, and those undergoing neoadjuvant chemotherapy and minimally invasive surgery. Although specific types of complication that could be prevented by prehabilitation could not be identified, the rate of minor (Clavien–Dindo below III) rather than major (Clavien–Dindo III or higher) complications was reduced.

Currently, perioperative FLOT (Fluorouracil; Folinic acid; Oxaliplatin, and Docetaxel) chemotherapy is the recommended treatment for advanced gastric cancer[4]. However, about 10 per cent of patients are unable to complete all cycles of neoadjuvant treatment owing to side-effects or intolerance[4]. In the present study, the majority of patients in both groups (over 80 per cent) started treatment with neoadjuvant chemotherapy and the discontinuation rate in the control group (13.7 per cent) was similar to that described in the literature. Such non-compliance with neoadjuvant treatment can be a serious issue, leading to inferior oncological outcomes. To mitigate the side-effects of radical cancer treatment, physical activity, including aerobic and resistance exercise, is recommended by the American Society of Clinical Oncology guidelines[31]. Prehabilitation, in the form of resistance training, has been shown to increase neoadjuvant chemotherapy completion rates in patients with breast cancer[32], and multimodal prehabilitation to increase adherence to neoadjuvant treatment for oesophagogastric cancer[9]. The present study has confirmed that a personalized, home-based, trimodal prehabilitation programme not only reduces the proportion of patients who discontinue neoadjuvant chemotherapy but also decreases the proportion of patients needing a drug dose reduction. Other benefits of multimodal prehabilitation demonstrated in this study were that it improved global health status, emotional functioning, and alleviated some symptoms, including appetite loss, pain, and anxiety. Similar positive effects of prehabilitation on the quality of life of patients with oesophagogastric cancer have been observed in previous studies[9,33–35]. However, unlike those in most other studies, the prehabilitation programme described here included psychological intervention and used HADS scores to demonstrate its effectiveness.

It is important to consider the cost-effectiveness of novel interventions alongside their established effectiveness[36]. Multimodal and supervised programmes may be the most effective approaches as they address the various challenges commonly faced by patients with gastric cancer, encompassing physical, nutritional, and psychological aspects[28]. However, such programmes can place significant demands on financial and healthcare professional resources. Additionally, logistical challenges may hinder patient participation. Semisupervised prehabilitation may serve as an excellent alternative to fully supervised programmes, as demonstrated in the present study, where it effectively reduced morbidity after gastric cancer surgery. Furthermore, in the present study, the intervention required only up to 8 h of healthcare professional input per patient, making the associated financial burden potentially more acceptable.

The present study has several strengths including the multimodal and personalized prehabilitation programme undertaken in patients' homes. This has been emphasized in a systematic review by Thomas *et al.*[37]. Home-based interventions allow greater patient participation, avoid frequent visits to healthcare facilities, and are generally preferred by patients[28]. The study results were robust, as the results of sensitivity and subgroup analyses were consistent with those of the primary intention-to-treat approach. There were no missing data for the primary outcome of postoperative complications. A limitation is the observed low participation rate of patients who met the inclusion criteria (43 per cent). Factors contributing to this were patient refusal, and insufficient staff for patient recruitment and delivery of the intervention as the study was carried out during the COVID-19 pandemic. Blinding of participants was not possible and there was a risk of contamination in the control group. Although participants in the prehabilitation group received routine telephone calls and interviews to monitor adherence to interventions, the study lacked objective tools for measuring adherence, which may have resulted in an overestimation of compliance with the programme. Finally, the majority of patients in the prehabilitation group received neoadjuvant chemotherapy, which extended the duration of prehabilitation to a mean of 92 days. It is unclear whether a shorter intervention would have been effective, especially in patients undergoing upfront surgery.

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Authors contributions

Augustinas Bausys (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing—original draft, Writing—review & editing), Martynas Luksta (Conceptualization, Investigation, Writing—review & editing), Giedre Anglickiene (Investigation, Writing—review & editing), Vyte V. Maneikiene (Investigation, Writing—review & editing), Marius Kryzauskas (Investigation, Writing—review & editing), Andrius Rybakovas (Investigation, Writing—review & editing), Audrius Dulskas (Investigation, Writing—review & editing), Justas Kuliavas (Investigation, Writing—review & editing), Eugenijus Stratilatovas (Investigation, Writing—review & editing), Lina Macijauskiene (Investigation, Writing—review & editing), Toma Simbelyte (Investigation, Writing—review & editing), Jelena Celutkiene (Conceptualization, Investigation, Writing—review & editing), Ieva E. Jamontaite (Investigation, Writing—review & editing), Alma Cirtautas (Investigation, Writing—review & editing), Svetlana Lenickiene (Conceptualization, Investigation, Writing—review & editing), Dalia Petrauskiene (Conceptualization, Investigation, Writing—review & editing), Evelina Cikanaviciute (Investigation, Writing—review & editing), Edita Gaveliene (Investigation, Writing—review & editing), Gertruda Klimaviciute (Conceptualization, Investigation, Writing—review & editing), Kornelija Rauduvyte (Investigation, Writing—review & editing), Rimantas Bausys (Conceptualization, Investigation, Writing—review & editing), and Kestutis Strupas (Conceptualization, Investigation, Writing—original draft, Writing—review & editing).

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The data sets generated and/or analysed during this study are not publicly available, but are available from the corresponding author upon reasonable request.

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CHAPTER 3: NEOADJUVANT CHEMOTHERAPY IMPACT ON HISTOLOGIC LYMPH NODE REGRESSION AND OPTIMAL TIME FOR SURGERY AFTER IT

PART 1: Histologic Lymph Nodes Regression after Preoperative Chemotherapy as Prognostic Factor in Non-metastatic Advanced Gastric Adenocarcinoma

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Research Paper

Histologic Lymph Nodes Regression after Preoperative Chemotherapy as Prognostic Factor in Non-metastatic Advanced Gastric Adenocarcinoma

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Abstract

Background: The study aims to evaluate the lymph node (LN) response to preoperative chemotherapy and its impact on long-term outcomes in advanced gastric cancer (AGC).

Methods: Histological specimens retrieved at gastrectomy from patients who received preoperative chemotherapy were evaluated. LN regression was graded by the adapted tumor regression grading system proposed by Becker. Patients were classified as node-negative (lnNEG) in the case of all negative LN without evidence of previous tumor involvement. Patients with LN metastasis were classified as nodal responders (lnR) in case of a regression score 1a-2 was detected in the LN. Nodal non-responders (lnNR) had a regression score of 3 in all of the metastatic nodes. Survival was compared using Kaplan-Meier and Cox regression analysis.

Results: Among 87 patients included in the final analysis 29.9 % were lnNEG, 21.8 % were lnR and 48.3 % were lnNR. Kaplan-Meier curves showed a survival benefit for lnR over lnNR (p=0.03), while the survival of lnR and lnNEG patients was similar. Cox regression confirmed nodal response to be associated with decreased odds for death in univariate (HR: 0.33; 95 % CI 0.11-0.96, p=0.04) and multivariable (HR 0.37; 95 CI% 0.14-0.99, p=0.04) analysis.

Conclusions: Histologic regression of LN metastasis after preoperative chemotherapy predicts the increased survival of patients with non-metastatic resectable AGC.

Key words: gastric cancer; preoperative chemotherapy; histological regression; nodal regression.

Introduction

Perioperative chemotherapy is the standard for resectable non-metastatic advanced gastric cancer (AGC) after large scale randomized control trials demonstrated an advantage over the surgery-first approach [1,2]. The justification for preoperative chemotherapy is the reduction of the primary tumor size, increased rates of R0 resection, and the treatment of occult micrometastasis which all translates to increased survival [3]. Although preoperative chemotherapy has been widely introduced into clinical practice guidelines, the discussion, whether current regimens are truly effective, is still ongoing [3,4]. Significant histologic tumor regression following chemotherapy where fibrosis becomes

predominant over tumor cells is observed in only about 17-50 % of patients [5–7]. The histologic tumor regression grading (TRG) system for gastric adenocarcinoma was proposed by Becker et al. [8] and it is based on an estimation of the percentage of vital tumor tissue in relation to the macroscopically identifiable tumor bed [8]. TRG and postoperative lymph node (LN) status are the two major prognostic factors for AGC patients' survival [5–7,9]. TRG system by Becker as well as others evaluate histologic regression within the primary tumor, but not in LN metastases [10]. Current evidence suggests histologic nodal regression after preoperative cytotoxic treatment results in improved survival of patients with rectal and esophageal cancers [11–14]. However, there is a lack of data on pathologic LN regression after preoperative chemotherapy and its impact on long-term outcomes in AGC, which is typically accompanied by LN metastasis.

Therefore, this study was designed to evaluate histologic LN regression in AGC after preoperative chemotherapy and its impact on survival.

Materials and Methods

Ethics

Vilnius regional biomedical research ethics committee approval was obtained before this study was conducted. All study-related procedures were performed in accordance with the Declaration of Helsinki of 1975, as revised in 1983.

Patients

The cohort study was conducted at two major gastrointestinal cancer treatment centers of Lithuania: National Cancer Institute, Vilnius, Lithuania, and Vilnius University hospital Santara Clinics, Vilnius, Lithuania. All patients who underwent preoperative chemotherapy between 2014 January and 2018 December followed by surgery for advanced gastric or gastroesophageal junction adenocarcinoma were included in the study. Patients with distant metastasis revealed during gastrectomy or those with R1/2 resection were excluded from further enrolment. The primary aim of the study was to evaluate the rate of histologic regression of LN metastasis after preoperative chemotherapy and its impact on overall survival (OS). The secondary aims included the nodal response impact on disease-free survival (DFS), the rate of primary tumor regression, and its association with nodal regression.

Diagnosis and treatment

The diagnosis was confirmed by esophagogastroduodenoscopy with biopsy in all patients. The staging consisted of the chest and abdominal CT and diagnostic laparoscopy with peritoneal lavage. All patients were discussed in a multidisciplinary team meeting and those with the non-metastatic ≥cT2N0 disease were considered for perioperative chemotherapy. Patients eligible according to physical status and comorbidities underwent preoperative chemotherapy where the exact regimen for the exact patient was selected by a medical oncologist. After preoperative chemotherapy was completed patients underwent a CT scan and were scheduled for elective surgery. The extent of surgery depended on tumor localization and all patients underwent open surgery. Subtotal gastrectomy was performed when a sufficient proximal resection margin could be ensured; otherwise open total gastrectomy was performed. The standard lymphadenectomy was a D2 lymph node dissection performed as described in the 4th version of Japanese gastric cancer treatment guidelines [15]. Patients were scheduled to continue perioperative chemotherapy after they recovered from surgery.

Pathological evaluation

The pathological evaluation was performed at the National Center of Pathology, Vilnius, Lithuania. Final tumor histology was provided ypTNM and staged according to the American Joint Committee on Cancer Staging, 8th edition. The histological type of tumors was classified according to the WHO Classification of Tumors of the Digestive Tract (2010) and Lauren classification of gastric carcinoma. Regional lymph nodes were macroscopically identified in surgical specimens. All lymph nodes were longitudinally sectioned through the hilus and embedded into paraffin blocks. All slides were stained with hematoxylin-eosin, additional immunostaining was performed if necessary. For the study, all slides were recalled from the institutional archive. They were reviewed by the senior pathologist trainee and experienced gastrointestinal pathologists to evaluate histologic regression grade after preoperative chemotherapy in the primary tumor and metastatic lymph nodes. Regression in the tumor was graded as described by Becker et al. [8]. For nodal regression, we adapted the same grading system. Histological signs of regression in the primary tumor and metastatic lymph nodes were similar and included: areas of fibrosis, necrosis, calcifications, acellular mucin pools, cholesterol deposits, and histiocytic reaction with hemosiderin-laden and foamy macrophages (Figure 1). Regression was graded: Grade 1, complete (0% residual tumor; Grade 1a) or subtotal tumor regression (<10% residual tumor per tumor bed; Grade 1b); Grade 2, partial tumor regression (10–50% residual tumor per tumor bed),

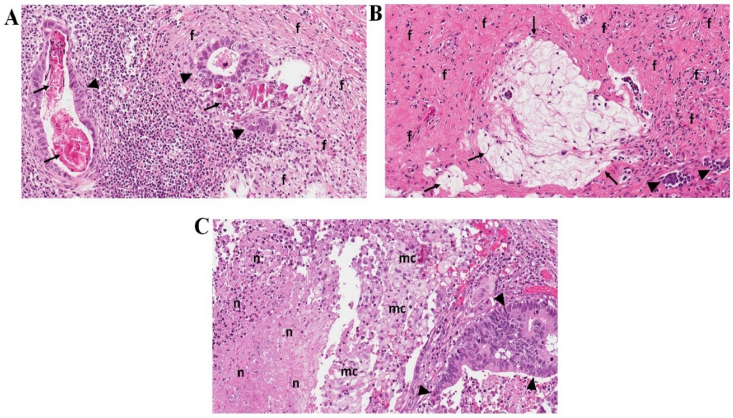

Figure 1. Representative pictures of lymph nodes presenting signs of histological regression (Haematoxylin-eosin staining; original magnification 20x). **A** - Lymph node with residual carcinoma (▲), foci of fibrosis (**f**) and calcifications (!); **B** - Lymph node with few residual carcinoma aggregates (▲), fibrosis (**f**), and acellular mucin pools (!); **C** - Lymph node with residual carcinoma (▲), foamy macrophages (**mc**), and areas of necrosis (**n**).

and Grade 3, minimal or no tumor regression (>50% residual tumor per tumor bed). Lymph nodes without metastasis or signs of nodal regression were classified as negative nodes.

For the purpose of the study, patients were grouped according to the regression scores recorded in the lymph nodes. Patients who had all negative nodes were allocated to the node-negative (lnNEG) group. Patients with a regression score of 1a-2 detected in at least some of the retrieved metastatic nodes were categorized as nodal responders (lnR). Non-responders (lnNR) had a score of 3 in all metastatic LN.

Follow-up

Esophagogastroduodenoscopy and CT were performed twice a year for the first two years and then annually. If patients underwent follow up visits outside of the original study institutions, data was still obtained directly from the patient or their physicians by phone interview. The date of death was obtained from Lithuania's Cancer register - a nationwide and population-based cancer registry, which covers all territory of Lithuania. The last follow-up data on death and recurrence were collected on the 1st of November, 2019.

Statistical analysis

All statistical analyses were conducted using the statistical program SPSS 24.0 (SPSS, Chicago, IL, USA). Continuous variables are presented as the mean ± standard deviation or median with interquartile range and were compared across groups using the one-way ANOVA or Kruskal-Wallis test as appropriate. Categorical variables are shown as proportions and were compared using the $\chi 2$ test or Fisher exact test, as appropriate.

Overall and disease-free survival rates were analyzed by the Kaplan–Meier method and were compared by the log-rank test. Overall survival was defined as the time from the first cycle of preoperative chemotherapy to death. Disease-free survival was defined as the time from the first cycle of chemotherapy to the locoregional or distant recurrence of the disease or death. To identify the prognostic significance of variables for long-term outcomes univariate Cox regression was performed and the results were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Those variables which resulted significantly in the univariate setting were inserted into a multivariable model and were adjusted for patients' age and comorbidities. In all statistical analyses, two-tailed tests were used and a p-value of <0.05 was considered to be significant.

Results

Patients and chemotherapy

Among 101 patients identified in the database 14 (10.8 %) were excluded because of metastatic disease revealed on gastrectomy or non-radical surgery. Eighty-seven patients were included in the final analysis. After histological re-examination 26 (29.9 %) were categorized as lnNEG patients while 61 (70.1 %) had LN metastasis or signs of complete histological regression. Of 61 node-positive patients, 19 (21.8 %)

were nodal responders (lnR) and 42 (48.3 %) were non-responders (lnNR) (Figure 2). The baseline clinicopathological characteristics of these patients are shown in table 1.

The vast majority (83/87; 95.4 %) of patients successfully underwent a full preoperative chemotherapy protocol. In contrast, significantly lower proportion of these received chemotherapy postoperatively (64/87; 72.4 %, p=0.01). The regimens of chemotherapy were not different between the study groups (Table 2).

Histologic regression

The median number of retrieved lymph nodes was 30 (23; 39) and 2782 lymph nodes were examined in total. Twenty-six patients in the lnNEG group had 737 nodes without metastasis or signs of regression. Within the lnNR group, 1426 lymph nodes were examined, and 342 (23.9 %) of them were metastatic, although none had a significant regression (regression score 3). Nineteen patients from the lnR group presented 619 lymph nodes of which 116 (18.7 %) were metastatic. Nodal regression by score 1a-2 was observed in 58 (50.0 %) nodes. Nine (47.3 %) of 19 lnR patients had a regression in all the metastatic lymph nodes including 3 (15.7 %) patients with a complete regression (score 1a) in all the metastatic LN and downstaging to ypN0. Ten (52.6 %) patients had a significant regression only in some of the metastatic nodes (Table 3).

Table 1. Baseline clinicopathologic characteristics of the study patients.

		Positive nodes		Negative nodes	
		lnNR (n=42)	lnR (n=19)	lnNEG (n=26)	p value
Age (years)		58.0±10.3	59.4±9.1	59.7±12.0	0.79
Sex	Male	27 (64.3 %)	15 (78.9 %)	14 (53.8 %)	0.22
	Female	15 (35.7 %)	4 (21.1 %)	12 (46.2 %)	
Tumor invasion (ypT)	1-2	9 (21.4 %)	5 (26.3 %)	14 (53.8 %)	0.01
	3-4	33 (78.6 %)	14 (73.7 %)	12 (46.2 %)	
TRG in primary tumor site	1a-2	9 (21.4 %)	8 (42.1 %)	10 (38.5 %)	0.168
	3	33 (78.6 %)	11 (57.9 %)	16 (61.5 %)	
Lymph node metastasis (ypN)	0	0 (0 %)	3 (15.8 %)	26 (100 %)	0.01
	1	12 (28.6 %)	7 (36.8 %)	0 (0 %)	
	2	12 (28.6 %)	5 (26.3 %)	0 (0 %)	
	3	18 (42.8 %)	4 (21.1 %)	0 (0 %)	
Tumor differentiation	G1	0 (0 %)	0 (0 %)	1 (3.8 %)	0.01
	G2	3 (7.1 %)	5 (26.3 %)	10 (38.5 %)	
	G3	39 (92.9 %)	14 (73.7 %)	15 (57.7 %)	
Lauren	Intestinal/Mix	15 (39.5 %)	10 (66.7 %)	13 (59.1 %)	0.13
	Diffuse	23 (60.5 %)	5 (33.3 %)	9 (40.9 %)	
Signet ring cells component	Negative	27 (64.3 %)	17 (89.5 %)	22 (84.6 %)	0.04
	Positive	15 (35.7 %)	2 (10.5 %)	4 (15.4 %)	
Tumor localization	Upper third	10 (23.8 %)	4 (21.0 %)	7 (26.9 %)	0.38
	Middle third	24 (57.2 %)	9 (47.4 %)	9 (34.6 %)	
	Lower third	8 (19.0 %)	6 (31.6 %)	10 (38.5 %)	
Lymphovascular invasion	No	16 (39.0 %)	7 (38.9 %)	23 (88.5 %)	0.01
	Yes	25 (61.0 %)	11 (61.1 %)	3 (11.5 %)	
Surgery	Total gastrectomy	31 (73.8 %)	9 (47.4 %)	13 (50 %)	0.05
	Subtotal gastrectomy	11 (26.2 %)	10 (52.6 %)	13 (50 %)	
CCI	1-3	22 (52.4 %)	11 (57.9 %)	9 (34.6 %)	0.23
	≥4	20 (57.6 %)	8 (42.1 %)	17 (65.4 %)	

CCI: Charlson Comorbidity Index; lnNR: lymph node non-responders; lnR: lymph node responders; lnNEG: lymph node-negative; TRG: tumor regression grade (by Becker).

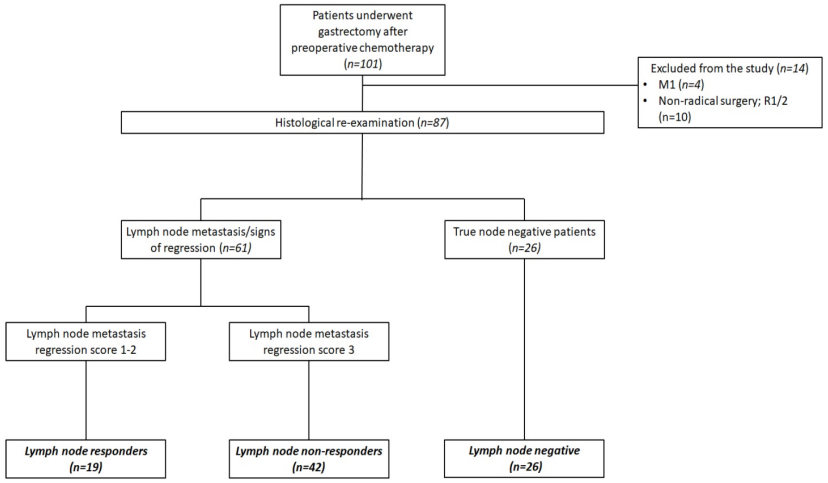

Figure 2. Flowchart of the study patients.

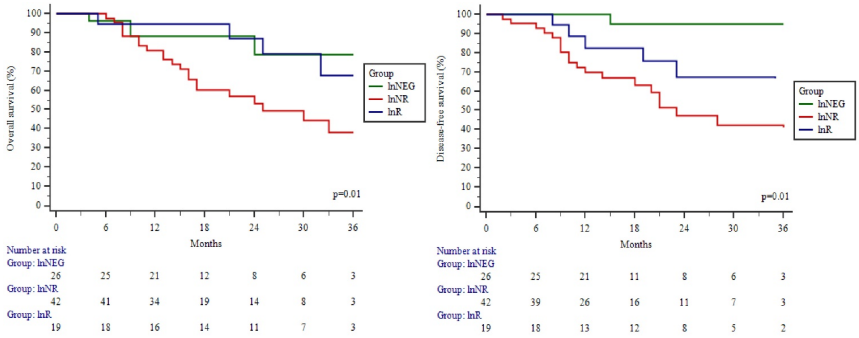

Figure 3. Overall and disease-free survival of the study patients by Kaplan-Meier analysis. Overall **(A)** and disease-free survival **(B)** of patients in different study groups. lnNEG: lymph nodes-negative; lnR: lymph nodes responder; lnNR: lymph nodes non-responder.

Table 2. Preoperative chemotherapy regimens in different study groups.

Chemotherapy regimen	Positive nodes		Negative nodes	
	lnNR (n=42)	lnR (n=19)	lnNEG (n=26)	p value
CF	25 (59.5 %)	10 (52.6 %)	18 (69.2 %)	0.60
ECX/EOX	9 (21.5 %)	6 (31.6 %)	3 (11.5 %)	
FLOT	8 (19.0 %)	3 (15.8 %)	5 (19.3 %)	

lnNR: lymph node non-responders; lnR: lymph node responders; lnNEG: lymph node-negative; CF: cisplatin/5-fluorouracil doublet; ECX: epirubicin, cisplatin, capecitabine; EOX: epirubicin, oxaliplatin, capecitabine; FLOT: fluorouracil, folinic acid, oxaliplatin and docetaxel.

Significant histological regression of the primary tumor by TRG1a-2 was observed in 27 (31.0 %) patients. Although, regression in a primary tumor was not associated with a nodal regression (p=0.168) as shown in table 1. Interestingly, even 11 (57.9 %) of lnR did not show a significant regression in the primary tumor. Overall, the preoperative chemotherapy effect by tumor or/and nodal regression score of 1a-2 was observed in only 38 (43.7 %) of 87 patients.

Survival

The overall and disease-free 3-year survival rate for the study cohort was 54.3 % and 51.3 % respectively. Significant differences were observed between the OS and DFS curves in different study groups (Figure 3A; 3B). The highest OS and DFS were in the lnNEG group, while lowest in the lnNR group. The differences between these groups were significant in terms of OS (p=0.01) and DFS (p=0.01). OS of nodal responders (lnR) was similar as patients without nodal metastasis (lnNEG; p=0.97) and significantly (p=0.03) higher compared to nodal non-responders (lnNR). Although, the difference between lnR and lnNR failed to be significant in terms of DFS (p=0.29). Univariate Cox regression showed lower odds for death in patients with a lnR (HR (95 % CI): 0.33 (0.113-0.967) (Table 4) and a significant benefit of lymph node response was confirmed by a subsequent multivariable analysis (Table 5).

Recurrence of disease was observed in 27 (31.0 %) patients. Peritoneal dissemination included 17 (19.5 %) cases, nodal recurrence 7 (8 %) cases and distant metastasis - 3 (3.4 %) cases. Nodal recurrence rate in the lnNR group (11.9 %) was notably higher compared to lnR (5.3 %) or lnNEG (3.8 %) groups, although differences failed to be significant.

Discussion

This study investigated the histologic regression of LN metastasis after preoperative chemotherapy for AGC. The results of the study demonstrated the nodal response to chemotherapy as a valuable prognostication tool to predict the survival of AGC patients.

The prognosis of resectable AGC remains unsatisfactory, although, it is very different between patients with or without LN metastasis [16–18]. The node-positive patients account for the majority of AGC cases and their prognosis is significantly impaired [18–20]. However, our study nicely demonstrated a better prognosis for those who achieved a significant histologic nodal regression after preoperative chemotherapy. The OS of lnR was significantly better compared to lnNR as showed by Kaplan-Meier and Cox regression analysis. Further, the OS of lnR was not different from true node-negative patients, despite the fact, that 50.0 % of nodal responders had significant histological regression in not all the metastatic nodes. We failed to show the same impact on the DFS, although, the tendency was clearly similar, and the relatively small sample size might be responsible for the lack of significance.

Table 3. Lymph node regression score in nodal responders' group.

No.	Gender, age	Chemotherapy regimen	Surgery	No. of retrieved LN	No. of metastatic LN's	No. of lymph nodes with regression grade score				Tumor regression grade
						1a	1b	2	3	
1.	F, 55	CF	Gastrectomy	23	2	*1*	*1*			TRG1a
2.	M, 80	EOX	Subtotal gastrectomy	27	13	*1*		*1*	*11*	TRG3
3.	M, 57	CF	Gastrectomy	29	5	*4*	*1*			TRG1b
4.	M, 70	CF	Subtotal gastrectomy	25	2	*1*		*1*		TRG3
5.	M, 53	EOX	Subtotal gastrectomy	34	2		*1*		*1*	TRG2
6.	M, 49	FLOT	Gastrectomy	31	1	*1*				TRG2
7.	F, 63	CF	Subtotal gastrectomy	25	7	*1*	*1*		*5*	TRG3
8.	M, 63	CF	Gastrectomy	40	4	*1*			*3*	TRG3
9.	M, 72	CF	Gastrectomy	26	1			*1*		TRG3
10.	M, 59	CF	Subtotal gastrectomy	36	20			*3*	*17*	TRG3
11.	M, 55	ECX	Subtotal gastrectomy	26	5		*2*	*1*	*2*	TRG3
12.	M, 68	FLOT	Subtotal gastrectomy	34	1			*1*		TRG1b
13.	M, 62	FLOT	Subtotal gastrectomy	34	8	*4*		*1*	*3*	TRG3
14.	M, 57	CF	Subtotal gastrectomy	56	8			*2*	*6*	TRG2
15.	F, 65	EOX	Gastrectomy	38	9	*9*				TRG2
16.	M, 58	CF	Gastrectomy	54	13	*13*				TRG3
17.	M, 57	ECX	Subtotal gastrectomy	18	6		*1*	*2*	*3*	TRG3
18.	F, 41	EOX	Gastrectomy	44	1			*1*		TRG2
19.	M, 46	CF	Gastrectomy	19	8			*1*	*7*	TRG3
In total:						36	*7*	*15*	*58*	

LN; lymph nodes; M: male; F: female; CF: cisplatin/5-fluorouracil doublet; ECX: epirubicin, cisplatin, capecitabine; EOX: epirubicin, oxaliplatin, capecitabine; FLOT: fluorouracil, folinic acid, oxaliplatin, and docetaxel; TRG: tumor regression grade (by Becker).

Table 4. Univariate Cox regression analysis for overall and disease-free survival.

		Death		*Recurrence of disease*	
		HR (95% CI)	*p*	*HR (95% CI)*	*p*
Age (years)		1.02 (0.98-1.06)	0.22	1.00 (0.96-1.03)	0.93
Lymph node response	lnNR	1.00 (reference)		1.00 (reference)	
	lnR	0.33 (0.11-0.96)	0.04	0.63 (0.26-1.51)	0.63
	lnNEG	0.30 (0.10-0.88)	0.02	0.06 (0.01-0.51)	0.01
Sex	Male	1.00 (reference)		1.00 (reference)	
	Female	1.09 (0.51-2.31)	0.81	0.65 (0.28-1.48)	0.30
Tumor invasion (ypT)	1-2	1.00 (reference)		1.00 (reference)	
	3-4	1.42 (0.63-3.22)	0.39	3.46 (1.19-9.99)	0.02
TRG in primary tumor site	1a-2	1.00 (reference)		1.00 (reference)	
	3	2.06 (0.84-5.09)	0.11	1.70 (0.72-4.01)	0.22
Lymph node metastasis (ypN)	N0	1.00 (reference)		1.00 (reference)	
	N+	2.28 (0.87-6.00)	0.09	7.12 (1.69-30.05)	0.01
Tumor differentiation	G1-2	1.00 (reference)		1.00 (reference)	
	G3	3.29 (0.99-10.92)	0.05	2.24 (0.77-6.49)	0.13
Lauren	Intestinal/Mix	1.00 (reference)		1.00 (reference)	
	Diffuse	1.59 (0.74-3.40)	0.23	1.84 (0.80-4.21)	0.14
Signet ring cells component	Negative	1.00 (reference)		1.00 (reference)	
	Positive	1.97 (0.91-4.26)	0.08	2.07 (0.94-4.55)	0.06
Tumor localization	Upper/middle third	1.00 (reference)		1.00 (reference)	
	Lower third	0.22 (0.08-0.68)	0.01	0.69 (0.32-1.48)	0.35
Lymphovasular invasion	No	1.00 (reference)		1.00 (reference)	
	Yes	1.56 (0.73-3.30)	0.24	2.84 (1.28-6.31)	0.01
CCI	1-3	1.00 (reference)		1.00 (reference)	
	≥4	1.04 (0.50-2.16)	0.91	0.57 (0.26-1.23)	0.15

lnNR: lymph node non-responders; lnR: lymph node responders; TRG: tumor regression grade; LV: lymphovascular invasion; CCI: Charlson Comorbidity Index.

The present study showed that only 31.1 % of node-positive patients are nodal responders and only 43.7 % of patients show a significant regression in LN or/and tumor. A similarly low rate of 29.4 % of nodal response has been documented in the previous study comparing histological regression after preoperative chemotherapy or chemoradiotherapy [21]. This calls into question the effectiveness of preoperative chemotherapy, despite it being rapidly introduced into clinical practice guidelines after MAGIC [1] and FNCLCC-FFCD [2] trials. Moreover, there is still insufficient evidence if preoperative chemotherapy is beneficial for patients who received an appropriate D2 lymphadenectomy [3,4,22]. Although, our study does not provide evidence against the concept because we could not exclude the potential benefit of preoperative chemotherapy on micrometastasis and an increased rate of R0 resection [23]. Another potential benefit of chemotherapy preoperatively is the high rate of treatment compliance. Our results confirmed it by showing successful completion of preoperative chemotherapy in >90 % of patients

compared to 72.4 % of patients receiving chemotherapy postoperatively. Such results are consistent with previous reports documenting compliance of about 70 % for AGC patients receiving chemotherapy in the adjuvant setting [24,25]. Therefore, it is clear, that preoperatively chemotherapy can be successfully utilized for a higher proportion of patients compared to postoperatively. On the other hand, nearly 15 % of patients receiving preoperative chemotherapy show the risk of disease progression at the time of preoperative treatment [26]. Therefore, the ideal clinical model would let clinicians identify those non-responders before the start of the treatment. A series of studies investigated novel biomarkers to predict the response to preoperative chemotherapy [27–33]. However, they are still not validated and widely used. Moreover, all of the current studies correlated biomarkers with a regression only in a primary tumor site [27–33]. Since our study demonstrated the importance of histological nodal regression, which is not always associated with a response in a primary tumor, current biomarkers may lack the accuracy to predict the real regression of the disease. Therefore, further studies investigating biomarkers for response prediction should test if novel tools can predict the nodal response too.

Several different chemotherapy regimens have been used in our study, without significant differences in nodal response. Although, due to the relatively small sample size this data should be interpreted cautiously. A recent randomized control trial demonstrated FLOT as the new gold standard for perioperative chemotherapy due to an increased rate of major histological regression of the tumor and improved survival [34,35]. Unfortunately, histological analysis of FLOT4-AIO trial did not include the nodal regression [34]. Therefore, it remains unclear if some of the available preoperative chemotherapy regimens may increase the rate of nodal response.

Various grading systems for different gastrointestinal cancers have the same aim to categorize the number of regressive changes following preoperative cytotoxic treatment and to provide prognostic information [36]. The grading system for advanced gastric cancer proposed by Becker et al. [8] was subsequently confirmed to provide highly valuable prognostic information [9]. Although, this system as all other refers to the regression only in the primary tumor site but not in the LN [36]. This study demonstrated the same system of Becker can be applied to evaluate the nodal regression and it provides even more accurate prognostic information. Therefore, we suggest that Becker system should be adapted to evaluate the histological regression not only in the primary tumor but also in the LN and this information should be implemented to routine pathological reports.

The role of nodal regression following preoperative chemo-/chemoradio- therapy to provide strong prognostic information has been already confirmed in oesophageal adenocarcinoma [11] and rectal cancer [14,37]. However, previous evidence for GC was conflicting [38,39]. A recent study by Zhu et al. concluded that the existence of a residual nodal tumor, rather than nodal regression change is useful to predict the prognosis and suggested unnecessity to routinely investigate nodal regression [38]. Although, the results from this Asian study did not completely refute the prognostic value of nodal regression, but rather showed only complete nodal tumor regression is clinically significant [38]. In contrast, the very recent study by Pereira et al. defined nodal responders as those with less than 43 % of residual tumor and showed improved survival of these patients [39]. Similarly, in our larger-scale study, we defined nodal responders as those with less than 50 % of the residual tumor in at least one of the metastatic LN and showed the improved long-term outcomes for these patients. The reason for such a discrepancy might be different grouping systems used in the different studies. Although our study confirmed, that a widely acknowledged tumor regression grading system by Becker may be adapted to evaluate the nodal response and prognosticate the survival of patients with non-metastatic resectable AGC.

Table 5. Multivariable Cox regression analysis for overall and disease-free survival.

		HR (95% CI)	*p*
Death			
Lymph node response	lnNR	1.00 (reference)	
	lnR	0.37 (0.14-0.99)	0.04
	lnNEG	0.39 (0.14-1.02)	0.05
Tumor localization	Upper/middle third	1.00 (reference)	
	Lower third	0.31 (0.10-0.89)	0.03
Age (years)		1.03 (0.98-1.09)	0.15
CCI	1-3	1.00 (reference)	
	≥4	0.74 (0.28-1.95)	0.55
Recurrence of disease			
Lymph node response	lnNR	1.00 (reference)	
	lnR	0.57 (0.24-1.34)	0.20
	lnNEG	0.132 (0.01-2.47)	0.17
ypT	1-2	1.00 (reference)	
	3-4	3.39 (1.12-10.23)	0.03
ypN	N0	1.00 (reference)	
	N+	1.79 (0.21-14.97)	0.59
Lymphovascular invasion	LV+	1.00 (reference)	
	LV-	0.93 (0.42-2.01)	0.85
Age (years)		1.05 (0.99-1.11)	0.07
CCI	1-3	1.00 (reference)	
	≥4	0.36 (0.12-1.02)	0.05

lnNR: lymph node non-responders; lnR: lymph node responders; TRG: tumor regression grade; LV: lymphovascular invasion; CCI: Charlson Comorbidity Index.

The main limitations of the present study include the retrospective design, the limited number of patients, and a wide variety of different preoperative chemotherapy regimens used in the study. Despite these drawbacks, we were able to demonstrate, that histologic nodal regression after preoperative chemotherapy should be investigated not only in the primary tumor but also in the lymph nodes. In the future, these regression scores may serve as a surrogate outcome to rapidly evaluate the preoperative treatment efficacy.

Abbreviation

AGC: advanced gastric cancer; TRG: tumor regression grade; LN: lymph node; CT: computed tomography; OS: overall survival; DFS: disease-free survival; HR: hazards ratios; CI: confidence intervals; lnR: nodal responders; lnNR: nodal non-responders; lnNEG: lymph node-negative.

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Data availability statement: Data is available from the corresponding author on reasonable request.

Competing Interests

The authors have declared that no competing interest exists.

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PART 2: Time interval between neoadjuvant chemotherapy and gastrectomy impact on short- and long-term outcomes in patients with advanced gastric cancer

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Impact of the Interval Between Neoadjuvant Chemotherapy and Gastrectomy on Short- and Long-Term Outcomes for Patients with Advanced Gastric Cancer

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ABSTRACT

Background. The optimal time between neoadjuvant chemotherapy (NAC) and gastrectomy for gastric cancer (GC) remains unknown. This study aimed to investigate the association between the time-to-surgery (TTS) interval and the major pathologic response (mPR).

Methods. In this study, 280 consecutive GC patients who underwent NAC followed by gastrectomy between 2014 and 2018 were retrospectively analyzed by the use of prospectively collected databases from three major GC treatment centers in Lithuania and Estonia. Based on TTS, they were grouped into three interval categories: the early-surgery group (ESG: $\leq$ 30 days; n = 70), the standard-surgery group (SSG: 31–43 days; n = 138), and the delayed-surgery group (DSG: $\geq$ 44 days, n = 72). The primary outcome of the study was the mPR rate. The secondary end points were postoperative morbidity, mortality, oncologic safety (measured as the number of resected lymph nodes and radicality), and long-term outcomes.

Results. The mPR rate for the ESG group (32.9%) was significantly higher than for the SSG group (20.3%) or the DSG group (16.7%) (p = 0.047). Furthermore, after adjustment for patient, tumor, and treatment characteristics, the odds for achievement of mPR were twofold higher for the patients undergoing early surgery (odds ratio [OR] 2.09; 95% confidence interval [CI] 1.01–4.34; p = 0.047). Overall morbidity, severe complications, 30-day mortality, R0 resection, and retrieval of at least 15 lymph nodes rates were similar across the study groups. In addition, the long-term outcomes did not differ between the study groups.

Conclusions. This study suggests that an interval of no more than 30 days between the end of NAC and gastrectomy is associated with a higher mPR rate, the same oncologic safety of surgery, and similar morbidity and mortality.

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third leading cause of cancer death.[1] Therefore, advancement in its treatment has a significant impact on the affected population. Randomized clinical trials have shown that perioperative chemotherapy administered before and after gastrectomy improves long-term outcomes.[2,3] Therefore, this multimodal treatment for resectable advanced GC has become the standard of care in Western countries.[4]

Neoadjuvant chemotherapy (NAC) before gastrectomy potentially treats occult micrometastases and induces primary tumor regression leading to downstaging of the

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disease and increased rates of R0 resections.[5] However, the response to NAC varies between individual patients, and only 20% to 37% of these patients achieve a major pathologic response (mPR), which is associated with significantly better long-term outcomes.[6–12]

Unfortunately, it remains unclear what factors increase the likelihood of mPR. Appropriate time to surgery (TTS) after neoadjuvant therapy was suggested as the factor increasing the probability of a significant pathologic response in various gastrointestinal cancers.[13] For example, the prolonged interval between neoadjuvant therapy and surgery increases the rate of pathological complete response (pCR) in rectal cancer.[14–18] Similarly, some studies recommend a prolonged interval between neoadjuvant chemoradiotherapy (nCRT) and esophagectomy to increase the pathologic response and long-term outcomes in esophageal cancer patients.[19,20] In contrast, a shorter interval between NAC and surgery was shown to maximize the benefit of neoadjuvant treatment for breast cancer patients.[21]

Currently, limited data exist to support the optimal time-to-surgery interval after NAC in GC.[13] Consequently, the current study aimed to identify an optimal time after the completion of NAC that might maximize the rate of mPR for patients with GC.

MATERIALS AND METHODS

Approvals by the Vilnius Regional Biomedical Research Ethics Committee and the Research Ethics Committee of the University of Tartu were obtained before this study was conducted. All study-related procedures were performed in accordance with the Declaration of Helsinki of 1964, as revised in 1983. Informed consent was not obtained from the participants because the study was a retrospective investigation.

Patients

This cohort study was conducted at three major upper gastrointestinal cancer treatment centers of Lithuania and Estonia: National Cancer Institute, Vilnius, Lithuania; Vilnius University Hospital Santara Clinics, Vilnius, Lithuania; and North Estonia Medical Centre, Tallinn, Estonia. The patients who underwent NAC followed by gastrectomy for advanced GC between January 2014 and December 2018 were identified in prospectively collected institutional databases. Patients who received conversion chemotherapy for a clinical stage 4 gastric cancer were excluded except those who had stage 4 disease diagnosed only by positive peritoneal lavage cytology without any evidence for other distant dissemination (Fig. 1).

Diagnosis, Treatment, and Follow-Up Evaluation of the Study Patients

The standard diagnostic pathway included esophagogastroduodenoscopy with biopsy, chest/abdominal computed tomography (CT), and diagnostic laparoscopy with peritoneal lavage. After gastric cancer was confirmed and staged, all the patients were discussed in multidisciplinary team meetings. Those with stage $\geq$ cT2 or N + who were eligible according to physical status and comorbidities were scheduled for NAC followed by surgery. The standard neoadjuvant treatment consisted of three or four cycles of chemotherapy, with the exact regimen and drugs selected by a medical oncologist.

After NAC was completed, the patients were scheduled for surgery. Subtotal gastrectomy was performed if a sufficient proximal resection margin could be ensured. Otherwise, total gastrectomy was performed. The extent of lymphadenectomy depended on each surgeon's decision, but the standard lymphadenectomy was a D2 lymph node dissection performed as described in the fourth version of the Japanese gastric cancer treatment guidelines.[22]

After the patients recovered from gastrectomy, they were allocated to receive three or four cycles of adjuvant chemotherapy. After the treatment was completed, the patients were followed up. The standard follow-up protocol consisted of esophagogastroduodenoscopy and CT performed twice a year for the first 2 years and then annually.

Time to Surgery

The TTS interval was defined as the days from the last day of NAC to the day of gastrectomy, as selected by an operating surgeon individually. Based on TTS, the patients were grouped into three interval categories: the early-surgery group (ESG, $\leq$ 30 days), the standard-surgery group (SSG, 31–43 days), and the delayed-surgery group (DSG, $\geq$ 44 days). The categories were chosen based on the distribution of TTS data. First and third quartiles were used as cutoff values for the early- and delayed-surgery groups, respectively, to maintain comparable sample sizes in each group. The SSG in our study was comparable with the 4- to 6-week interval most commonly used in practice and large-scale randomized controlled trials (RCTs) investigating perioperative chemotherapy for GC.[23]

Histologic Examination

All the histologic specimens were reevaluated for this study by experienced upper gastrointestinal cancer pathologists (V.S., D.S., K.T.). The final tumor histology was provided by ypTNM and staged according to the American Joint Committee on Cancer Staging, eighth

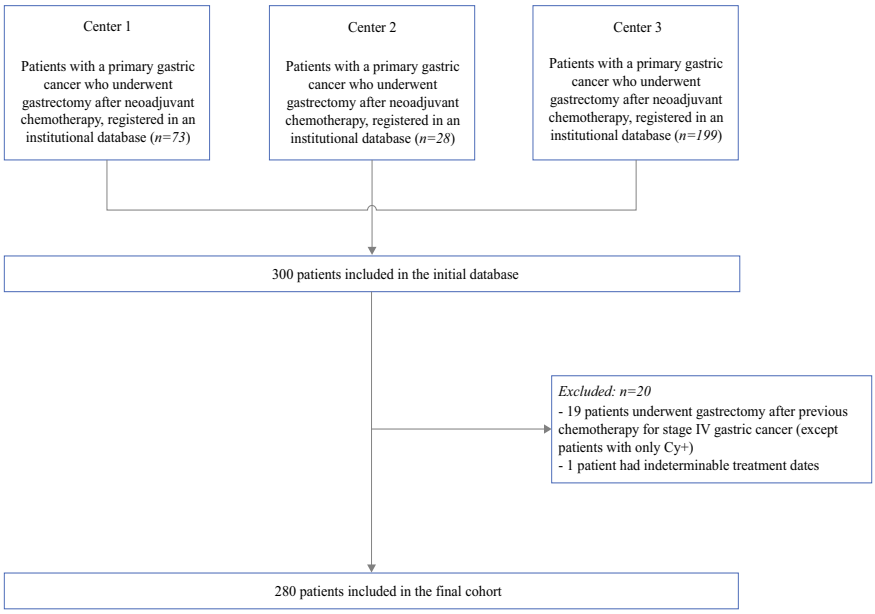

FIG. 1 Flowchart of the study patients

edition. Tumor regression classification consisted of three grades described by Becker et al.[24] as follows: grade 1 (complete [TRG1a] or subtotal regression, with $< 10\%$ residual tumor per tumor bed [TRG1b]), grade 2 (partial tumor regression, with 10% to 50% residual tumor per tumor bed [TRG2]), and grade 3 (minimal or no tumor regression, with $> 50\%$ residual tumor per tumor bed [TRG3]). Carcinomas with complete (TRG1a) or subtotal (TRG1b) regression were considered to indicate achievement of mPR as suggested by Becker et al.[11]

Study Outcomes

The primary outcome of the study was the mPR rate. The secondary end points were the overall postoperative complications rate, severe postoperative complication rate, anastomotic leakage rate, postoperative or 30-day mortality rate, negative resection margin (R0) rate, adequate lymphadenectomy (retrieval of ≥ 15 lymph nodes) rate, overall survival (OS), and disease-free (DFS) survival. All postoperative complications were graded by Clavien-Dindo classification, and severe complications were defined as grade 3 or higher. Postoperative or 30-day mortality rates were defined as intrahospital mortality after gastrectomy or deaths within 30 days after surgery in case patients were discharged earlier.

Statistical Analysis

All statistical analyses were conducted using the statistical program SPSS 24.0 (SPSS, Chicago, IL, USA). Continuous variables are presented as the mean $\pm$ standard deviation or median with first quartile (Q1) and third quartile (Q3). These variables were compared across groups using the Kruskal–Wallis test. Categorical variables were shown as proportions and compared using the Chi square test or Fisher's exact test, as appropriate. A multivariable logistic regression model was used to evaluate the association between time from the end of NAC to gastrectomy and mPR. To address potential confounding factors, the model was adjusted for patients (gender, age), tumor (localization, signet ring cells component, ulceration, lymphovascular invasion), and neoadjuvant treatment (type of chemotherapy) characteristics. Odds ratios (ORs) are presented with a 95% confidence intervals (95% CIs). Similarly, logistic regression was used to investigate the association between TTS and the secondary outcomes of the study. The multivariable model adjusted the secondary

outcomes for age, gender, comorbidities, type of surgery, and type of preoperative chemotherapy.

The Kaplan–Meier method was used to analyze the OS and DFS rates, which were compared between the study groups using the log-rank test. To correct the TTS impact on long-term outcomes for clinical variables (age, gender, stage of the disease, and preoperative chemotherapy type), the Cox proportional hazard regression analysis was used. Hazards ratios (HRs) were presented with 95% CIs. In all statistical analyses, two-tailed tests were used, and a p value lower than 0.05 was considered significant.

RESULTS

Baseline Characteristics

The study enrolled 280 patients, and the TTS interval after NAC ranged from 10 to 119 days, with a median time of 36 days (Q1, 30 days; Q3, 44 days). The median and interquartile values were used as cutoffs to divide the study population into three groups, with 70 patients allocated to ESG, 138 patients to SSG, and 72 patients to DSG (Fig. 2). After this grouping, the median TTS differed significantly between the study groups as follows: ESG (26 days; Q1, 22 days; Q3, 28 days) versus SSG (36 days; Q1, 33 days; Q3, 40 days) versus DSG (53 days; Q1, 47 days; Q3, 64 days) ($p = 0.001$).

The baseline clinicopathologic characteristics were comparable between the groups except for the slight differences in NAC regimens. The frequency of epirubicin, cisplatin, capecitabine (ECX)/epirubicin, oxaliplatin, capecitabine (EOX) was slightly higher in the ESG group compared with the higher rate of fluorouracil, folinic acid, oxaliplatin, and docetaxel (FLOT) in the SSG and DSG groups (Table 1).

Primary Outcome: mPR

In the study cohort, 63 patients (22.5%) achieved mPR, although the variation was substantial across the study groups ($p = 0.047$). The mPR rate in the ESG group (32.9%) was significantly higher than in the SSG (20.3%; $p = 0.046$) and DSG (16.7%; $p = 0.025$) groups. Furthermore, after adjustment for patients (gender, age), tumor (localization, signet ring cells component, ulceration, lymphovascular invasion), and neoadjuvant treatment characteristics, the odds for achievement of mPR were twofold higher for the patients undergoing early surgery (OR, 2.09; 95% CI, 1.01–4.34; $p = 0.047$). Tumors with the signet ring cell component (OR, 0.39; 95% CI, 0.18–0.80; $p = 0.011$) and lymphovascular invasion (OR, 0.38; 95% CI, 0.17–0.82; $p = 0.014$) had lower odds for achievement of mPR. Neither type of preoperative chemotherapy nor other tumor and patient-related characteristics were associated with mPR (Table 2).

Secondary Outcomes: Postoperative Morbidity, Quality of Surgery, and Adjuvant Therapy

The vast majority of the patients (97.5%) received gastrectomy with D2 lymphadenectomy. The groups did not differ in terms of rates for overall morbidity (ESG, 38.6% vs. SSG, 44.9% vs. DSG, 41.7%; $p = 0.672$), severe complications (ESG, 12.9% vs. SSG, 13.0% vs. DSG, 11.1%; $p = 0.917$), anastomotic leakage (ESG, 2.9% vs. SSG, 3.6% vs. DSG, 4.2%; $p = 0.914$), or 30-day mortality (ESG, 0% vs. SSG, 2.9% vs. DSG, 1.4%; $p = 0.315$). Also, the oncologic safety of surgery by R0 resection (ESG, 92.9% vs. SSG, 94.2% vs. DSG, 94.4%; $p = 0.908$) and by retrieval of at least 15 lymph nodes (ESG, 81.4% vs. SSG, 81.2% vs. DSG, 85.9%; $p = 0.671$) (Table 1) was similar.

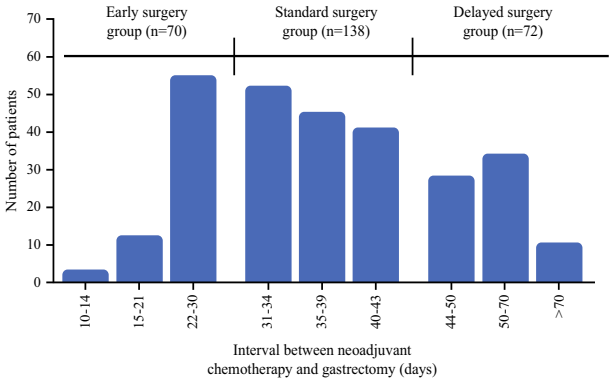

FIG. 2 Distribution of the timing of gastrectomy after neoadjuvant chemotherapy. Based on to the interval between the end of neoadjuvant chemotherapy and gastrectomy, the patients were grouped into three interval categories: early-surgery group (ESG, ≤ 30 days), standard-surgery group (SSG, 31–43 days), delayed-surgery group (DSG, ≥ 44 days)

TABLE 1 Baseline clinicopathologic and treatment characteristics of the patients who received early (≤ 30 days), standard (31–43 days), or delayed (≥ 44 days) gastrectomy after neoadjuvant chemotherapy

Characteristics	Early-surgery group (n = 70) n (%)	Standard-surgery group (n = 138) n (%)	Delayed-surgery group (n = 72) n (%)	p value
Median time from NAC to surgery: days (Q1; Q3)	26 (22; 28)	36 (33; 40)	53 (47; 64)	0.001
Median age: years (Q1; Q3)	62 (57; 72)	64 (58; 70)	62 (53; 71)	0.698
Sex				
Male	39 (55.7)	79 (57.2)	44 (61.1)	0.792
Female	31 (44.3)	59 (42.8)	28 (38.9)	
Median CCI (Q1; Q3)	4 (3; 5)	4 (4; 6)	5 (3; 6)	0.372
Tumor localization				
Upper third	15 (21.4)	40 (29.0)	17 (23.6)	0.490
Middle third	30 (42.9)	59 (42.8)	27 (37.5)	
Lower third	25 (35.7)	39 (28.3)	28 (38.9)	
Tumor differentiation				
G1–2	17 (27.4)	29 (22.1)	19 (27.1)	0.627
G3–4	45 (72.6)	102 (77.9)	51 (72.9)	
Signet ring cells component				
No	46 (65.7)	86 (62.3)	50 (69.4)	0.584
Yes	24 (34.3)	52 (37.6)	22 (30.6)	
Lymphovascular invasion				
No	50 (71.4)	86 (62.8)	42 (59.2)	0.288
Yes	20 (28.6)	51 (37.2)	29 (40.8)	
Lauren type				
Diffuse	11 (52.4)	26 (57.8)	13 (56.5)	0.918
Intestinal/mix	10 (47.6)	19 (42.2)	10 (43.)	
Ulceration				
No	22 (31.4)	43 (31.4)	18 (25.0)	0.592
Yes	48 (68.6)	94 (68.6)	54 (75.0)	
ypT				
0–2	28 (40.0)	45 (32.6)	24 (33.3)	0.550
3–4	42 (60.0)	93 (67.5)	48 (66.7)	
ypN				
0	34 (48.6)	65 (47.1)	27 (37.5)	0.275
1	13 (18.6)	23 (16.7)	15 (20.8)	
2	10 (14.3)	16 (11.6)	17 (23.6)	
3	13 (18.6)	34 (24.6)	13 (18.1)	
cTNM stage				
1–3	70 (100)	137 (99.3)	70 (97.2)	0.235
4	0 (0)	1 (0.7)	2 (2.8)	
pTNM stage				
0–1	15 (21.4)	20 (14.5)	9 (12.5)	0.072
2	27 (38.6)	57 (41.3)	24 (33.3)	
3	25 (35.7)	56 (40.6)	29 (40.3)	
4	3 (4.3)	5 (3.6)	10 (13.9)	
Chemotherapy regimen				
FLOT	10 (14.3)	36 (26.1)	14 (19.4)	0.030
Fluoropyrimidine and platinum-based doublet	19 (27.1)	46 (33.3)	27 (37.5)	
ECX/EOX	41 (58.6)	56 (40.6)	29 (40.3)	

TABLE 1 (continued)

Characteristics	Early-surgery group (n = 70) n (%)	Standard-surgery group (n = 138) n (%)	Delayed-surgery group (n = 72) n (%)	p value
Other	0 (0)	0 (0)	2 (2.8)	
All scheduled neoadjuvant chemotherapy was completed	63 (90.0)	128 (92.8)	61 (84.7)	0.184
Type of surgery				
Total gastrectomy	47 (67.1)	91 (65.9)	45 (62.5)	0.827
Subtotal gastrectomy	23 (32.9)	47 (34.1)	27 (37.5)	
Lymhadenectomy				
≤ D1+	1 (1.4)	2 (1.5)	1 (1.4)	0.999
D2	68 (98.6)	135 (98.5)	70 (98.6)	
Median surgery time: min (Q1; Q3))	217 (170; 266)	235 (182; 285)	252 (173; 310)	0.327
R				
R0	65 (92.9)	130 (94.2)	68 (94.4)	0.908
R1–2	5 (7.1)	8 (5.8)	4 (5.6)	
Median retrieved LNs: n (Q1; Q3)	27 (17; 40)	27 (17; 37)	26 (17; 34)	0.880
Postoperative complications (any)	27 (38.6)	62 (44.9)	30 (41.7)	0.672
Severe postoperative complications (Clavien-Dindo ≥ 3)	9 (12.9)	18 (13.0)	8 (11.1)	0.917
30-Day mortality rate	0 (0)	4 (2.9)	1 (1.4)	0.315
Anastomotic leak rate	2 (2.9)	5 (3.6)	3 (4.2)	0.914
Pancreatic fistula	2 (2.9)	14 (10.1)	7 (9.7)	0.168
Postoperative chemotherapy full completion rate				
Yes	33 (47.1)	73 (52.9)	38 (52.8)	0.468
No	33 (47.1)	53 (38.4)	24 (33.3)	
Not ordinated	3 (4.3)	11 (8.0)	8 (11.1)	
Unknown	1 (1.4)	1 (0.7)	2 (2.8)	

NAC neoadjuvant chemotherapy, *Q1* quartile 1, *Q3* quartile 3, *CCI* Charlson comorbidity index, *ypT* pathologic primary tumor stage after neoadjuvant chemotherapy, *ypN* pathologic regional lymph nodes stage after neoadjuvant chemotherapy, *cTNM* clinical stage according to tumor-node-metastasis (TNM) classification, *pTNM* pathologic stage according to tumor-node-metastasis (TNM) classification, *FLOT* fluorouracil, folinic acid, oxaliplatin, and docetaxel, *ECX* epirubicin, cisplatin, capecitabine, *EOX* epirubicin, oxaliplatin, capecitabine, *R* resection margin, *R0* negative resection margin, *R1–2* microscopically or macroscopically positive margin, *LN* lymph node

After adjustment for patients (age, gender, Charlson Comorbidity Index [CCI]) and treatment characteristics (type of surgery, type of preoperative chemo), the groups did not differ in terms of secondary outcomes (overall postoperative complications, severe postoperative complications, anastomotic leakage, postoperative/30-day mortality, R0 resection, and retrieval of ≥ 15 lymph nodes) (Table 3).

Long-Term Outcomes

The mean time to follow-up evaluation was 27 ± 17 months. Univariate Kaplan–Meier analysis showed a significantly higher 3-year OS (72.9% vs. 56.8%; p = 0.011) and DFS (72.8% vs. 44.4%; p = 0.001) for the patients who achieved mPR (Fig. 3a, b). Although a higher proportion of patients achieved mPR in the ESG, OS and DFS showed no improvement in (Fig. 3c, d). Furthermore, the multivariable Cox regression analysis demonstrated no evidence that the risk of death or cancer recurrence was higher in any one of the TTS groups after adjustment for age, gender, stage of the disease, and chemotherapy agents (Table 4).

DISCUSSION

This study suggests that an interval of 30 days or less between the completion of NAC and gastrectomy is associated with a higher probability of mPR. Postoperative

TABLE 2 Multivariable logistic regression evaluating patient, tumor, and treatment characteristics for the major pathological response

Variable	Category	OR (95% CI)	*p* value
Time between NAC and gastrectomy	Standard-surgery group (31–43 days)	1 (Reference)	
	Early-surgery group (≤ 30 days)	2.09 (1.01–4.34)	0.047
	Delayed surgery group (≥ 44 days)	0.77 (0.33–1.77)	0.543
Gender	Male	1 (Reference)	
	Female	0.53 (0.27–1.03)	0.063
Age (years)	≤ 60	1 (Reference)	
	61–70	1.75 (0.82–3.72)	0.144
	≥ 71	1.42 (0.60–3.33)	0.417
Tumor localization	Upper third	1 (Reference)	
	Middle third	0.71 (0.30–1.67)	0.440
	Lower third	2.08 (0.92–4.67)	0.076
Signet ring cells component	No	1 (Reference)	
	Yes	0.43 (0.20–0.93)	0.032
Ulceration	No	1 (Reference)	
	Yes	0.87 (0.42–1.79)	0.710
Lymphovascular invasion	No	1 (Reference)	
	Yes	0.38 (0.17–0.82)	0.014
Type of chemotherapy	FLOT	1 (Reference)	
	Fluoropyrimidine and platinum-based doublet	0.40 (0.15–1.07)	0.071
	ECX/EOX	0.92 (0.40–2.15)	0.864
	Other	5.20 (0.24–109.97)	0.289

OR odds ratio, *CI* confidence interval, *NAC* neoadjuvant chemotherapy, *FLOT* fluorouracil, folinic acid, oxaliplatin, and docetaxel, *ECX* epirubicin, cisplatin, capecitabine, *EOX* epirubicin, oxaliplatin, capecitabine

morbidity, mortality, and oncologic safety of surgery, measured as the number of resected lymph nodes and radicality, were similar across the different study groups.

Perioperative chemotherapy became the standard for resectable advanced GC in Western countries after the MAGIC[2] and FNCLCC/FFCD[3] studies showed improvement in long-term outcomes. The rationale behind NAC is the greater possibility of tumor downstaging and eradication of micrometastases to reduce distant relapse. However, only 20% to 37% of GC tumors show significant histologic regression and are classified as mPR.[6–12] It remains unclear why the efficacy of NAC for GC tumors varies, but clinical observations suggest that TTS might amplify the benefits of neoadjuvant therapy.[13]

Whereas only limited data on optimal TTS after NAC in GC is found, more evidence exists for other localized gastrointestinal cancers that require neoadjuvant therapies. A significant amount of retrospective and prospective data, summarized systematically by Du et al.,[25] indicates that a prolonged interval (> 8 weeks) improves the pCR rate in rectal cancer. Furthermore, a recent randomized controlled study concluded that extending the interval between nCRT and surgery more drastically, from 8 to 12 weeks, results in a further twofold increase in pCR rates.[26] Similarly, a series of studies have shown that prolonging the interval between nCRT and esophagectomy increases the rate of pCR for patients with adenocarcinoma or squamous cell carcinoma of the esophagus.[19,27–29]

In contrast, a short interval between NAC and surgery seems to be most beneficial for breast cancer patients.[21,30] A study by Omarini et al.[21] demonstrated improved long-term outcomes and increased pathologic response rates for patients undergoing early surgery within 21 days after completion of NAC. Additionally, the study by Sanford et al.[30] showed that delaying breast cancer surgery for more than 6 weeks after NAC results in lower rates of pathologic response. Moreover, delaying surgery for more than 8 weeks impairs the OS. These findings correlate with our study demonstrating increased benefits of NAC by a higher rate of mPR for patients who receive early gastrectomy in 30 or fewer days. Such findings indicate that despite the difference in tumor origin, the patients who receive nCRT benefit from delayed surgery, whereas the patients who receive NAC benefit from early surgery. No clear explanation exists for such differences, although different schedules of administration and different tumoricidal properties of chemotherapy and radiotherapy could be contributing factors.

TABLE 3 Multivariable logistic regression analysis (adjusted for age, gender, CCI, type of surgery, type of neoadjuvant chemotherapy): association of time between neoadjuvant chemotherapy and gastrectomy with the secondary outcomes (overall postoperative complications, severe postoperative complications, anastomotic leakage; postoperative/30-day mortality, R0 resection, and retrieval of ≥ 15 lymph nodes)

Outcome	Variable (adjusted for age, gender, CCI, type of surgery, type of neoadjuvant chemotherapy)	OR (95% CI)	*p* value
Overall postoperative complications	Standard-surgery group (31–43 days)	1 (Reference)	
	Early-surgery group (≤ 30 days)	0.69 (0.36–1.29)	0.251
	Delayed-surgery group (≥ 44 days)	0.80 (0.43–1.49)	0.682
Severe postoperative complications	Standard-surgery group (31–43 days)	1 (Reference)	
	Early-surgery group (≤ 30 days)	0.97 (0.40–2.38)	0.963
	Delayed-surgery group (≥ 44 days)	0.74 (0.29–1.83)	0.516
Anastomotic leakage	Standard-surgery group (31–43 days)	1 (Reference)	
	Early-surgery group (≤ 30 days)	0.76 (0.13–4.18)	0.753
	Delayed-surgery group (≥ 44 days)	1.16 (0.26–5.15)	0.839
Postoperative or 30-day mortality	Standard-surgery group (31–43 days)	1 (Reference)	
	Early-surgery group (≤ 30 days)	N/A	N/A
	Delayed-surgery group (≥ 44 days)	0.46 (0.04–4.54)	0.513
R0 resection	Standard-surgery group (31–43 days)	1 (Reference)	
	Early-surgery group (≤ 30 days)	1.17 (0.35–3.83)	0.796
	Delayed-surgery group (≥ 44 days)	0.89 (0.25–3.13)	0.856
Retrieval of ≥ 15 lymph nodes	Standard-surgery group (31–43 days)	1 (Reference)	
	Early-surgery group (≤ 30 days)	1.03 (0.48–2.22)	0.930
	Delayed-surgery group (≥ 44 days)	1.39 (0.61–3.18)	0.428

CCI Charlson comorbidity index, *R0* negative resection margin, *OR* odds ratio, *95% CI* 95% confidence interval, *N/A* not available

Neoadjuvant radiotherapy usually is administered continuously as daily fractions until the sufficient total dose accumulates. Irradiation of the tumor leads to cell death by inducing single- and double-strand breaks in DNA[31] and delayed cellular lysis.[32] Furthermore, the massive cell death resulting from irradiation leads to the release of stress molecules and antigens into the tumor microenvironment. This stimulates an immune response, which further increases the tumoricidal capacity of the neoadjuvant radiotherapy over time.[28]

In contrast, NAC for GC is administered as three or four cycles of multidrug chemotherapy with intervals of several weeks between. The chemotherapy kills proliferating cells by either cell cycle-specific or cell cycle-nonspecific mechanisms.[31] However, regrowth of the tumor between treatment cycles may occur. As suggested by the Gompertzian model of tumor growth, which is concordant with many experimental and clinical observations, smaller tumors grow faster, so regrowth between treatment cycles is more rapid with greater cell death.[33] This might explain why increasing the treatment intensity by dose escalation or by reduction of intervals between therapies improves clinical responses.[33] It also can explain why the patients who received early gastrectomy within 30 days after NAC had higher rates of mPR in our study.

Additionally, tumor response may depend on the type of chemotherapy. The FLOT regimen is considered to be the new gold standard in Western countries because it has shown higher rates of mPR and better long-term outcomes than the epirubicin, cisplatin, fluorouracil (ECF)/ECX regimen.[7,9] In our study, the groups did not receive homogeneous NAC because FLOT was used more frequently in the SSG and DSG groups. However, although the most effective chemotherapy (FLOT) was less frequent

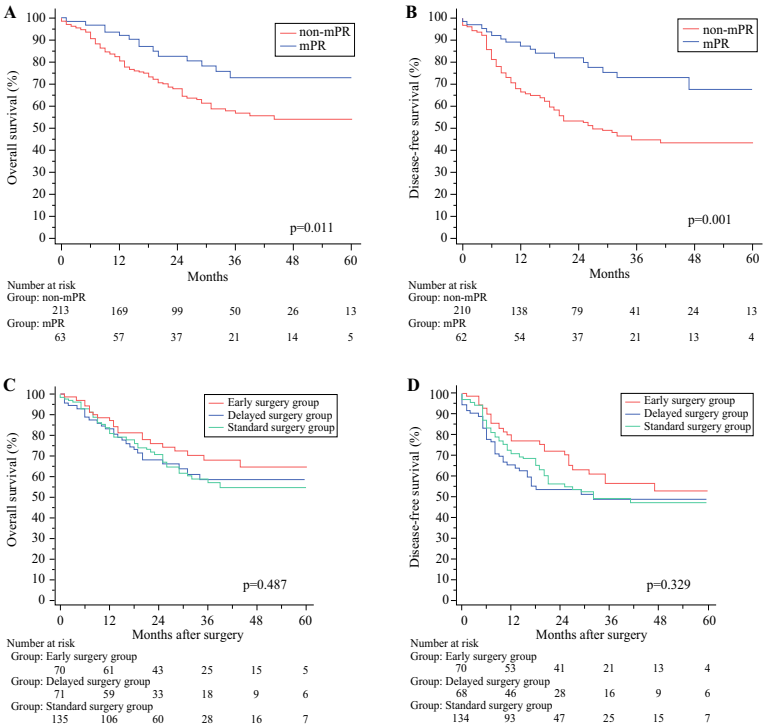

FIG. 3 Overall and disease-free survival of the study patients by Kaplan–Meier analysis. The patients who achieved a major pathologic response showed significantly higher **a** overall and **b** disease-free survivals, but the **c** overall and **d** disease-free survivals did not differ between the different time-to-surgery groups

in the ESG group, the patients who recieved early surgery still achieved higher rates of mPR. Thus, it strengthens the evidence that appropriate timing can improve the efficacy of NAC even if the regimens administered vary.

In clinical practice, the interval between NAC and gastrectomy depends on multiple factors, including the patient's general condition and comorbidities. But one of the most important aspects is the time required to recover from the short-term side effects of chemotherapy, particularly hematologic toxicity. A TTS interval that is too short may lead to higher postoperative morbidity, although the current study demonstrated that early gastrectomy, within 30 days after NAC, is safe because the overall postoperative morbidity, severe complications, anastomotic leakage, and postoperative mortality rates were similar between the patients receiving gastrectomy at standard and delayed times. From the perspective of the patients, unnecessary delay in surgery may increase their anxiety and psychological morbidity.[21] Thus, clinicians should attempt to offer the shortest interval between NAC and gastrectomy given patients who appropriately recover from chemotherapy-induced side effects.

Our results contrast with those of a previously published study from Asia suggesting that a prolonged interval (> 6 weeks) is associated with greater odds of a pathologic response than shorter intervals.[13] However, that study and the current study had some major methodologic differences, with the previous study defining responders only as the patients with complete regression, who achieved ypT0N0M0.[13] In contrast, we graded tumor regression by the common Becker system and defined responding tumors as those with complete and subtotal regression.[11] The rationale for such grading is based on the comparable long-term outcomes for patients with a complete or subtotal

TABLE 4 Multivariable Cox regression analysis of overall and disease-free survival

Variable	Category	Overall survival		Disease-free survival	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Time from chemotherapy to surgery	Standard-surgery group (31–43 days)	1 (Reference)		1 (Reference)	
	Early-surgery group (≤ 30 days)	0.70 (0.42–1.18)	0.187	0.74 (0.47–1.16)	0.195
	Delayed-surgery group (≥ 44 days)	0.80 (0.48–1.32)	0.390	0.95 (0.62–1.46)	0.833
Age (years)	18–60	1 (Reference)		1 (Reference)	
	61–70	1.14 (0.71–1.85)	0.572	1.05 (0.69–1.59)	0.817
	≥71 years	1.16 (0.68–1.99)	0.576	1.09 (0.68–1.74)	0.704
Type of chemotherapy	FLOT	1 (Reference)		1 (Reference)	
	Fluoropyrimidine and platinum-based doublet	1.27 (0.66–2.43)	0.460	1.02 (0.60–1.74)	0.932
	ECX/EOX	1.04 (0.55–1.96)	0.905	0.87 (0.52–1.46)	0.621
	Other	1.48 (0.17–12.61)	0.719	3.05 (0.38–24.49)	0.293
Stage of disease	1	1 (Reference)		1 (Reference)	
	2	1.18 (0.49–2.85)	0.704	1.41 (0.63–3.15)	0.396
	3	6.29 (2.84–13.95)	0.001	7.81 (3.73–16.34)	0.001
	4	6.62 (2.31–19.02)	0.001	8.46 (3.29–21.72)	0.001

HR hazards ratio, *CI* confidence interval, *FLOT* fluorouracil, folinic acid, oxaliplatin, and docetaxel, *ECX* epirubicin, cisplatin, capecitabine, *EOX* epirubicin, oxaliplatin, capecitabine

regression, considering that these outcomes are significantly better than those for patients with a regression grade of 2 or 3.[10,34] Therefore, we used this definition for mPR and set it as the primary outcome of the current study. Also, the majority of the patients in the previously published study received S-1-based chemotherapy, which is uncommon in the West, and our patients received different types of NAC. These methodologic differences may have been responsible for the discrepancies in the findings. Larger well-characterized cohorts are needed for a full elucidation of this topic.

Our study had several limitations. First, the decisions made for TTS had an unidentifiable bias. These choices were possibly made in settings of personal experience and predicted tumor response or survival. Second, given that our study was retrospective, it was subject to the biases and confounding factors linked to such methods of research. Third, to our surprise, the current study failed to show improved long-term outcomes in ESG despite the increased rates of mPR. Similar findings were documented in the UK MRC OE05 study, which investigated four cycles of ECX versus two cycles of cisplatin and fluorouracil (CF) for esophageal or gastroesophageal-junction adenocarcinoma.[35] The increased rate of significant pathologic response after four cycles of ECX did not translate to improved survival.[35] Thus, the appropriateness of mPR as the primary outcome may be questioned. However, the improved long-term outcomes for patients who achieve mPR were well-documented by Becker et al.[11] and confirmed in current study as well. Thus, we consider mPR as an acceptable surrogate end point for evaluation of NAC efficacy. Rather, the failure to show improved long-term outcomes in ESG was determined by the insufficient power of the study, which was limited by a relatively small sample of 280 patients, and especially by the limited number of patients who achieved mPR in each study group (23 [32.9%] of 70 in the ESG group vs. 28 [20.3%] of 138 in the SSG group vs. 12 [16.7%] of 72 in the DSG group). This, in addition to short follow-up times, may have resulted in underestimation of the impact that different TTS lengths had on long-term outcomes. Therefore, the findings of the current study must be validated with larger cohorts. Despite these limitations, to the best of our knowledge, this is the largest study to investigated the optimal time to gastrectomy after NAC.

CONCLUSION

The interval of fewer than 30 days from the end of NAC to gastrectomy is optimal because it is associated with higher mPR rates, the same oncologic safety as surgery, and similar morbidity and mortality. However, the longer

interval may be considered if the patient needs time to recover after chemotherapy because no clear evidence of impaired long-term outcomes exists.

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CHAPTER 4: GASTRECTOMY ASSOCIATED DYSBIOSYS AND ITS‘ IMPACT ON QUALITY OF LIFE

PART 1: Gastrectomy impact on the gut microbiome in patients with gastric cancer: A comprehensive review

Vaidota Maksimaityte*, Augustinas Bausys*, Marius Kryzauskas, Martynas Luksta, Ieva Stundiene, Klaudija Bickaite, Bernardas Bausys, Tomas Poskus, Rimantas Bausys, Kestutis Strupas

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MINIREVIEWS

Gastrectomy impact on the gut microbiome in patients with gastric cancer: A comprehensive review

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Abstract

Gastric cancer is one of the most common malignancies worldwide and gastrectomy remains the only potentially curative treatment option for this disease. However, the surgery leads to significant physiological and anatomical changes in the gastrointestinal (GI) tract including loss of the gastric barrier, an increase in oxygenation levels in the distal gut, and biliary diversion after gastrectomy. These changes in the GI tract influence the composition of the gut microbiome and thus, host health. Gastrectomy-induced dysbiosis is characterized by increased abundance of typical oral cavity bacteria, an increase in aero-tolerant bacteria (aerobes/facultative anaerobes), and increased abundance of bile acid-transforming bacteria. Furthermore, this dysbiosis is linked to intestinal inflammation, small intestinal bacterial overgrowth, various GI symptoms, and an increased risk of colorectal cancer.

Key Words: Gut microbiota; Dysbiosis; Gastric cancer; Gastrectomy; Microbiome; Comprehensive review

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Core Tip: In most cases of gastric cancer (GC) the only life-saving treatment is gastrectomy. Gastrectomy results in significant changes in gut microbiota: Higher abundance of oral cavity bacteria, aero-tolerant bacteria, and bile transforming bacteria, and these changes in the microbiome are related to host health. In this review we discuss current knowledge and the results of recent studies on the changes in gut microbiome after gastrectomy in patients with a history of GC.

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INTRODUCTION

Gastric cancer (GC) is an important oncological problem responsible for over 1000000 new cases and more than 783000 deaths worldwide annually, making it the fifth most common cancer and the third leading cause of cancer death[1]. Surgery remains the only potentially curative treatment option for this disease[2]. However, gastrectomy has some adverse effects in long-term survivors, including persistent gastrointestinal (GI) symptoms[3-5] and an increased risk of metachronous cancers[6-8]. Gastrectomy leads to significant changes in the GI tract, including changes in pH, oxygenation levels, and biliary diversion. These alterations of the GI tract create a strong impetus on changes in the gut microbiome (Figure 1), which was suggested to be involved in postoperative outcomes[6]. Gastrectomy-induced dysbiosis is characterized by increased abundance of typical oral cavity bacteria, an increase in aero-tolerant bacteria (aerobes/facultative anaerobes), and increased abundance of bile acid-transforming bacteria.

The microbiome of the human gut is a complex and diverse population of bacteria, fungi, archaea, and viruses that inhabit the intestinal tract, mainly the large intestine[9,10]. The stable human gut bacterial species are divided into six main phyla: *Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Verrucomicrobia,* and *Euryarchaeota* [11]. These microbes have tremendous potential to impact host physiology, both in health and disease[12]. They contribute metabolic functions, protect against pathogens, educate the immune system, and, through these basic functions, affect directly or indirectly most of our physiologic functions[12]. Recent advancements revealed the gut microbiome's role in a series of different diseases including Alzheimer's disease [13,14], obesity[15], inflammatory bowel diseases (IBD)[16,17], cancer[18,19], functional GI disorders[20], and others. Furthermore, the role of the microbiome in postoperative weight loss and other outcomes are documented after sleeve gastrectomy and Roux-en-Y gastric bypass in bariatric patients[21-26]. Several recent studies investigated the gut microbiome after gastrectomy for GC[6,27-29]. This comprehensive review provides an overview of the current evidence on gut microbiome after gastrectomy for GC and its clinical implication.

LITERATURE SEARCH

A comprehensive literature search was conducted using the PubMed database up to 31st December, 2020. The search terms used were "gastrectomy AND microbiome". No time restrictions for publications were used, but only manuscripts published in the English language were reviewed. All titles and abstracts were independently reviewed by two reviewers (V.M. and A.B.) to identify clinical studies investigating the impact of gastrectomy on the gut microbiome in GC patients. After relevant abstracts were identified the full-text articles were retrieved. To ensure a comprehensive literature search an additional manual search of the reference lists was performed.

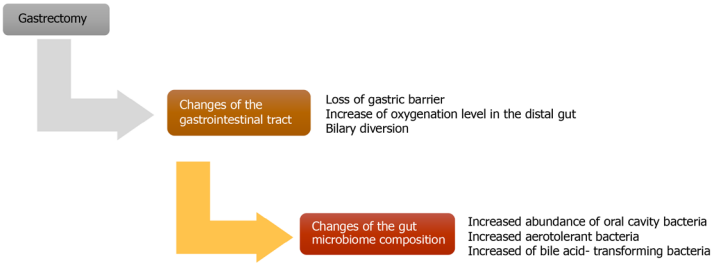

Figure 1 Gastrectomy impact on the gastrointestinal tract environment and gut microbiome.

COMPREHENSIVE REVIEW

Following a comprehensive review of the current literature, we identified 4 studies which investigated the gut microbiome after total or subtotal gastrectomy for GC, and these are summarized in Table 1. Three of these four studies were cross-sectional and investigated gut microbiome composition in GC patients at a median time of 3.75 years [27], 5 years[6], and 8.25 years[28] after gastrectomy and compared it with the corresponding controls. One small-scale study was longitudinal and investigated the gut microbiome composition before and approximately one week after gastrectomy[29].

Gut microbiome diversity and richness may be related to host health[30]. A reduction in the GI microbiome biodiversity was reported in obesity, inflammatory bowel disease, colorectal malignancy, and type 2 diabetes[21,30-33]. The impact of gastrectomy on bacterial richness and alpha diversity remains controversial because of conflicting results in current studies. Erawijantari *et al*[6] showed increased richness and diversity by increased Chao1 and Shannon indices in gastrectomized patients[6]. However, bacterial richness and alpha diversity may depend on the type of GI tract reconstruction. The study by Lin *et al*[28] showed increased richness and alpha diversity only after subtotal gastrectomy with Roux-en-Y reconstruction (RYGJ), but not in the case of Billroth II reconstruction (B2)[28]. Furthermore, similar richness and even decreased alpha diversity after subtotal gastrectomy with B2 reconstruction was reported by Horvath *et al*[27]. The impact of gastrectomy on bacterial richness and alpha diversity seems to be a long-term effect of the surgery since these changes were not observed by Liang *et al*[29] in the early perioperative period[29]. All the studies managed to identify and highlight specific features of the gut microbiome composition in the postsurgical period[27-29,34].

GASTRIC BARRIER LOSS AFTER GASTRECTOMY AND ITS IMPACT ON GUT MICROBIOME COMPOSITION

One of the typical changes in the GI tract after subtotal gastrectomy includes loss of the gastric barrier[27] due to reduced gastric acid secretion[27,35-37]. A pH of 4 is considered a threshold value for a powerful bactericidal effect[38] and it is significantly exceeded after subtotal gastrectomy, as the gastric pH increases from physiological levels to values above 6.0, irrespective of the type of reconstruction[39]. A very similar increase in gastric pH from approximately 2.0 to over 6.0 is described following proton pump inhibitor (PPI) intake[27]. In such conditions oral bacteria may survive during gastric passage and colonize the distal part of the GI tract, causing gut microbiome oralization, the phenomenon previously described in PPI users[40-43]. The comparable loss of gastric barrier function after subtotal gastrectomy and by PPI use may result in a similar impact on the gut microbiome.

Thus, it was not surprising, that a higher abundance of typical oral cavity bacteria-*Streptococcus, Veillonella, Prevotella, Oribacterium,* and *Mogibacterium*[44], were observed in the gut microbiome of gastrectomized patients[6,27,28]. Some of these bacteria are linked to host health and treatment efficacy. A recent study linked *Veillonella* with tumor response to Nivolumab in patients with progressive GC[45]. *Streptococcus* is a prevalent bacterial taxon in the oral cavity and the most commonly described

Table 1 Clinical studies investigating gut microbiome composition in patients after gastrectomy for gastric cancer

Ref.	Type of study	Participants (groups)	Exclusion criteria	Type of gastrectomy and method of reconstruction	Main findings of the study	Other metabolites investigated
Erawijantari *et al*[6], 2020	CSS	Gastrectomy group: Patients with a history of gastrectomy for GC (n = 50). Control group: Healthy controls without a history of gastrointestinal surgery (n = 56)	Recurrence of gastric cancer (gastrectomy group). History of gastrointestinal surgery (for controls)	Total (n = 12) gastrectomy and subtotal gastrectomy (n = 38). Types of reconstruction: Stomach-stomach (n = 1); Billroth I (n = 2); Jejunal interposition (n = 6); Pylorus-preserving gastrectomy (n = 8); Roux-en-Y (n = 29)	Higher species diversity and richness in gastrectomized patients. Higher abundance of aerobes, facultative anaerobes, and oral microbes in gastrectomized patients	Phosphate and amino acid transporters were more abundant in gastrectomized patients. Primary and conjugated forms of bile acid enriched in the control group and deoxycholic acid more abundant in gastrectomized patients
Liang *et al* [29], 2019	LS	Gastrectomy group: Patients with a diagnosed GC one week before (n = 20) and ≥ 7 d after (n = 6) gastrectomy. Control group: Healthy controls (n = 22)	History of antibiotics, PPI or H2 receptor antagonist use 1 mo prior to inclusion. Endoscopic finding of peptic ulcer, tumor rupture, pyloric obstruction. Patients with a history of radiotherapy/chemotherapy and/or previous surgery	Distal gastrectomy (n = 6). Types of reconstruction: Billroth II (n = 1); Roux-en-Y (n = 5)	Increased abundance of *Bacteroidetes*, *Fusobacteria*, and *Verrucomicrobia* and decreased abundance of *Proteobacteria*, *Firmicutes*, and *Actinobacteria* after distal gastrectomy. The richness and diversity by Chao1; ACE; Shannon; and Simpson indices were similar before and after distal gastrectomy. LEfSe analysis attributed *Verrucomicrobiae* (genus *Akkermansia*) and genus *Escherichia/Shigella*, *Lactobacillus*, and *Dialister* to patients after gastrectomy, and the genus *Klebsiella* to patients before gastrectomy	Significantly decreased level of valeric acid after distal gastrectomy
Horvath *et al* [27], 2021	CSS	Gastrectomy group: Patients with a history of distal gastrectomy with Billroth II reconstruction for early gastric cancer (n = 14). Control group: Patient's in-house relatives without a history of gastric surgery (n = 8)	Chemotherapy or radiotherapy 12 mo before inclusion. Gastric stump cancer. Usage of antibiotics, pro-, pre-, or synbiotics, H2-blocker, or PPI 1 month before inclusion. History of any gastrointestinal tract resections other than SGB2. Recurrence of gastric cancer, and current nongastric malignancies	Distal gastrectomy (n = 14). Types of reconstruction: Billroth II (n = 14)	Alpha diversity assessed by Shannon index was significantly decreased in gastrectomy patients. Median bacterial richness quantified by Chao1 index was similar. Beta diversity analysis showed significant differences between the microbiome composition of patients and controls; ANCOM identified the genus *Escherichia-Shigella* to be more abundant in gastrectomized patients. LEfSe attributed 11 additional genera to the gastrectomy group and 17 genera to the control (approximately half of them already have been implicated in PPI-induced or PPI-associated dysbiosis in previous reports). Increased abundance of *Escherichia-Shigella*, *Enterococcus*, *Streptococcus*, and other typical oral cavity bacteria (*Veillonella*, *Oribacterium*, *and Mogibacterium*) in gastrectomized patients	Fecal calprotectin marker was higher in gastrectomized patients. Fecal calprotectin was positively correlated with the abundance of *Streptococcus* and negatively correlated with the abundance of *Ruminococcaceae*, *Barnesiella*, *Ruminococcus* 2, *Ruminococcus* 1, and *Anaerostipes*. Abdominal discomfort was associated with a significantly higher abundance of *Holdemanella* and lower abundance of *Agathobacter*; Diarrhea was associated with a significantly higher abundance of *Mogibacterium* and significantly lower abundance of *Ruminococcus* 1; Bloating was associated with a significantly higher abundance of *Agathobacter* and *Streptococcus*. Patients who suffered from diarrhea also showed significantly higher serum levels of CRP and a trend to higher calprotectin level in stool compared with patients without diarrhea
Lin *et al*[28], 2018	CSS	Gastrectomy group: Patients with a history of distal gastrectomy	Age < 20 yr. Other underlying malignancies. Pre- and postoperative chemotherapy or chemoradiotherapy for GC. Other endocrine disorders such as DM,	Distal gastrectomy (n = 111). Types of reconstruction: Billroth	Significantly increased richness of gut microbiome after RYGJ by Chao1 index. Tendency of increased richness of gut microbiome after SGB2 by Chao1	GC patients after subtotal gastrectomy with RYGJ had a lower occurrence of metabolic syndrome and type II diabetes

	for early GC (n = 111). Control group: Age and sex-matched subjects without a history of GI tract surgery (n = 344)	thyroid, pituitary, or adrenal disease. Moderate to severe cardiovascular, pulmonary, hepatic, or renal disease. Recurrent or uncured GC even after curative gastric surgery. The occurrence of complications after GC resection including anastomotic leakage, bleeding, intermittent intestinal adhesion, dumping syndrome, *etc*. Patients who received proton pump inhibitors, histamine-2 receptor antagonists, nonsteroidal anti-inflammatory drugs, antibiotics, or probiotics within one month of sample collection	II (n = 37); Roux-en-Y (n = 74)	index. Diversity assessed by Shannon index was similar in BII patients but higher in RYGJ patients. LEfSe attributed 24 known genera, which were differently abundant between SGB2 and controls, and 43 genera differently abundant between RYJG and controls. *Oscillospira, Prevotella, Coprococcus, Veillonella, Clostridium, Desulfovibrio, Anaerosinus, Slackia, Oxalobacter, Victivallis, Butyrivibrio, Sporobacter, and Campylobacter* were more abundant after subtotal gastrectomy irrespective of the type of reconstruction. Increased number of aero-tolerant *Streptococcus* and *Escherichia* in the RYGJ group and *Klebsiella* in the SGB2 group. Increased abundance of typical oral microbiota (such as *Streptococcus spp.* and *Veillonella spp.)* in the gut microbiome of gastrectomized patients

CSS: Cross-sectional study; LS: Longitudinal study; GC: Gastric cancer; PPI: Proton pump inhibitors; SGB2: Subtotal gastrectomy with Billroth II reconstruction; CRP: C-reactive protein; RYGJ: Subtotal gastrectomy with Roux-en-Y reconstruction.

bacterium in PPI-induced dysbiosis[27,41,43,46,47]. Previously, this bacterium was linked to intestinal inflammation and gut permeability in cirrhosis patients[40]. Similarly, *Streptococcus* was also associated with intestinal inflammation in gastrectomized patients[27]. Chronic intestinal inflammation may be involved in the pathogenesis of intermittent or permanent chronic diarrhea, which is present in up to 40% of long-term survivors after gastrectomy[3,48-50]. Previously post-gastrectomy diarrhea was attributed to vagotomy, endocrine hypofunction-related dyscoordination of the digestive tract, and abnormalities in the regulation of GI tract hormone secretion [50]. Although, as shown in IBD patients, chronic inflammation leads to damage of intestinal mucosa, dysregulation of intestinal ion transport, impaired and increased accessibility to the intestinal mucosa for pathogens[51]. Dysregulation of the expression and/or function of epithelial ion transporters and channels leads to electrolyte retention and water accumulation causing diarrhea[30]. Loss of epithelial barrier function contributes to diarrhea *via* a leak-flux mechanism, while mucosal penetration of enteric pathogens drives subsequent tissue damage[51]. Furthermore, patients suffering diarrhea after gastrectomy showed an increased abundance of *Mogibacterium* and decreased abundance of *Ruminococcus 1*[27]. *Mogibacterium* is increased in Crohn's patients[52] and decreased *Ruminococcus 1* was associated with diarrhea in an experimental porcine model[53].

Other common GI symptoms in gastrectomized patients are abdominal discomfort and bloating[27,48-50]. Both of these symptoms were associated with a decrease in *Agathobacter*[27]. These butyrate producers live in symbiosis with *Bifidobacteria*, which provides acetate as a substrate for butyrate production[54]. Abdominal discomfort was also, associated with increased abundance of *Holdemanella*[27]. There is a lack of evidence on the impact of *Holdemanella* on host health, although, their taxonomic family *Erysipelotrichaceae* contains highly immunogenic species and is associated with

pro-inflammatory conditions[27,55].

INCREASED OXYGEN LEVEL IN THE GUT AFTER GASTRECTOMY AND ITS IMPACT ON THE GUT MICROBIOME

The important anatomical and physiological changes in the GI tract after gastrectomy include increased oxygen in the distal part of the gut[56], which may provide an appropriate niche for aerobic and facultative anaerobic microbes. The studies on the gut microbiome after gastrectomy consistently showed an increased abundance of aero-tolerant microorganisms[27,28,34]. Erawijantari *et al*[6] demonstrated an increased abundance of aerobes (*Streptococcus, Enterococcus)* and facultative anaerobes (*Escherichia, Enterobacter,* and *Streptococcus)* in patients after gastrectomy. The study by Lin *et al*[28] showed a higher amount of aero-tolerant *Proteobacteria* phylum microorganisms including *Streptococcus, Escherichia*, and *Klebsiella*[28]. Similar, studies by Liang *et al*[29] and Horvath *et al*[27] demonstrated increased numbers of aerobes (*Streptococcus*) and facultative anaerobes (*Escherichia*) in patients after subtotal gastrectomy[27,29]. The increase in *Escherichia* was the most prominent difference between the microbiome of gastrectomy patients and controls documented in all studies[27-29,34]. *Escherichia* is a common protagonist in small intestinal bacterial overgrowth (SIBO)[57], which is a heterogeneous syndrome characterized by an increased number and/or abnormal type of bacteria in the small bowel[57]. SIBO occurs in the majority of patients after gastrectomy[58], and the clinical manifestation of this syndrome includes bloating, flatulence, abdominal discomfort, diarrhea, and abdominal pain[57], symptoms which are common in long-term survivors after gastrectomy[3,48-50].

Taken together, there is evidence associating GI symptoms after gastrectomy with specific changes in the gut microbiome composition, although further studies are warranted to confirm these findings and the exact mechanisms involved.

THE IMPACT OF BILIARY DIVERSION AFTER GASTRECTOMY ON THE GUT MICROBIOME

GI tract reconstruction following gastrectomy may lead to biliary diversion. The altered bile acid flow potentially stimulates the growth of bile acid-transforming bacteria[34]. The study by Erawijantari *et al*[6] extensively analyzed the fecal metabolomic profile and showed increased abundance of the secondary bile acid - deoxycholic acid (DCA) in gastrectomized patients[6]. Deconjugation of human primary bile acids and their subsequent biotransformation to secondary bile acids is a well-recognized function carried out by the human gut microbiome with its implications for human health[59]. The 7α-dehydroxylation reaction has been described as the most quantitatively important process for the formation of secondary bile acids performed by the gut microbiome, specifically the bacteria that belong to the genus *Clostridium*[60]. The increased abundance of *Clostridium* following gastrectomy was confirmed in several studies[28,34]. Altered bile acid pool composition has been associated with several diseases including colorectal cancer[61,62], IBD, and metabolic syndrome[60].

DCA is a carcinogen in liver cancer and colorectal cancer[34,61,62]. Increased DCA in the intestine causes DNA damage through oxidative stress in intestinal epithelial cells and activates the epidermal growth factor receptor or Wnt pathways to promote colorectal cancer (CRC)[63]. These mechanisms may be responsible for the increased risk of metachronous CRC in GC patients[7,8]. Furthermore, the altered bile flow-induced gut microbiome changes were suggested as one of the potential mechanisms for the metabolic effect of gastrectomy[28]. Patients after subtotal gastrectomy with RYGJ or B2 reconstruction were shown to have a lower body mass index or waist circumference compared to age and sex-matched healthy controls in the study by Lin *et al*[28]. Also, subtotal gastrectomy had some more positive effects such as higher serum high-density lipoprotein, lower total cholesterol, and triglyceride levels[28]. Only patients who underwent RYGJ showed a lower prevalence of metabolic syndrome and type 2 diabetes[28]. The exact mechanisms linking subtotal gastrectomy with metabolic improvement remain unclear; however, some gut microbiome involving pathways were suggested[28]. They include: (1) The impact of the gut microbiome on the enteroendocrine function; (2) Altered bile acid flow, which is a

driver for changes in microbiome composition; and (3) Decreased levels of circulating lipopolysaccharides and altered bacterial components promoting hepatic insulin sensitivity[28].

LIMITATIONS OF THE CURRENT KNOWLEDGE AND PERSPECTIVES FOR FUTURE RESEARCH

The knowledge provided by the current studies has some limitations. First, most of the studies were cross-sectional design[27,28,34], and the only longitudinal study by Liang *et al*[29] was limited by a very small sample size and short follow-up[29]. Thus, there is a lack of data showing microbiome composition changes pre- and post-gastrectomy. Second, some studies included controls who were on gastric acid suppression medications or did not record the history of antibiotic use. These medications have a strong effect on the gut microbiome, thus, the impact of gastrectomy may have been underestimated[64]. Third, the current studies included patients with different extents of gastrectomy (total *vs* subtotal) and different types of reconstructions (B2, RYGJ, Billroth I). The impact of gastrectomy on the gut microbiome may be specific for the type of surgery; thus, future studies should clarify the impact of types of reconstruction after gastrectomy. Together, the present knowledge provides evidence on the impact of gastrectomy on the gut microbiome. These changes are driven by an altered environment in the GI tract, including loss of the gastric barrier, an increase in oxygenation levels in the distal gut, and biliary diversion. Further well-designed and appropriate size longitudinal studies are necessary to confirm this concept. These studies should incorporate data on health-related quality of life, especially on GI symptoms, metabolomics, and markers on intestinal inflammation and permeability to provide robust evidence on the impact of gastrectomy-induced dysbiosis on host health.

Several ongoing studies are already investigating gut microbiome changes through the GC treatment pathway. The LEGACY-2 trial (NCT04015466) is a large-scale international study aiming to study biological factors, including microbiome impact on clinical outcomes. The NeoChance trial (NCT04196465) is investigating the microbiome as a predictive/prognostic biomarker in patients who receive neoadjuvant immune checkpoint inhibitor IMC-001 for resectable GC. The NutriGIT (NCT04476082) study is investigating the nutritional status of patients with various GI cancers, including GC, and one of the study outcomes is changes in the gut microbiome. Together, these studies will increase the knowledge on microbiome changes through GC treatment and will highlight the impact of these changes on treatment outcomes. However, current studies are not designed to specifically investigate gastrectomy-induced dysbiosis; thus, such studies are still necessary.

The recent studies linked gut microbiome composition with the effectiveness of anti-cancer therapy[45,65]. An exploratory analysis of genus from the DELIVER trial showed that *Odoribacter* and *Veillonella* were associated with tumor response to Nivolumab in patients with advanced GC[45]. As mentioned previously, the abundance of typical oral bacteria-*Veillonella* increases following subtotal gastrectomy, due to the oralization phenomenon[27]. However, there is currently a lack of evidence to reliably characterize the impact of gastrectomy-induced dysbiosis on the effectiveness of anti-cancer therapy. As systemic therapy before and/or after surgery is the modern standard for GC, it would be of interest to investigate the association between gut microbiome and the efficacy of therapy in future studies.

CONCLUSION

Gastrectomy for GC impacts the composition of the gut microbiome. These changes are characterized by oralization, an increase in aero-tolerant bacteria (aerobes/facultative anaerobes), and increased abundance of bile acid-transforming bacteria. These changes are driven by an altered environment in the GI tract, including loss of the gastric barrier, an increase in oxygenation levels in the distal gut, and the biliary diversion after gastrectomy. Gastrectomy-induced dysbiosis is associated with host health. However, current evidence is limited; therefore, further longitudinal studies looking at different reconstructions of the GI tract are needed to confirm the concept and to investigate the mechanisms related to the impact of the gut microbiome on the health of GC patients.

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PART 2: Distal gastrectomy with Billroth II reconstruction is associated with oralization of the gut microbiome and intestinal inflammation: a Proof-of-Concept Study

Angela Horvath; Augustinas Bausys; Rasa Sabaliauskaite; Eugenijus Stratilatovas; Sonata Jarmalaite; Burkhard Schuetz; Philipp Stiegler; Rimantas Bausys; Vanessa Stadlbauer; Kestutis Strupas

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ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH AND BIOMARKERS

Distal Gastrectomy with Billroth II Reconstruction is Associated with Oralization of Gut Microbiome and Intestinal Inflammation: A Proof-of-Concept Study

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ABSTRACT

Background. Subtotal gastrectomy with Billroth II reconstruction (SGB2) results in increased gastric pH and diminished gastric barrier. Increased gastric pH following PPI therapy has an impact on the gut microbiome, intestinal inflammation, and possibly patient health. If similar changes are present after SGB2, these can be relevant for patient health and long-term outcomes after surgery. The aim of the study is to investigate whether SGB2 is associated with specific changes in gut microbiome composition and intestinal inflammation.

Patients and Methods. This cross-sectional proof-of-concept study includes patients after SGB2 (n = 14) for early gastric cancer and their nongastrectomized in-house relatives as controls (n = 8). Fecal microbiome composition, intestinal inflammation (fecal calprotectin), gut permeability (DAO, LBP, sCD14), systemic inflammation (CRP) markers, and gastrointestinal symptoms are investigated. This study is registered at ClinicalTrials.gov (NCT03418428).

Results. Microbiome oralization following SGB2 was defined by an increase in *Escherichia–Shigella*, *Enterococcus*, *Streptococcus*, and other typical oral cavity bacteria (*Veillonella*, *Oribacterium*, and *Mogibacterium*) abundance. The fecal calprotectin was increased in the SGB2 group [100.9 (52.1; 292) vs. 25.8 (17; 66.5); p = 0.014], and calprotectin levels positively correlated with the abundance of *Streptococcus* (r_s = 0.639; p_{adj} = 0.023). Gastrointestinal symptoms in SGB2 patients were associated with distinct taxonomic changes of the gut microbiome.

Conclusions. SGB2 is associated with oralization of the gut microbiome; intestinal inflammation and microbiome changes were associated with gastrointestinal symptoms. These novel findings may open gut microbiome as a new target for therapy to improve quality of life and general patient health in long-term survivors after SGB2.

Gastrectomy is the only potentially curative treatment option for gastric cancer (GC), one of the most common malignancies worldwide.[1,2] Most patients with non-metastatic GC require total or subtotal gastrectomy with extended lymph node dissection. The method to reconstruct the gastrointestinal (GI) tract integrity after subtotal gastrectomy (SG) remains controversial, while Billroth I (B1), Billroth II (B2), or Roux-en-Y (RY) are all available and acceptable methods.[3] Irrespective of type of reconstruction, SG results in serious anatomical and physiological changes in the GI tract, including increase in gastric pH due to

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reduced secretion of the gastric acid.[4–6] Therefore, there is a strong rationale to expect alterations that are typical for gastric acid suppression in the gut microbiome following SG.

Changes in the gastric and distal GI microbiome following gastric acid suppression have been proposed by studies investigating the impact of proton pump inhibitors (PPI) on the microbiome.[7–10] PPI intake alters the composition and increases the diversity of the gastric microbiome.[7] In the distal GI tract that is naturally rich in microbes, the microbial diversity decreases after PPI intake.[8–10] Moreover, the fecal microbiome shows increased levels of predominantly oral bacteria, such as *Streptococcus, Veillonella, Rothia*, or *Oribacterium*, as well as an increase of potential pathogens, such as *Enterococcus, Escherichia–Shigella*, or *Haemophilus*, after PPI therapy. At the same time, autochtonous and beneficial bacteria, including *Faecalibacterium*, *Ruminococcaceae*, and *Lachnospiraceae*, decrease significantly.[8,9,11–13] Recently, the increase in oral bacteria in the stool of patients with liver cirrhosis was linked to intestinal inflammation, gut barrier disruption, and 3-year mortality.[14] The described alterations in the microbial composition were partly attributed to the loss of the gastric acid barrier.[15] Since gastric pH increases after SG with B2 reconstruction (SGB2), we hypothesize that similar alterations of the microbiome might occur in gastrectomized patients. This study investigates whether SGB2 is associated with specific increased gastric pH-related changes in gut microbiome composition and intestinal inflammation.

PATIENTS AND METHODS

Study Participants

Patients older than 18 years with a history of subtotal gastrectomy for early gastric cancer (EGC) were included in the study group (SGB2 group). The EGC was defined as invasive gastric cancer that invades no more deeply than the submucosa, irrespective of lymph node metastasis.[16] EGC patients were selected to avoid the potential impact of the disease or intensive adjuvant chemotherapy on the gut microbiome. All patients underwent open subtotal gastrectomy with a D2 lymphadenectomy as described in the fourth version of the Japanese Gastric Cancer Treatment guidelines [17] at the National Cancer Institute, Vilnius, Lithuania. Following resection, the gastrointestinal tract integrity was reconstructed by the antecolic end to side gastrojejunostomy on a long loop with a handsewn anastomosis (Billroth II). Braun's side to side jejunostomy was performed in all cases approximately 30 cm below gastrojejunostomy. Patient's in-house relatives without a history of gastric surgery were included in the control group. The exclusion criteria for the participants were as follows: (1) chemotherapy or radiotherapy 12 months prior to inclusion, (2) gastric stump cancer, (3) usage of antibiotics, pro-, pre-, or synbiotics, H2-blocker, or PPI 1 month prior to inclusion, (4) history of any other gastrointestinal tract resections than SGB2, (5) recurrence of gastric cancer, and (6) current nongastric malignancies.

Stool Sample Collection and Sequencing

To evaluate the gut microbiome, fresh stool samples were collected from the study participants and immediately stored at − 80 °C until the DNA extraction. DNA was extracted with the MagNA Pure LC DNA Isolation Kit III (Bacteria, Fungi) (Roche, Mannheim, Germany) according to the manufacturer's instructions. Hypervariable region V1–V2 was amplified (primers: 27F-AGAGTTTGATCCTGGCTCAG; R357-CTGCTGCCTYCCGTA) and sequenced using Illumina Miseq technology (Illumina, Eindhoven, the Netherlands), as previously published.[18] Sequencing data are made publicly available in the National Center for Biotechnology Information (NCBI) sequence read archive (accession no. PRJNA592441).

Processing of Sequence Data

Raw sequencing data were processed using QIIME 2 tools on a local Galaxy instance (https://galaxy.medunigraz.at/).[19] Denoising (primers removing, quality filtering, correcting errors in marginal sequences, removing chimeric sequences, removing singletons, joining paired-end reads, and dereplication) was done with DADA2.[20] Taxonomy was assigned based on Silva 132 database release at 99% operational taxonomic unit level with a naïve Bayes classifier.

Laboratory Assessment

Enzyme-linked immunsorbent assay (ELISA) was used to measure fecal calprotectin, serum diamine oxidase (DAO) (both: Immundiagnostik, Bensheim, Germany), lipopolysaccharide binding protein (LBP, Hycult Biotech, Uden, the Netherlands), and soluble CD14 (sCD14, R&D Systems, Minneapolis, MN).

Gastrointestinal Symptoms

The Lithuanian versions of the European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and gastric cancer-specific module—EORTC QLQ-STO22—were used to

assess patient's quality of life. For the analysis, the answers to the questions on the abdominal discomfort, diarrhea, and abdominal bloating were dichotomized into "symptoms" and "no symptoms" categories. Gastrointestinal symptoms were associated with the microbiome composition.

Statistical Analysis

For statistical analysis of microbiome compositions, the web-based application Calypso (version 8.84) was employed. Features were normalized by total sum scaling and square root transformation. Alpha diversity analysis was quantified by the Shannon index. For further analysis, features were summarized to the corresponding genera. Beta diversity was examined by principal coordinate analysis (PCoA) based on a Bray–Curtis dissimilarity matrix with analysis of similarity (ANOSIM), as well as redundancy analysis (RDA) with one or multiple explanatory variables. Analysis of composition of microbiomes (ANCOM) and linear discriminant analysis (LDA) effect size (LEfSe) were used to compare the abundance of genera between groups. Network analysis was used to visualize significant correlations between taxa in both the SGB2 and control groups using Spearman correlation and only considering positive associations.

For statistical analysis of patients' characteristics and gut permeability data, SPSS 23 was used. Categorical variables were compared with the Chi squared test, and continuous variables with the Mann–Whitney U test. Spearman's rank correlation coefficient was used to explore associations between variables. p value < 0.05 was considered to be significant. Benjamini–Hochberg correction was applied where appropriate.

RESULTS

Fourteen patients were included in the SGB2 group, and eight participants in the control group. The baseline clinicopathological characteristics are presented in Table 1. Six (75.0%) controls were spouses, and two (25.0%) were children. Participants in the control group were younger than the patients and predominantly female. The median time from surgery to enrollment was 45 (Q1;Q3: 26;63) months, while the minimum and maximum times were 6 and 101 months, respectively. Three (21.4%) patients received adjuvant chemotherapy following surgery, although in all cases, at least 12 months prior to the enrollment. None of the patients had disease recurrence at time of enrollment (Fig. 1).

Microbiome Composition

In total, 2,042,502 sequencing reads were generated. After denoising, an average of 39,085 (min: 24,549; max: 49,361) reads per sample were available for analysis. Alpha diversity assessed by Shannon index after rarefication (sampling depth: 24,549 reads) was significantly decreased in gastrectomy patients compared with controls ($p = 0.025$, Fig. 2a). Median bacterial richness quantified by Chao1 index was comparable between groups ($p = 0.69$).

Beta diversity analysis showed significant differences between the microbiome composition of patients and controls (ANOSIM: $r = 0.442$; $p = 0.001$) (Fig. 2b). ANCOM identified the genus *Escherichia–Shigella* to be more abundant in SGB2 patients compared with controls (fold-change = 302.7) (Fig. 2c). LEfSe corroborated this finding and attributed 11 additional genera to SGB2 and 17 genera to the control group. Of these 29 genera, 13 (45%) have been implicated in PPI-induced or PPI-associated dysbiosis in previous reports (Fig. 3). Network analysis of the 30 most abundant bacterial families showed associations between *Enterococcaceae*, *Synergistaceae, Enterobacteraceae, Fusobacteraceae, Streptococcaceae, Clostridiales* vadinBB60 group, and *Prevotellaceae* within the microbiomes of patients, and between *Barnesiellaceae, Bacteroidaceae, Ruminococcaceae, Lachnospiraceae, Erysipelotrichaceae*, and *Coriobacteriaceae* in the microbiomes of controls (Fig. 4). To exclude sex and age differences as potential confounders, RDA with multiple explanatory variables was performed but did not detect a significant influence of age (variance = 9.39; $F = 1.07$; $p = 0.358$) or sex (variance = 8.54; $F = 0.97$; $p = 0.529$) on the composition of the microbiome next to SGB2 (variance = 20.34; $F = 2.32$; $p = 0.001$).

Inflammation and Gut Permeability

Fecal calprotectin as a marker of intestinal inflammation was significantly higher in SGB2 patients compared with controls. DAO, LBP, and sCD14 as markers for gut permeability and C-reactive protein (CRP) levels as a marker for systemic inflammation were comparable between groups. Details are given in Table 2.

Correlation analysis was done with all genera attributed either to the SGB2 or the control group (Fig. 3), and biomarkers of inflammation and gut barrier function. Fecal calprotectin was positively correlated with the abundance of *Streptococcus* ($r_s = 0.639$; $p_{adj} = 0.023$) and negatively correlated with the abundance of *Ruminococcaceae UCG014* ($r_s = -0.755$; $p_{adj} = 0.002$), *Barnesiella* ($r_s = -0.748$; $p_{adj} = 0.002$), *Ruminococcus 2* ($r_s = -0.649$; $p_{adj} = 0.014$), *Ruminococcus 1* ($r_s = -0.616$; $p_{adj} = 0.022$),

TABLE 1 Clinicopathologic characteristics of study patients; data given as median (Q1; Q3)

	SGB2 (n = 14)	Controls (n = 8)	p
Age (years)	68 (64; 74)	59 (41; 65)	0.035
Sex			
Male	10 (71.4%)	1 (12.5%)	0.024
Female	4 (28.6%)	7 (87.5%)	
BMI (kg/m^2)	24.7 (21.5; 28.4)	24.9 (22.0; 32.8)	0.616
Smoking	7 (50%)	1 (12.5%)	0.167
Systolic BP (mmHg)	130 (126; 135)	126 (122; 136)	0.525
Diastolic BP (mmHg)	79 (76; 90)	75 (71; 80)	0.297
CRP level (mg/l)	0.7 (0.3; 5.1)	0.8 (0.3; 1.6)	0.868
Tumor invasion			
Mucosal	5 (35.7%)	–	
Submucosal	9 (64.3%)	–	
Lymph node metastasis	4 (28.5%)		
Adjuvant chemotherapy	3 (21.4%)	–	
Medication			
Antihypertensive drugs (ACEI; BB; CCB; ARB, diuretics or combination)	10 (71.4%)	3 (37.5%)	0.187
Statins	1 (7.1%)	0 (0%)	0.999
Anticoagulants/antiplatelet drugs	2 (14.2%)	0 (0%)	0.515
Benzodiazepines/antipsychotic drugs/antidepressants	2 (14.2%)	1 (12.5%)	0.999
Gastrointestinal symptoms			
Abdominal discomfort	9 (69%)	5 (62.5%)	0.751
Diarrhea	7 (54%)	1(12.5%)	0.058
Bloating	6 (46%)	4 (50%)	0.864

BMI Body mass index, *BP* blood pressure, *CRP* C-reactive protein, *ACEI* angiotensin-converting enzyme inhibitors, *BB* beta-blockers, *CCB* calcium channel blockers, *ARB* angiotensin II receptor blockers

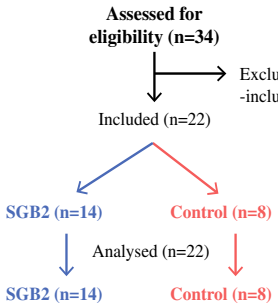

FIG. 1 Trend flowchart of enrollment

and *Anaerostipes* (r_s = −0.572; p_{adj} = 0.041). Age, years since surgery, DAO, LBP, sCD14, and CRP levels were not significantly correlated with any of the indicated genera.

Associations with Gastrointestinal Symptoms

The most commonly documented gastrointestinal symptoms after SGB2 were abdominal discomfort (n = 9; 69%), diarrhea (n = 7; 54%), and bloating (n = 6; 46%). Patients who complained about abdominal discomfort showed higher abundance of *Holdemanella* (p = 0.034) and lower abundance of *Agathobacter* (p = 0.006) in their fecal microbiome. Diarrhea was associated with a significantly higher abundance of *Mogibacterium* (p = 0.035) and significantly lower abundance of *Ruminococcus 1* (p = 0.035). Patients who reported bloating showed a significantly lower abundance of *Agathobacter* (p = 0.035) and *Streptococcus* (p = 0.035). Details are shown in Fig. 5. Patients who suffered from diarrhea also showed significantly higher serum levels of CRP and a trend to higher calprotectin level in stool compared with patients without diarrhea [CRP (mg/l): 5 (0.4; 5.6) vs. 0.3 (0.3; 0.4), p = 0.035, respectively, and calprotectin (ng/mg): 371.4 (80.0; 526.5) vs. 66.2 (35.3; 100.9), p = 0.132, respectively]. DAO, LBP, and sCD14 levels were not different

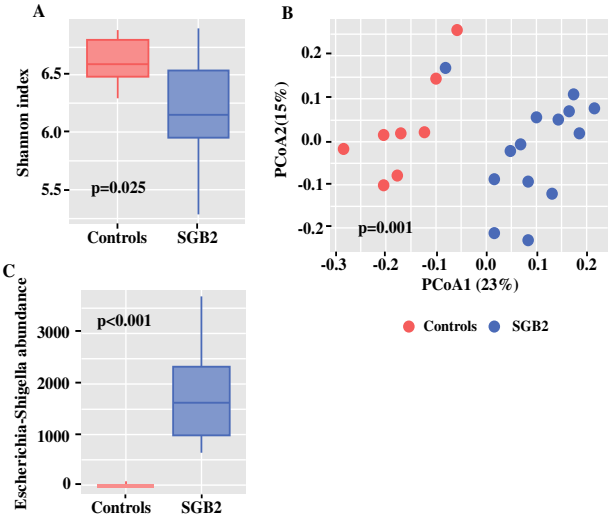

FIG. 2 Changes in microbiome of SGB2 patients compared with controls: **a** Shannon index as a measurement of alpha diversity, **b** principal coordinate analysis plot based on Bray–Curtis dissimilarity, and **c** abundance of *Escherichia–Shigella* in microbiome of SGB2 patients and controls

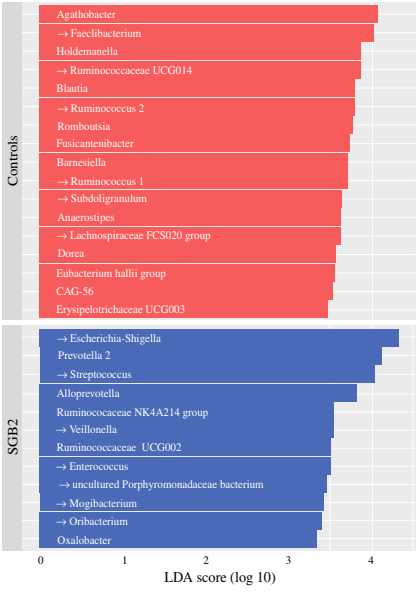

FIG. 3 LDA effect size (LEfSe) results; genera marked with an arrow previously indicated in PPI-induced or PPI-associated dysbiosis

among patients with and without diarrhea. Neither abdominal discomfort nor bloating was associated with increased inflammation or gut permeability markers.

DISCUSSION

We investigated the alteration in the fecal microbiome of patients after SGB2. Our results clearly show the impact of SGB2 on the general gut microbiome composition, with decreased alpha diversity by Shannon index after SGB2 and significant differences in beta diversity between patients and healthy controls as well as taxonomic composition. Taxon comparisons revealed that approximately half of the genera with altered abundance have been linked to PPI therapy in previous studies. PPI intake increases the gastric pH from the physiological level of approximately 2.0 to over 6.0,[21] considerably higher than pH 4, which is considered to be the threshold value for powerful bactericidal effect.[22] Similar to PPI intake, SGB2 causes permanent increase of the gastric pH to values above 6.0.[23] Therefore, our findings can be explained by the comparable loss of gastric barrier function after SGB2 and by PPI use. Vice versa, our results support the notion that PPI-induced microbiome changes are caused by acid suppression and are most likely not due to direct drug-induced effects on microbes.

The steep increase in *Escherichia–Shigella* was the most prominent difference between the microbiome of SGB2 patients and that of healthy controls. *Escherichia* is a

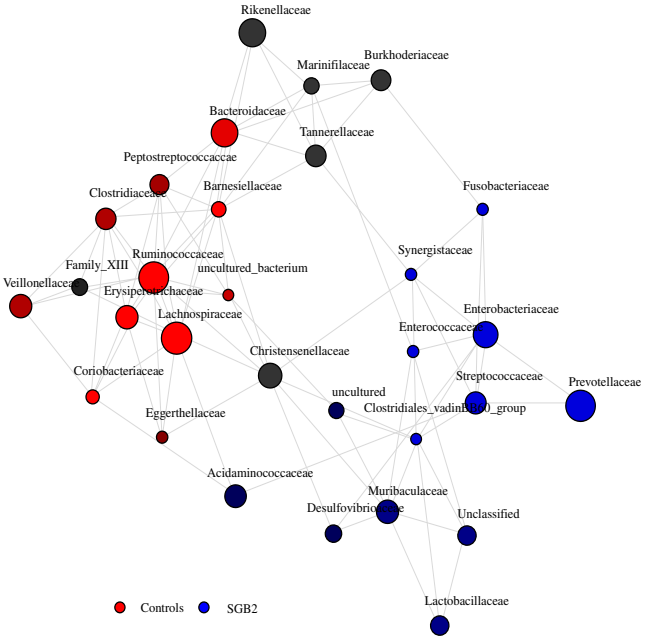

FIG. 4 Network analysis representing positive correlations between 30 most abundant genera

TABLE 2 Intestinal inflammation and permeability markers in patients and controls; data given as median (Q1; Q3)

	SGB2 (n = 14)	Controls (n = 8)	p
Fecal calprotectin (ng/mg)	100.9 (52.1; 292)	25.8 (17; 66.5)	0.014
DAO (U/ml)	24.3 (11.2; 32.3)	19.6 (14.2; 27.2)	0.616
LBP (μg/ml)	15.8 (11.9; 20.1)	14.3 (11.6; 19.9)	0.868
sCD14 (μg/ml)	1.7 (1.6; 2.1)	1.7 (1.5; 1.9)	0.441

DAO Serum diamine oxidase, *LBP* lipopolysaccharide binding protein

common protagonist in small intestinal bacterial overgrowth (SIBO),[24] which occurs in the majority of patients after gastrectomy and is associated with intestinal and postprandial symptoms.[25] A similar observation was made in children after PPI therapy.[26] Although members of the genus *Escherichia–Shigella* are not sensitive to pH variations in their environment, these seem to profit from the altered milieu, since these were also found to be increased in the general population after PPI intake.[8,27] The observed increase in *Enterococcus*, a bacterium that is also often involved in SIBO, however, is directly attributable to the increased gastric pH. In a model of gastric barrier dysfunction, both genetic and pharmaceutical blockage of acid secretion in the stomach resulted in increased survival of orally gavaged *Enterococcus*.[15] Moreover, after SGB2, patients showed a significant increase in *Streptococcus*. *Streptococcus* is a prevalent bacterial taxon in the oral cavity and the most commonly described bacterium in PPI-induced dysbiosis.[8,9,11–13] This was recently linked to intestinal inflammation and gut permeability in cirrhosis patients.[14] In the present study, we showed that *Streptococcus* is also associated with intestinal inflammation in patients after SGB2. Together with other oral bacteria (*Veillonella*, *Oribacterium*, and *Mogibacterium*), the observed increase in *Streptococcus* abundance supports the hypothesis of oralization after gastric acid barrier disruption, also in patients after SGB2. Furthermore, several beneficial commensals were decreased in the microbiome of SGB2 patients. The loss of these commensals correlated with the increase in calprotectin levels in stool. Especially

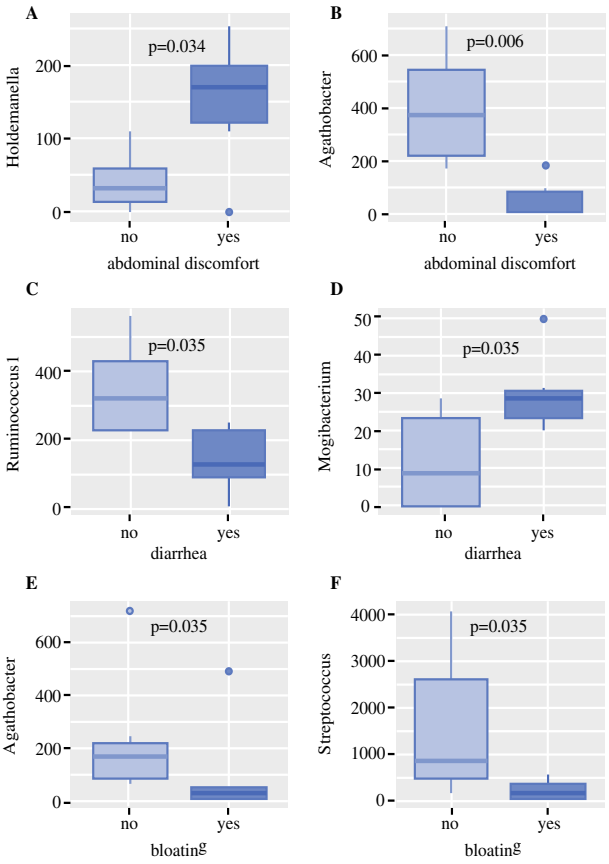

FIG. 5 Symptom-related microbiome changes in patients after SGB2: **a**, **b** significant differences in genera of interest between patients with and without abdominal discomfort, **c**, **d** significant differences in genera of interest between patients with and without diarrhea, and **e**, **f** significant differences in genera of interest between patients with and without bloating

the diminished abundance of *Faecalibacterium*, *Subdoligranulum*, and members of the *Ruminococcaceae* and *Lachnospiraceae* family again is similar to PPI dysbiosis.[9,11,12,14]

Besides the important pathophysiological information, our study may also have clinical implications for patients after SGB2. Chronic intestinal inflammation after SGB2 plays an important role in the patients' health and quality of life. Although overall quality of life scores show an immediate deterioration after surgery followed by an increase to approximately normal levels within the first year, gastrointestinal symptoms remain a significant issue long after SG.[28–30] In the present study, calprotectin levels were markedly increased in SGB2 patients and strongly associated with the presence of *Streptococcus* in the stool. A very similar pattern can be found in patients with long-term PPI use, in whom increased calprotectin levels and associations between oralization and inflammation have been described in previous reports.[14,31,32] Chronic intestinal inflammation has been described in the pathogenesis of chronic diarrhea after SGB2.[33] Intermittent or permanent chronic diarrhea is one of the most common problems in long-term survivors after gastrectomy,[28,34,35] present in about 40% of patients.[36] In the present study, approximately 54% of patients also suffered from diarrhea and showed higher calprotectin levels on average than patients without diarrhea, although this observation did not reach statistical significance, and validation in bigger studies is

warranted. In patients with diarrhea, *Ruminococcus 1* was depleted, and *Mogibacterium* was overrepresented. *Ruminococcus 1* is a ubiquitous genus in the human microbiome that has the ability to degrade complex carbohydrates and provide nutrients for other commensals.[37] *Ruminococcus* species have been associated with a stable human microbiome in previous reports,[38] and decreased abundance was associated with diarrhea in a porcine animal model.[39] *Mogibacterium* was found to be increased in Crohn's disease and colorectal cancer patients.[40,41] Other common gastrointestinal symptoms were abdominal discomfort and bloating. Both symptoms were associated with a decrease of *Agathobacter*. *Agathobacter* are butyrate producers who live in symbiosis with *Bifidobacteria*, giving them access to acetate as a substrate for butyrate production.[42] Moreover, an increased abundance of *Holdemanella* was observed in patients with abdominal discomfort. Comprehensive studies on *Holdemanella* on human health are lacking, however, their taxonomic family *Erysipelotrichiaceae* contains highly immunogenic species and is associated with proinflammatory conditions.[43] Interestingly, patients who reported bloating also showed a reduced abundance of *Streptococcus*. *Streptococcus* is the foremost genus in PPI-associated dysbiosis and has been linked to inflammation and gut barrier dysfunction before. However, the genus *Streptococcus* entails also beneficial species, such as *S. salivarius* subsp. *thermophilus* that is utilized in various probiotic products. VSL#3, which contains a *Streptococcus* species among others, has been shown to reduce bloating in patients with irritable bowel syndrome.[44,45] Similarly, another multispecies probiotic containing *S. thermophilus* improved self-perceived gastrointestinal wellbeing.[46] More in-depth studies are necessary to clarify the role of different *Streptococcus* species in gastrointestinal health and disease. Nevertheless, the associations between gastrointestinal symptoms and the microbiome in SGB2 patients highlight the importance of comprehensive studies in this field to improve patients' postoperative outcomes and wellbeing.

Acid-unrelated changes in the microbiome of SGB2 patients include an increase of *Oxalobacter* abundance. *Oxalobacter* is an oxalate-metabolizing commensal that increases the colonic excretion of oxalate, which in turn, reduces the strain of calcium oxalate on the kidney.[47] In the present study, *Oxalobacter* was exclusively found in patients after SGB2 and was absent in healthy controls. Although clinical trials that utilized *Oxalobacter* as a probiotic in patients with primary hyperoxaluria were unsuccessful,[48] the natural occurrence of *Oxalobacter* after SGB2 might be a beneficial adaptation to the altered gastrointestinal physiology after SGB2.

The microbiome faces a variety of influencing factors, such as diet, gender, and age of the patient, that also need to be considered in cohort studies. By selecting in-house relatives as controls, we minimized the diet-related impact on gut microbiome composition as similar microbiome of individuals who share a household has already been shown previously,[49,50] but we had to accept an age and gender bias. Our multivatriate analysis showed that the impact of age and gender was overshadowed by the strong influence of SGB2 on the microbiome composition. This was not unexpected since the age difference between the groups was rather small, and the changes in the microbiome after SGB2 such as the steep *Enterococcus* increase were more dominant compared with changes due to age. However, comparisons are hard to draw, since data on the aging microbiome are limited, and the findings are inconsistent.[51,52] Gender-related differences in microbiome composition have been previously described in health and disease.[53–55] Natural male predominance in the gastric cancer group and the expected female predominance in our control group might hinder the detection of gender-related differences further. Chemotherapy may also have an impact on gut microbiome composition. Dysbiosis has been described in the short term after chemotherapy application and linked to mucositis and impaired capability to resist pathogen colonization.[56,57] However, there is a lack of data supporting whether dysbiosis persists in the long term, while this is still under investigation in an ongoing study.[58] Chemotherapy may have some long-lasting slight impact on the gut microbiome composition, potentially similar to long-lasting imprint described in healthy adults after exposure to short-term broad-spectrum antibiotics.[59] Therefore, in our present study, we could not rule out history of chemotherapy as a potential cofounder affecting microbiome, and excluded patients who received chemotherapy within the past 12 months.

Our results are in stark contrast to previously published sequencing data in patients with SG and B2 or RY reconstruction.[60] In said study, the genera *Oxlobacter*, *Veillonella*, *Streptococcus*, *Escherichia*, *Shigella*, and *Oribacterium* among others were attributed to the control groups, while these were a crucial part of the microbiome alteration after SGB2 in the present study. Although the previous study had a rather big sample size, healthy controls were insufficiently characterized, and the use of medication was not analyzed as a potential confounder, which might lead to misinterpretation of the results. As we showed in our study, changes after gastrectomy can mimic drug-induced changes in the microbiome and, therefore, obscure the effect of the surgery. Especially, gastric pH-associated changes might be vulnerable to uncharacterized drug use in the control groups since PPI use is among the

most dominant confounders in microbiome analysis in the general population.[61] Large well-characterized cohorts are needed to fully elucidate this topic.

Our proof-of-concept study has several limitations. First is the relatively small sample size of the study. To prove the concept of increased gastric pH-related changes in the microbiome, the cross-sectional design of the present study was sufficient, although this is lacking data to show microbiome composition changes pre- and post-SGB2. Even with the relatively small but homogenous cohort and well-selected controls of this study, we were able to clearly confirm our hypothesis and show that SGB2 is associated with changes in the gut microbiome that can be attributed to the increased gastric pH. Second, our study investigated the fecal microbiome composition only in patients who underwent SG with B2 reconstruction. Therefore, it remains unclear whether other types of anastomosis, such as B1 or RY, might have the same impact on the gut microbiome. Future studies including all types of anastomosis will be important for generalization of our findings. However, since B1 gastroduodenal anastomosis is a common technique, especially in Asian countries,[62] and RNY is the preferred method in Western countries,[63] these studies might require prospective multicenter studies on an international scale. However, the same increase of gastric pH to the level above 6 has been reported after SG irrespective of B1 or B2 anastomosis; [23] therefore, it seems likely that the oralization of the gut microbiome phenomena would be attributable to the SG itself, irrespective of the reconstructive method.

CONCLUSIONS

Our study shows that SGB2 is associated with microbiome oralization and intestinal inflammation. These findings prove that an increase in gastric pH irrespective of the reason for this increase is associated with typical microbiome changes. These novel findings may open gut microbiome as a new target for therapy to improve quality of life and general patient health in long-term survivors after SGB2.

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DISCLOSURE The authors declare no conflict of interest.

ETHICAL APPROVAL Vilnius regional biomedical research ethics committee approval (no. 158200-17-966- 477) was obtained before this study was conducted. The study was conducted according to the Declaration of Helsinki, and all participants gave written informed consent prior to enrolment. The study was registered at the ClinicalTrials.gov database before the start of recruitment (NCT03418428).

INFORMED CONSENT Informed consent was obtained from all patients.

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CHAPTER 5: SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES

SUMMARY & DISCUSSION

Chapter 1 of this thesis provides an introduction to the issue of gastric cancer, explores the principles of modern gastric cancer surgery, delves into the contemporary concept of neoadjuvant treatment, and examines the long-term impact of treatment on the health-related quality of life (HRQOL) of survivors. It draws attention to several shortcomings in current treatment methods, such as the significant rates of postoperative morbidity and mortality following gastrectomy. Additionally, it underscores the lack of clarity regarding the impact of neoadjuvant treatment on lymph node metastases. Furthermore, it addresses the unknown pathophysiology of various gastrointestinal symptoms that commonly affect patients who have undergone gastrectomy. Also, hypohesis and tasks for this project are overwieved in the chapter.

Prehabilitation has emerged as a strategy aimed at reducing postoperative morbidity following major oncologic surgeries. It involves improving a patient's functional capacity prior to the surgical procedure, enabling them to better tolerate the postoperative period and mitigate associated decline. In essence, the goal is to enhance the patient's physical well-being before surgery, leading to improved surgical outcomes. ***Part 1*** of **Chapter 2** provides a comprehensive summary of the current evidence pertaining to prehabilitation before esophagogastric cancer resections. The available studies exhibit significant heterogeneity in terms of design, interventions employed, and measured outcomes. Nevertheless, all of these studies confirm the positive effects of prehabilitation, ranging from enhanced physical performance and nutritional status to improved quality of life and even reduced postoperative morbidity. However, the optimal interventions for prehabilitation remain unclear, preventing their standardization and widespread adoption. Therefore, further research focusing on multimodal prehabilitation is imperative to develop optimal programs specifically tailored for patients with esophagogastric cancer (1). In ***Part 2*** of **Chapter 2** the protocol for multi-center, open-label randomized control trial comparing 90-days postoperative morbidity rate after gastrectomy for gastric cancer between patients with or without prehabilitation was developed (2). The study was conducted and results of the RCT are presented in ***Part 3*** of **Chapter 2.** Prehabilitation program that included exercise interventions focused on endurance, respiratory muscle strength, stretching, and resistance training as

well as nutritional and psychological support was shown to: 1) increase patients' physical capacity before the surgery (mean 6MWT change, +31 m, 95% CI: 14-48 m; p=0.001); 2) decrease rate of non-compliance with neoadjuvant treatment (RR=0.20, 95% CI: 0.20-0.56); 3) reduce number of patients with postoperative complications at 90 days after surgery by 60% (RR 0.40, 95% CI: 0.24-0.66) and 4) improves quality of life. Thus, it was concluded, that personalized, multimodal, home-based prehabilitation reduces postoperative complications in GC patients scheduled for surgery with or without preceding neoadjuvant chemotherapy. Also, prehabilitation improves patients' physical capacity, adherence to neoadjuvant treatment protocols, and quality of life.

Chapter 3 delves into the exploration of contemporary concerns surrounding neoadjuvant chemotherapy. It specifically focuses on the ambiguous influence of chemotherapy on lymph node metastases and the debatable ideal timing for surgery following the completion of neoadjuvant chemotherapy. In ***Part 1*** of the cohort study, an analysis was conducted on the histological specimens of 87 gastric cancer (GC) patients who underwent neoadjuvant chemotherapy. Among these patients, lymph node metastases were identified in 70.1% (n=61) of cases. Interestingly, only 19 patients (31.1%) were classified as nodal responders based on histological regression observed within lymph nodes. Notably, the regression of lymph node metastases was not found to be correlated with regression in the primary tumor. However, it was associated with improved long-term outcomes for the patients (3).

An international cohort study was conducted to investigate the optimal timing for gastrectomy following neoadjuvant chemotherapy (***Part 2***). The study included 280 GC patients who underwent neoadjuvant chemotherapy followed by surgery. Based on the duration between chemotherapy completion and surgery, the patients were categorized into three groups: the early-surgery group (ESG) with a time interval of ≤ 30 days (n = 70), the standard-surgery group (SSG) with an interval of 31-43 days (n = 138), and the delayed-surgery group (DSG) with an interval of ≥ 44 days (n = 72). The results showed that the rate of major pathologic response (mPR) was significantly higher in the ESG group (32.9%) compared to the SSG group (20.3%) and the DSG group (16.7%) (p = 0.047). After adjusting for patient, tumor, and treatment characteristics, the odds of achieving mPR were twice as high for patients who underwent early surgery (odds ratio [OR] 2.09; 95% confidence interval [CI] 1.01-4.34; p = 0.047). Importantly, the overall morbidity, severe complications, 30-day mortality, R0 resection (complete tumor removal), and retrieval of at least 15 lymph nodes rates were similar

across all three study groups. Furthermore, the long-term outcomes did not differ between the groups.In summary, the findings of this study suggest that early surgery, within 30 days of completing neoadjuvant chemotherapy, is associated with a higher rate of major pathologic response without compromising patient safety or long-term outcomes (4).

Chapter 4 delves into the effects of gastrectomy on the gut microbiome and its role in causing gastrointestinal symptoms that negatively impact patients' quality of life. ***Part 1*** provides an overview and summary of the current knowledge in this field. Although the available evidence is limited, we now understand that gastric cancer (GC) surgery brings about significant physiological and anatomical changes in the gastrointestinal (GI) tract. These changes include the loss of the gastric barrier, elevated oxygen levels in the distal gut, and biliary diversion following gastrectomy. Such alterations in the GI tract have a profound impact on the composition of the gut microbiome, ultimately affecting the well-being of the host. Dysbiosis induced by gastrectomy is characterized by an increase in the abundance of oral cavity bacteria, a rise in aero-tolerant bacteria (aerobes/facultative anaerobes), and an upsurge in bile acid-transforming bacteria. Moreover, this dysbiosis may be associated with intestinal inflammation, small intestinal bacterial overgrowth, various GI symptoms, and an elevated risk of colorectal cancer (5). ***Part 2*** of this chapter focuses on describing the dysbiosis induced by subtotal gastrectomy and its connection to gastrointestinal symptoms. To investigate this, a cross-sectional study was conducted, including patients who underwent distal gastrectomy for early gastric cancer, as well as their non-gastrectomized relatives who served as controls. The oralization of the microbiome following distal gastrectomy was characterized by an increase in the abundance of *Escherichia-Shigella, Enterococcus, Streptococcus*, and other typical oral cavity bacteria (*Veillonella, Oribacterium*, and *Mogibacterium*). The levels of fecal calprotectin, a marker of intestinal inflammation, were found to be elevated in the group of patients who underwent gastrectomy [100.9 (52.1; 292) vs. 25.8 (17; 66.5); $p = 0.014$], and these calprotectin levels positively correlated with the abundance of Streptococcus ($rs = 0.639$; $padj = 0.023$). Distinct taxonomic changes in the gut microbiome were associated with gastrointestinal symptoms such as abdominal discomfort, diarrhea, and bloating. The most commonly reported symptoms after distal gastrectomy were abdominal discomfort (69%), diarrhea (54%), and bloating (46%). Patients who experienced abdominal discomfort exhibited a higher abundance of *Holdemanella* ($p = 0.034$) and a lower abundance of *Agathobacter* ($p = 0.006$) in their fecal microbiome. Diarrhea was linked to a significantly higher abundance of *Mogibacterium* ($p = 0.035$) and a significantly lower abundance of *Ruminococcus 1*

($p = 0.035$). Patients reporting bloating displayed a significantly lower abundance of *Agathobacter* ($p = 0.035$) and *Streptococcus* ($p = 0.035$). These novel findings suggest that targeting the gut microbiome could serve as a new therapeutic approach to enhance the quality of life and overall health of long-term survivors following distal gastrectomy for gastric cancer. In conclusion, the main findings of present research project are:

1) Prehabilitation reduce morbidity in patients undergoing gastrectomy for gastric cancer;
2) Histologic regression of lymph node metastasis after preoperative chemotherapy predicts the increased survival of patients with non-metastatic resectable advanced gastric cancer;
3) An interval of no more than 30 days between the end of neoadjuvant chemotherapy and gastrectomy is associated with a higher major pathologic response rate, the same oncologic safety of surgery, and similar morbidity and mortality;
4) Subtotal gastrectomy with Billroth II reconstruction is associated with oralization of the gut microbiome. Intestinal inflammation and microbiome changes were associated with gastrointestinal symptoms.

FUTURE PERSPECTIVES TO IMPLEMENT PREHABILITATION IN TO THE DAILY PRACTICE

The growing body of evidence (1), including present findings, suggests that prehabilitation prior to GC surgery could be integrated into daily clinical practice, particularly due to its positive impact on short-term treatment outcomes. However, it is essential to consider the cost-effectiveness of novel interventions alongside their established effectiveness (6). To date, different approaches of prehabilitation have been explored, including unimodal or multimodal interventions, as well as home-based or supervised programs. Determining the most suitable type of prehabilitation for daily practice remains unclear (1). Multimodal and supervised programs may be the most effective approaches as they address the various challenges commonly faced by GC patients, encompassing physical, nutritional, and psychological aspects (1). Supervised prehabilitation enables strict monitoring of program adherence and facilitates necessary adjustments. However, such programs can place significant demands on financial and healthcare professional resources. Additionally, logistical challenges may hinder patient participation. Semi-supervised prehabilitation may serve as an excellent alternative to fully supervised programs, as demonstrated in the present study, where it effectively reduced morbidity after GC surgery. Furthermore, in the present

study, the intervention required only up to 8 hours of healthcare professional input per patient, making the associated financial burden potentially more acceptable.

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SANTRAUKA

Daktaro disertacijos tezės pateikiamos ginti kaip mokslinių straipsnių rinkinys. Visos disertacijos dalys yra susijusios, o kai kurios jų pažodžiui cituojamos iš žemiau pateiktų publikuotų straipsnių:

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Skrandžio vėžys

Skrandžio vėžys (SKV) yra penktas dažniausias piktybinis navikas pasaulyje. Kasmet nustatoma daugiau kaip 1 mln. naujų ligos atvejų ir daugiau kaip 750 tūkst. mirčių nuo šios ligos (1). Lietuvoje ši onkologinė liga taip pat yra penkta pagal dažnį, kasmet užregistruojama daugiau kaip 800 atvejų (Lietuvos vėžio registro duomenys). SKV galima suskirstyti į dvi dideles grupes atsižvelgiant į anatominę susirgimo lokalizaciją: kardialinės dalies SKV, atsirandantis proksimalinėje skrandžio dalyje, ir nekardialinės dalies SKV, atsirandantį distalesnėse skrandžio dalyse (2). Skirtingos lokalizacijos navikams būdingi skirtingi rizikos veiksniai ir patogenezės mechanizmai. Nekardialinės dalies SKV dažniausiai sukelia lėtinė *Helicobacter pylori* infekcija. Kiti nekardialinės SKV rizikos veiksniai yra alkoholio ir tabako vartojimas, didelis perdirbtos, sūdytos ar rukytos mėsos bei žuvies vartojimas ar nepakankamas vaisių ir daržovių vartojimas. Kardialinės dalies SKV paprastai nėra susijęs su *H.Pylori* infekcija. Manoma, kad pagrindiniai rizikos veiksniai sirgti šios dalies SKV yra nutukimas ir gastroezofaginio refliukso liga (1,3,4). Pastaruosius kelis dešimtmečius daugumoje šalių sergamumas ir mirtingumas nuo nekardinės dalies SKV nuolat mažėjo. Tokią teigiamą tendenciją galima paaiškinti sėkmingomis pastangomis siekiant mažinti sergamumą, įskaitant *H.Pylori* paplitimo mažėjimą ir maisto konservavimo bei laikymo technologijų tobulinimą. Priešingai, Vakarų šalyse sergamumas kardialinės dalies SKV nuo 1960-ųjų iki 1980-ųjų didėjo, tačiau šiuo metu, atrodo, stabilizavosi (1,5). Naujausi epidemiologiniai tyrimai nurodo, kad sergamumas SKV (tiek kardialine, tiek nekardialine) didėja tarp jaunų suaugusiųjų (<50 metų). Ankstesniuose Jungtinėse Amerikos Valstijose atliktuose tyrimuose, kuriuose daugiausia dėmesio skirta nekardialiniam

skrandžio vėžiui, nustatyta, kad sergamumo SKV padidėjimas tarp jaunų asmenų daugiausia pastebimas tarp baltųjų rasės asmenų gyvenančių aukštesnio ekonominio gerbūvio vietovėse. Tokie sergamumo pokyčiai aiškinami nauja hipoteze teigiančia, kad sergamumas SKV tarp jaunų asmenų didėja dėl išaugusio sergamumo autoimuniniu gastritu bei išaugusio antibiotikų ir antacidinių vaistų vartojimo keičiančio skrandžio mikrobiotą (1, 5). Nepaisant to, kad bendras sergamumas SKV mažėja, ši ligas išlieka aktualia onkologine problema visame pasaulyje.

Skrandžio vėžio chirurginis gydymas

Chirurginis SKV gydymas išlieka pagrindinis ir vienintelis visiško pasveikimo leidžiantis tikėtis gydymo metodas (6). SKV chirurgijos tikslas - pašalinti naviką išlaikant pakankamą rezekcinį kraštą bei atliekant pakankamos apimties limfonodektomiją. Operacijos apimtis pasirenkama atsižvelgiant į naviko dydį, histologinį tipą bei naviko anatominę lokalizaciją. Šiuo metu vis dar vyksta diskusijos dėl to koks proksimalinis rezekcijos kraštas yra būtinas, tačiau šiandieninės Japonijos Skrandžio Vėžio Gydymo Gairės rekomenduojama išlaikyti ne mažesnį kaip 3 cm kraštą tais atvejais kai navikas yra ≥T2 bei pasižymi ekspansyviu augimu ir bent 5 cm kai navikas yra infiltratyvaus augimo (7). Jei navikas infiltruoja stemplę auksčiau minėtų atstumų išlaikyti nereikia, pakanka pašalinti naviką sveikų audinių ribose (7). Skrandžio rezekcija yra pranašesnė už gastrektomiją dėl mažesnio pooperacinių komplikacijų dažnio, todėl šiai operacijai teikiama pirmenybė visais atvejais, kai galima užtikrinti pakankamą proksimalinį rezekcijos kraštą (8).

Operuojant SKV limfadenektomijos apimtis klasifikuojama pagal D lygio kriterijus: D1, D1+ arba D2. Trumpai tariant, D1 lygis apima perigastrinių limfmazgių pašalinimą, o D2 - antrojo lygio limfmazgių esančių greta kepenų arterijos, pilvinio kamieno ir blužnies arterijos pašalinimą. Konkrečios šalintinos limfmazgių grupės atliekant skirtingos apimties limfonodektomiją priklauso nuo atliekamos operacijos tipo (gastrektomija ar skrandžio rezekcija). Įprastai D1 limfonodektomija atliekama ankstyvo SKV atveju, o D2 limfonodektomija atliekama operuojant lokaliai paženguſį SKV (7). D2 limfadenektomijos nauda buvo aiškiai įrodyta Nyderlanduose atliktame didelės apimties atsitiktinių imčių kontroliniame tyrime (RKT). Šis tyrimas palyginęs D1 ir D2 limfonodektomiją po 15 metų stebėjimo parodė, kad D2 limfadenektomija sumažino lokalių ir regioninių recidyvų skaičių bei sumažino mirtingumo nuo skrnadžio vėžio rodiklį (9). Reikėtų atkreipti dėmesį, D2 limfonodektomija šiame tyrime buvo susijusi su didesne

pooperacinių komplikacijų rizika, tačiau šiuolaikinė chirurginė metodika yra tobulesnė, leidžianti atlikti D2 limfonodektomiją išsaugant blužnį. Todėl D2 limfadenektomija rekomenduojama visiems pacientams, sergantiems rezektabiliu lokaliai pažengusiu SKV (9).

Kaip ir daugelyje kitų chirurgijos sričių, taip ir operuojant SKV, kai kuriuose centruose buvo pasiūlyta ir įdiegta minimaliai invazinė chirurgija, kaip alternatyva atviroms operacijoms. Keletas Rytų šalyse atliktų RKT palygino atvirą ir minimaliai invazyvią SKV chirurgiją. Šie tyrimai nesukėlė abejonių dėl onkologinės minimaliai invazinių operacijų kokybės ir netgi parodė mažesnį pooperacinių komplikacijų dažnį po minimaliai invazinių operacijų. Vis dėl to atokiųjų gydymo rezultatų taikant minimaliai invazines operacijas šiandiena dar trūksta (10-15). Vakaruose taip pat atlikta keletas nedidelės apimties RKT lyginančių šias dvi chirurgines prieigas. Nepaisant panašių onkologinę operacijos kokybę atspindinčių rodiklių rezultatų, abu RKT neparodė, kad minimaliai invazinės operacijos yra susijusios su mažesniu pooperacinių komplikacijų dažniu. Taip pat vis dar laukiama atokiųjų rezultatų (16,17).

Deja, nepaisant pastarojo meto chirurgijos ir anesteziologijos mokslo pažangos, operacijos dėl SKV išlieka iššūkiu ir pacientams ir chirurgams nes jos vis dar yra susijusios su dideliu pooperacinių komplikacijų dažniu ir ženkliu pooperaciniu mirštamumu, kurie gali viršyti atitinkamai 50 % ir 5 % (18-20). Dažniausios komplikacijos po operacijų dėl SKV yra pooperacinės infekcijos (pneumonija, operacinės vietos infekcijos, šlapimo takų infekcijos ir kitos), dvylikapirštės žarnos bigės ar anastomozės nesandarumas, pooperacinė žarnų nepraeinamumas, plaučių embolija, pooperacinis kraujavimas ir pagrindinių lėtinių ligų, tokių kaip širdies nepakankamumas, inkstų nepakankamumas ir kitų, pablogėjimas (8,21). Todėl šiandiena vis dar išlieka būtinybė ieškoti naujų gydymo būdų ir strategijų, kurie leistų SKV operacijų rezultatus.

Neoadjuvantinė chemoterapija gydant skrandžio vėžį

Šiuolaikinis SKV gydymas retai pradedamas nuo operacijos. Nesant akstyvos diagnostikos programų dažniausiai liga nustatoma jau pažengusi, o pacientams kurie serga lokaliai pažengusiu SKV (≥cT2N0), kuris yra rezektabilus rekomenduojama taikyti neoadjuvantinį ir (arba) perioperacinį gydymą. Manoma, kad neoadjuvantinė chemoterapija gali sunaikinti okultines naviko mikrometastazes, sumažinti pirminį naviką ir todėl padidinti radikalių operacijų proporciją. Yra žinoma, kad visi šie galimi neoadjuvantinės

chemoterapijos metodo privalumai iš tiesų pagerina ilgalaikius SKV pacientų gydymo rezultatus (22).

MAGIC RKT buvo vienas pirmųjų tyrimų, įrodžiusių, kad perioperacinė chemoterapija pagerina pacientų sergančių SKV išgyvenamumą (penkerių metų išgyvenamumas 36 %, palyginti su 23 %) (23). Perioperacinės chemoterapijos režimas, taikytas šiame RKT buvo 3 vaistų derinys: epirubicinas, cisplatina ir fluorouracilas (ECF). Panašią neoadjuvantinės chemoterapijos naudą patvirtino ir kitas didelės apimties RKT atliktas Prancūzijoje, kuris parodė, kad perioperacinė chemoterapija cisplatina ir fluorouracilu pagerina 5 metų bendrąjį (BI) išgyvenamumą iki 38 %, palyginti su 24 % vien tik chirurginės operacijos grupėje (24). Be to, neseniai atliktas 2/3 fazės FLOT4-AIO RKT parodė, kad neoadjuvantinės chemoterapijos nauda gali būti dar didesnė taikant šiuolaikinį FLOT (fluorouracilas, leukovorinas, oksaliplatina ir docetakselis) chemoterapijos režimą. Lyginant su ECF (arba ECX, kur X reiškia kapecitabiną), FLOT 5 metų BI rodikliai pagerino nuo 36 iki 45 % (25). Vis dėl to, neoadjuvantinės chemoterapijos gydymo koncepcija nėra vertinama vienareikšmiškai. Taip yra dėl keletos priežasčių. Pirma, didžiausi RKT, kuriuose buvo vertinta galima neoadjuvantinės chemoterapijos nauda, sulaukia kritikos dėl to, jog operuotų pacientų onkologinė operacijos kokybė dažnu atveju buvo nepakankama, ypač vertinant limfonodektomijos apimtį. Antra, šiuose tyrimuose dalyvavo sergantieji ne tik SKV, bet ir stemplės adenokarcinoma sergantys pacientai, kurie galimai pasižymi didesniu jautrumu chemoterapiniam gydymui (26). Dėl šių priežasčių neoadjuvantinė chemoterapija yra standartinis gydymo metodas tik Vakarų šalyse, o Rytuose ji taikoma rečiau, nes ten chirurginis gydymas su D2 limfadenektomija yra istoriškai susiklostęs gydymo standartas. Be to, daugumoje tyrimų daugiausia dėmesio skiriama chemoterapijos poveikiui pirminiam navikui, o duomenų apie tai, kaip ji veikia limfmazgių metastazes trūksta (27). Be to, neoadjuvantinis citotoksinis gydymas gali turėti neigiamą poveikį pacientų fizinei ir mitybos būklei, skatinti sarkopenijos vystymąsi ir progresavimą, dėl to mažėja pacientų fiziologinis rezervas bei didėja su operacija susijusi rizika (6, 28-30). Siekiant sumažinti tokią riziką, dabar įprasta operuoti pacientus praėjus bent 4-8 savaitėms po paskutinio neoadjuvantinės chemoterapijos ciklo. Manoma, kad toks laikotarpis yra būtinas trumpalaikių šalutinių reiškinių, o ypač hematologinio toksiškumo regresavimui, (31). Tačiau toks laiko pasirinkimas yra nepagrįstas tvirtais mokslo įrodymais, todėl optimalus laikas chirurginei intervencijai po neoadjuvantinės chemoterapijos nėra aiškus.

Gyvenimo kokybė po radikalaus skrandžio vėžio gydymo

Skrandžio vėžio (SKV) chirurginis gydymas turi pastebimą neigiamą poveikį su sveikata susijusiai gyvenimo kokybei (SSGK). Labiausiai SSGK pablogėja praėjus keliems mėnesiams po operacijos, tačiau per kitus 6-12 mėnesių ji palaipsniui atsistato ir pasiekia lygį artimą buvusiam iki operacijos (32,33). Tačiau daugelis dėl SKV operuotų pacientų ir toliau patiria įvairių virškinamojo trakto simptomų. Vienas iš dažniausiai pasitaikančių tokių simptomų - protarpinis arba nuolatinis viduriavimas, kuris vargina iki 40 proc. pacientų (34-38). Be to, dažnai pasitaiko pilvo skausmai, vidurių užkietėjimas, virškinimo sutrikimai ir refliuksas (38,39). Šiuo metu yra ribotas supratimas apie patofiziologinius mechanizmus, lemiančius šių simptomų atsiradimą, todėl trūksta veiksmingų gydymo būdų. Viena iš egzistuojančių hipotezių siūlo, kad šių simptomų patogenezėje svarbų vaidmenį vaidina operacijos sukelta disbiozė, tačiau šiai hipotezei patvirtinti arba paneigti reikia papildomų aukštos kokybės įrodymų.

Šios disertacijos struktūra

Tyrimo hipotezės, uždaviniai ir metodai

Šioje disertacijoje apibendrinami keli atskiri, bet susiję mokslo darbai, kurie atlikti siekiant pagerinti pacientų, operuojamų dėl SKV, gydymo rezultatus bei patikrinti keturias hipotezes:

1) Personalizuota daugiarūšė priešoperacinė reabilitacija pagerina skrandžio vėžiu sergančių pacientų fizinį pasirengimą, neoadjuvantinio gydymo toleranciją ir su sveikata susijusią gyvenimo kokybę bei sumažina pooperacinių komplikacijų dažnį.
2) Neoadjuvantinės chemoterapijos sukelta histologinė skrandžio vėžio naviko ir limfmazgių metastazių regresija yra susijusi su geresnėmis ilgalaikėmis išeitimis.
3) Optimalus laiko intervalas tarp neoadjuvantinės chemoterapijos pabaigos ir operacijos gali padidinti reikšmingos histologinės naviko regresijos dažnį.
4) Operacijos dėl skrandžio vėžio sukelta disbiozė yra susijusi su virškinamojo trakto simptomais.

Siekiant patikrinti hipotezes, atsakyti į mokslinius klausimus ir užpildyti dabartinių žinių spragas, buvo numatyti tyrimo uždaviniai. Užduotys ir metodai, naudoti siekiant atsakyti į mokslinius klausimus, apibendrinti 1 lentelėje.

1 lentelė. Tyrimo užduotys (mokslinis klausimas) ir metodai, naudoti siekiant atsakyti į mokslinius klausimus

Uždavinys (mokslinis klausimas)	*Metodai*
1. Apžvelgti ir apibendrinti dabartinius įrodymus apie priešoperacinės reabilitacijos taikymą šiuolaikinėje stemplės ir skrandžio vėžio chirurgijoje.	Šiam uždaviniui buvo atlikta išsami literatūros apžvalga, o išvados pateiktos **2 skyriaus I dalyje.**
2. Patikrinti hipotezę nr. 1 ir užpildyti šiuolaikinių mokslo žinių spragas.	Šiai užduočiai įvykdyti buvo parengtas RKT protokolas (**2 skyrius (II dalis)**). Vėliau pagal šį protokolą buvo atliktas tyrimas ir pateikti RKT rezultatai (**2 skyrius (III dalis)**).
3. Įvertinti ar neoadjuvantinės chemoterapijos sukelta histologinė regresija skrandžio navike ir/ar limfmazgių metastazėse yra susijusi su geresniais atokiaisiais gydymo rezultatais.	Šiam uždaviniui įvykdyti buvo atliktas retrospektyvus tyrimas, kurio rezultatai pateikti **3 skyriaus 1 dalyje.**
4. Nustatyti optimalų intervalą tarp neoadjuvantinės chemoterapijos pabaigos ir operacijos, siekiant maksimaliai padidinti ženklios histologinės naviko regresijos dažnį.	Šiam uždaviniui įgyvendinti buvo atliktas tarptautinis kohortinis tyrimas kurio rezultatai pristatomi **3 skyriaus II dalyje.**
5. Įvertinti ryšį tarp operacijos dėl SKV sukeltos disbiozės ir gastrointestinių simptomų.	Šiam uždaviniui įgyvendinti buvo atlikta išsami literatūros apžvalga siekiant apibendrinti šiandieninias mokslo žinias apie operacijos dėl SKV įtaką žarnų mikrobiomos pokyčiams (**4 skyrius (I dalis)**). Vėliau siekiant įvertinti operacijos dėl SKV sukeltos disbiozės ir gastrointestinių simptomų ryšį atliktas skerspjūvio tipo tyrimas kurio rezultatai pateikiami **4 skyriaus II dalyje.**

Tyrimo rezultatų apibendrinimas

Šio darbo **1 skyriuje** pristatoma skrandžio vėžio problematika, nagrinėjami šiuolaikinės skrandžio vėžio chirurgijos principai, gilinamasi į šiuolaikinę neoadjuvantinio gydymo koncepciją ir nagrinėjamas ilgalaikis

gydymo poveikis su sveikata susijusiai gyvenimo kokybei. Įvardijama keletas dabartinių gydymo metodų trūkumų, pavyzdžiui, didelį pooperacinių komplikacijų dažnį po operacijų dėl SKV. Taip pat atkreipiamas dėmesys į šiandieninių mokslo žinių spragas klausimuose aktualiuose gydant SKV, pavyzdžiui neaiškų neoadjuvantinės chemoterapijos poveikį limfinių mazgų metastazėms ar neaiškią po operacijų dėl SKV varginančių gastrointestinių simptomų patogenezę. Šiame skyriuje iškeliamos tyrimo hipotezės ir suformuluojami uždaviniai.

2 skyriaus 1 dalyje pateikiama išsami dabartinių įrodymų, susijusių su priešoperacinės reabilitacijos taikymu modernioje esofagogastrinėje chirurgijoje apžvalga. Iki šiol atlikti tyrimai yra labai heterogeniški vertinant jų metodologiją, tirtas intervencijas ir vertintus rezutatus. Vis dėlto visi šie tyrimai patvirtina teigiamą priešoperacinės reabilitacijos poveikį kuris atskirų tyrimų duomenimis varijuoja nuo teigiamos įtakos fiziniam paciento pajėgumui ar mitybos būklei iki geresnės gyvenimo kokybės ar net mažesnio pooperacinių komplikacijų dažnio. Deja, esantys įrodymai nėra pakankami sukurti optimalią priešoperacinės reabilitacijos programą, ją standartizuoti ir plačiai pritaikyti. Todėl, siekiant sukurti efektyviais programas, specialiai pritaikytas pacientams, sergantiems stemplės ir skrandžio vėžiu, būtina atlikti tolesnius tyrimus, daugiausia dėmesio skiriant daugiarūšės priešoperacinei reabilitacijai (1). Šiam žinių trūkumui užpildyti suplanuotas randomizuotas kontrolinis tyrimas, kurio protokolas publikuotas ir pateiktas **2 skyriaus 2 dalyje.** Šis tyrimas skirtas įvertinti ar priešoperacinė reabilitacija gali sumažinti 90 dienų pooperacinių komplikacijų dažnį po operacijų dėl SKV (2). Tyrimas atliktas, o jo rezultatai aprašomi **2 skyriaus 3 dalyje.** Priešoperacinė reabilitacija kurią sudarė treniruotės skritos fizinei būklei gerinti, psichologinė ir dietologinė pagalba: 1) pagerino pacientų fizinį pajėgumą prieš operaciją (vidutinis 6MWT pokytis +31 m, 95 % PI: 14-48 m; p=0,001); 2) sumažino dalį pacientų, kurie negalėjo gauti viso planuoto neoadjuvantinio gydymo (RR=0,20, 95 % PI: 0,20-0,56), 3) 60 % sumažino 90 dienų pooperacinių komplikacijų dažnį (RR 0,40, 95 % PI: 0,24-0,66) ir 4) pagerino SKV pacientų gyvenimo kokybę. Įertinus gautus rezultatus padaryta išvada, kad kad individualizuota, daugiarūšė, namuose vykdoma priešoperacinė reabilitacija sumažina pooperacinių komplikacijų dažnį po operacijų dėl SKV. Be to, priešoperacinė reabilitacija pagerina pacientų fizinį pajėgumą, neoadjuvantinio gydymo protokolų laikymąsi ir gyvenimo kokybę.

3 skyriuje nagrinėjami šiandieniniai iššūkiai susiję su neoadjuvantinės chemoterapijos taikymu. Ypaatingas dėmsys skiriamas klausimams

nagrinėjantiems chemoterapijos įtaką limfinių mazgų metastazių regresijai ir optimaliam laikui operacijai po neoadjuvantinio gydymo. Pirmojoje dalyje aprašomas atliktas kohortinis tyrimas kuriame analizuoti 87 skrandžio vėžiu (SKV) sergančių pacientų, gydytų neoadjuvantine chemoterapija operaciniai preparatai. Iš šių pacientų 70,1 % (n=61) atvejų nustatytos limfmazgių metastazės. Įdomu tai, kad tik 19 pacientų (31,1 %) galėjo būti vertinti kaip patyrę reikšmingą chemoterapijos sukeltą limfinių mazgų metastazių regresiją. Įdomu tai, kad regresija ≥limfmazgiuose nėra susijusi su chemoterapiniu efektu pirminiame navike, tačiau yra prognostiškai reikšminga leidžianti tikėtis geresnių atokiųjų rezultatų (3). Antroji šio skyriaus dalis skirta tyrimui kuris atliktas siekiant identifikuoti optimalų laiką operacijai po neoadjuvantinio gydymo. Šis tarptautinis kohortinis tyrimas įtraukė 280 pacientų, kurie suskirstyti į tris grupes atsižvelgiant į laiką operacijai: ankstyvos chirurgijos grupė(ACG) (≤ 30 d.) (n = 70), standartinės chirurgijos grupė (SCG) (31-43 d.) (n=138) ir vėlyvos chirurgijos grupė (VCG) (≥ 44 d.) (n = 72).Tyrimo rezultatai parodė, kad reikšminga histologinė naviko regresija dažniausiai pasiekiama ACG (32.9%), palyginus su SCG (20.3%) ar VCG (16.7%) (p = 0.047). Statistinė analizę koregavus atsižvelgiant į paciento, naviko ir gydymo charakteristikas pacientai operuoti ankstyvu periodu po neoadjuvantinės chemoterapijos turėjo du kart (OR: 2.09; 95% PI: 1.01-4.34; p = 0.047) didesnį šansą pasiekti reikšmingą histologinę naviko regresiją. Svarbu paminėti, kad pooperacinių komplikacijų, R0 tipo operacijų, pakankamos limfonodektomijos (≥15 limfmazgių) dažnis tarp grupių nesiskyrė. Vertinant atokiuosius rezultatus skirtumų tarp grupių taip pat nestebėta. Apibendrinant, šio tyrimo rezultatai nurodo, kad operacija per 30 d. po neoadjuvantinės chemotherapijos pabaigos yra saugi ir leidžianti tikėtis didesnio reikšmingos histologinės regresijos dažnio(4).

4 skyriuje nagrinėjama chirurginio SKV gydymo įtaka žarnyno mikrobiotai ir šių pokyčių reikšmė įvairių gastrointestinių simptomų patogenezėje. **1 dalyje** apžvelgiami ir apibendrinami šiandieninėje literatūroje pateikiamos žinios ir įrodymai. . Nors šiandiena esančios žinios yra ribotos, tačiau jų pakanka suprasti, kad operacija dėl SKV sukelia reikšmingus fiziologinius ir anatominius virškinamojo trakto (VT) pokyčius. Šie pokyčiai apima skrandžio barjerinės funkcijos praradimą, padidėjusį deguonies kiekį distaliniame VT ir tulžies apykaitos pokyčius. Tokie VT aplinkos pokyčiai turi neabejotiną įtaką žarnų mikrobiotai ir paciento sveikatai. Operacijos sukeltai disbiozei būdinga tai, jog žarnų mikrobiotoje daugėja bakterijų būdingų burnos ertmei, aerobinių bakterijų ir tulžies rūgštis metabolizuojančių bakterijų. Tokia disbiozė gali būti susijusi su lokaliu uždegimu žarnyne,

plonojo žarnyno bakterijų išvešėjimo sindromu, įvairiais VT simptomais ir padidėjusia kolorektinio vėžio rizika (5). Šio skyriaus **2 dalis** skirta pjūviniam tyrimui kuris atskleidžia skrandžio rezekcijos sukeltos disbiozės įtaką VT simptomų patogenezėje. Į tyrimą įtraukti pacientai kuriems atlikta skrandžio rezekcija dėl ankstyvo SKV ir jų neoperuoti giminės gyvenantys kartu. Tyrimo metu nustatyta, kad operuotiems pacientams būdingas žarnų mikrobiotos "oralizacijos" fenomenas pasireiškiantis žarnų mikrobiotoje išaugusiu *Escherichia-Shigella, Enterococcus, Streptococcus* genties bakterijų kiekiu bei kitų įprastai burnos ertmėje aptinkamų bakterijų (*Veillonella, Oribacterium*, and *Mogibacterium*). Operuotų pacientų grupėje stebėtas reikšmingas išmatų kalprotektino, uždegimo žarnyne žymens, kiekio padidėjimas [100.9 (52.1; 292) vs. 25.8 (17; 66.5); p = 0.014], kurs koreliavo su *Streptococcus* genties bakterijų paplitimu (rs = 0.639; padj = 0.023). Specifiniai taksonominiai žarnų mikrobiotos pokyčiai buvo susiję su VT simptomais – diskomforto jausmu pilve, viduriavimu ir pilvo pūtimu. Diskomforto pilve simptomą jautė net 69 % operuotų pacientų, vidurivimas vargino 54 % pacientų, o pilvo pūtimas buvo būdingas 46 %. Pacientų kuriuos vargino pilvo pūtimas žarnų mikrobiota pasižymėjo didesniu *Holdemanella* (p = 0.034) ir mažesniu *Agathobacter* (p = 0.006) genties bakterijų kiekiu. Viduriuojančių pacientų žarnų mikrobiota išsiskyrė didesniu *Mogibacterium* (p = 0.035) ir mažesniu *Ruminococcus 1* (p = 0.035) genties bakterijų kiekiu, o tų pacientų kuriuos vargino pilvo pūtimas mikrobiotoje aptikta mažiau *Agathobacter* (p = 0.035) ir *Streptococcus* (p = 0.035) genties bakterijų. Šio tyrimo rezultatai atskleidė, kad žarnų mikrobiota galėtų būti naujas terapinis taikinys siekiant pagerinti dėl SKV operuotų pacientų gyvenimo kokybę. Apibendrinant šio tyrimo pagrindinės išvados yra:

1) Priešoperacinė reabilitacija sumažina pooperacinių komplikacijų skaičių po radikalių operacijų dėl skrandžio vėžio;
2) Priešoperacinės chemotherapijos lemta histologinė limfinių mazgų metastazių regresija leidžia prognozuoti geresnius atokiuosius pacientų sergančių lokaliai išplitusiu skrandžio vėžiu gydymo rezultatus;
3) Ankstyva radikali operacija per 30 dienų po neoadjuvantinio chemoterapinio gydymo pabaigos yra susijusi su dažnesniu reikšmingo patologinio naviko atsako dažniu bei nemenkesniu operacijos onkologiniu saugumu ir pooperacinių komplikacijų dažniu;
4) Skrandžio rezekcija su Billroth II rekonstrukcija yra susijusi su žarnų mikrobiotos oralizacijos fenomenu. Lokalus uždegimas žarnyne bei mikrobiotos pokyčiais susiję su pacientus varginančiais gastrointestiniais simptomais.

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CURRICULUM VITAE

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Education

2022	**Medical University of Graz** | Graz, Austria *Doctoral degree program in medical science*
2020	**Digestive and Endocrine Surgery Department, Hopital Nouvel Civil (NHC)** | Strasbourg, France *Minimally Invasive and Robotic Digestive and Endocrine Surgery Fellowship*
2017-2018	**Division of Transplantation Surgery, Medical University of Graz** | Graz, Austria *Clinical and research fellow*
2016-2021	**Vilnius University Faculty of Medicine** | Vilnius, Lithuania *Residency of abdominal surgery*
2017	*Course on Laboratory Animal Sciences (FELASA, category B)*
2010 – 2016	**Vilnius University Faculty of Medicine** | Vilnius, Lithuania *Medicine*

Experience

Since 2023	*Member of Medicine Study Programme Committee at Vilnius University Faculty of Medicine*

Since 2022	*Editor at BMC Surgery*
Since 2021	*Abdominal Surgeon (Surgical Oncologist) at National Cancer Institute*
Since 2021	*Junior researcher at Centre for Visceral Medicine and Translational Research, Vilnius University, Faculty of Medicine*
Since 2016	*Assistant lecturer at the Department of Pathology, Forensic medicine and Pharmacology, Vilnius University, Faculty of Medicine*
2017-2020	*National Representative of Lithuania at Europan Society of Surgical Oncology*

Awards and Scholarships

2022	*Best oral presentation at EAA-ISGA-ICEM Joint International Meeting*
2022	*Sophie Valentina Ambroza scholarship for academic achievments (Vilnius University)*
2021, 2023	*Scholarships for academic achievements by Research Council of Lithuania*
2015, 2016, 2017, 2018, 2019	*Vilnius University promotion scholarship for high activity in research*
2016	*TOP 20 poster at the European Society of Surgical Oncology 36th Congress*
2015	*Sophie Valentina Ambroza scholarship for research activities (Vilnius University)*

Scientific projects

- CORSiCA research project: international cohort study. 2017-2020. Role: Junior investigator.
- Glyce - novel cardioprotective and anti-tumorigenic substance against colorectal cancer. 2017-2020. Role: Investigator.
- Early versus late closure of preventive ileostomy after rectal resection for cancer: randomized control trial. 2011-2017. Role: Investigator
- Intestinal Microbiome After Gastrectomy (DiGMA study). Collaborative research project of Vilnius University, National Cancer Institute and Medical University of Graz. 2018-2021. Role: Investigator.
- The problem of colorectal anastomosis safety. Since 2019. Role: Investigator.
- Personalized trimodal prehabilitation for gastrectomy. Since 2019. Role: Principal investigator.
- Gut microbiome in colorectal cancer surgery. Since 2019. Role: Principal investigator.
- Gut After Gastrectomy: gastrectomy impact on the gut microbiome, intestinal inflammation and these changes role in treatment outcomes. Since 2022. Role: main investigator. Project funded by Research Council of Lithuania.

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+ various contributions to national and international scientific meetings

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Personal skills

Foreign language

	UNDERSTANDING		SPEAKING	WRITING
	Listening	Reading		
English	C1	C1	C1	C1
German	A1	A1	A1	A1

PC skills	Microsoft Office™, SPSS, GraphPad, MedCalc
Professional interests	Surgical oncology; gastric cancer; gut microbiome research

NOTES

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