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Optimization of early gastric cancer treatment in the Lithuanian population. Comparison of traditional surgical and minimally invasive treatment methods

DOCTORAL DISSERTATION

Medicine and health sciences,
Medicine M 001

VILNIUS 2019

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Ankstyvo skrandžio vėžio gydymo optimizavimas Lietuvos populiacijoje. Tradicinio chirurginio ir minimaliai invazyvių gydymo metodų palyginimas

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CONTENT

1 ABBREVIATIONS

EGC – early gastric cancer

GC – gastric cancer

LNM – lymph node metastasis

DFS – disease-free survival

DSS - disease-specific survival

OS – overall survival

ER – endoscopic resection

HR – Hazard ratio

OR – odds ratio

ESD – endoscopic submucosal dissection

EMR – endoscopic mucosal resection

EGD – Esophagogastroduodenoscopy

CT – computed tomography

pT1 - The tumor has grown into the *lamina propria, muscularis mucosae,* or the *submucosa*.

pT2 - The tumor has grown into the *muscularis propria* layer

95 % CI – 95 % confidence interval

2 ACKNOWLEDGMENTS

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 R**, Bausys A, Vysniauskaite I, Maneikis K, Klimas D, Luksta M, Strupas K, Stratilatovas E. Risk factors for lymph node metastasis in early gastric cancer patients: Report from Eastern Europe country-Lithuania. BMC Surg. 2017 23;17(1):108.

2. **Bausys R**, Bausys A, Maneikis K, Belogorceva V, Stratilatovas E, Strupas K. Safety of expanded criteria for endoscopic resection of early gastric cancer in a Western cohort. BMC Surg. 2018 25;18(1):79.

3. **Bausys R**, Bausys A, Vysniauskaite I, Maneikis K, Stratilatovas E, Strupas K. Surgical treatment outcomes of patients with T1-T2 gastric cancer: does the age matter when excellent treatment results are expected? World J Surg Oncol. 2018 16;16(1):79.

4. **Bausys R**, Bausys A, Stanaitis J, Vysniauskaite I, Maneikis K, Bausys B, Stratilatovas E, Strupas K. Propensity score-matched comparison

of short-term and long-term outcomes between endoscopic submucosal dissection and surgery for treatment of early gastric cancer in a Western setting. Surg Endosc. 2018 Dec 3; doi: 10.1007/s00464-018-06609-6

3 INTRODUCTION

3.1 Scientific background

Gastric cancer (GC) is one of the most common malignancy worldwide and radical surgery remains the only potentially curative treatment option for it (1). A significant proportion of GC patients present with lymph node metastasis (LNM) when they are diagnosed with the disease or undergo surgery (2). The LNM has a major negative role in patients' prognosis, and surgery can be considered as curative only in case if no microscopic or macroscopic disease is left afterward (3), including removal of all metastatic lymph nodes. Therefore, gastrectomy with appropriate lymph node dissection has historically been the gold standard treatment for resectable gastric cancer irrespective of the stage of disease (4,5).

Early gastric cancer (EGC) is defined as GC in which tumor invasion is limited to the mucosa or submucosa, irrespective of the presence of lymph node metastasis (LNM). Surgery provides excellent long-term outcomes for EGC, with 5-year overall survival over 90 % (6,7). Although, traditional surgery is associated with significant postoperative morbidity, mortality, and impaired quality of life (8–10). The increasing lifetime expectancy and improved treatment of age-related chronic diseases lead to a greater number of elderly patients suffering from GC. While surgery is standard in patients with a stable clinical condition, the surgical outcomes in elderly patients, especially in those with comorbidities, remains unclear (11–13).

Theoretically, GC surgery could be limited to the excision of the gastric tumor if it would be possible to reliably identify patients without LNM preoperatively. The current standard for preoperative evaluation of LNM is mostly based on CT/ MRI imaging. However, available methods do not have the correct high sensitivity and specificity for the detection of LNM in gastric cancer (14,15). After clinical observation, that some EGC cases carry no or very low risk of LNM local endoscopic resection (ER), which includes endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), has been suggested as an alternative treatment option. In these cases,

it is considered that local excision of the tumor via the endoscopic approach is enough to cure the disease. As mentioned previously, current radiological imaging possibilities do not provide enough accurate tests to diagnose LNM preoperatively. Therefore, histomorphologic characteristics of the tumor are used to identify the EGC with a negligible risk of LNM. In these cases, the endoscopic approach is accepted and is considered a standard treatment option by the Japanese gastric cancer treatment guidelines (16).

Many recent studies showed similar short- and long-term outcomes of surgery and ER for EGC treatment with reduced morbidity and improved quality of life following ER (17–24). However, all these studies were conducted in Asian populations and these findings translation to Western population is still on a hard discussion because of several serious reasons. First, the diagnostic criteria for gastric cancer differ between West and Asia (25) and these difference are extremely important in the case of EGC. In Japan and some other countries, the histologic diagnosis is based on the degree of structural and cells abnormality of the tumor glands (25–27). In contrast, in Western counterparts, gastric cancer is diagnosed only with histological evidence of invasion to lamina propria or beyond the submucosa (25,28). These differences lead to different diagnosis: lesions diagnosed as a high-grade dysplasia in the West are diagnosed as EGC in Japan (25,29). Second, the Western patients with GC are different from patients in Asia by a higher BMI, older age, higher prevalence of proximal tumors and diffuse-type cancer (30) and it is still not clear if the etiopathogenesis of GC is the same between those two regions. Third, two recently published studies showed non-Asian race itself as a risk factor for LNM (31,32).

Hence, the feasibility of ER concept for EGC is unclear in Western populations including Lithuania.

3.2 Study hypothesis

EGC treatment with ER is safe and feasible in the Lithuanian population.

3.3 The aim of the study

To provide the evidence for the safety and feasibility of ER for EGC treatment in a Lithuanian population, which can be considered as a Western type.

3.4 Study tasks

1. To compare short- and long- term outcomes of EGC patients treated with surgery or ER in a Lithuanian population.
2. To determine the risk factors for lymph node metastasis in the Lithuanian population of EGC patients.
3. To assess the rate of LNM in a Lithuanian cohort of patients who fall under the standard or expanded criteria for ER.
4. To investigate the rate of LNM in a Lithuanian population of patients who exceeds the standard and expanded criteria for ER of EGC.
5. To determine the factors for postoperative morbidity and mortality following traditional surgical treatment of early stages gastric cancer.

3.5 The novelty of the study

To our best knowledge, this was the first study comparing ER and surgery for EGC in a Western setting.

4 METHODS

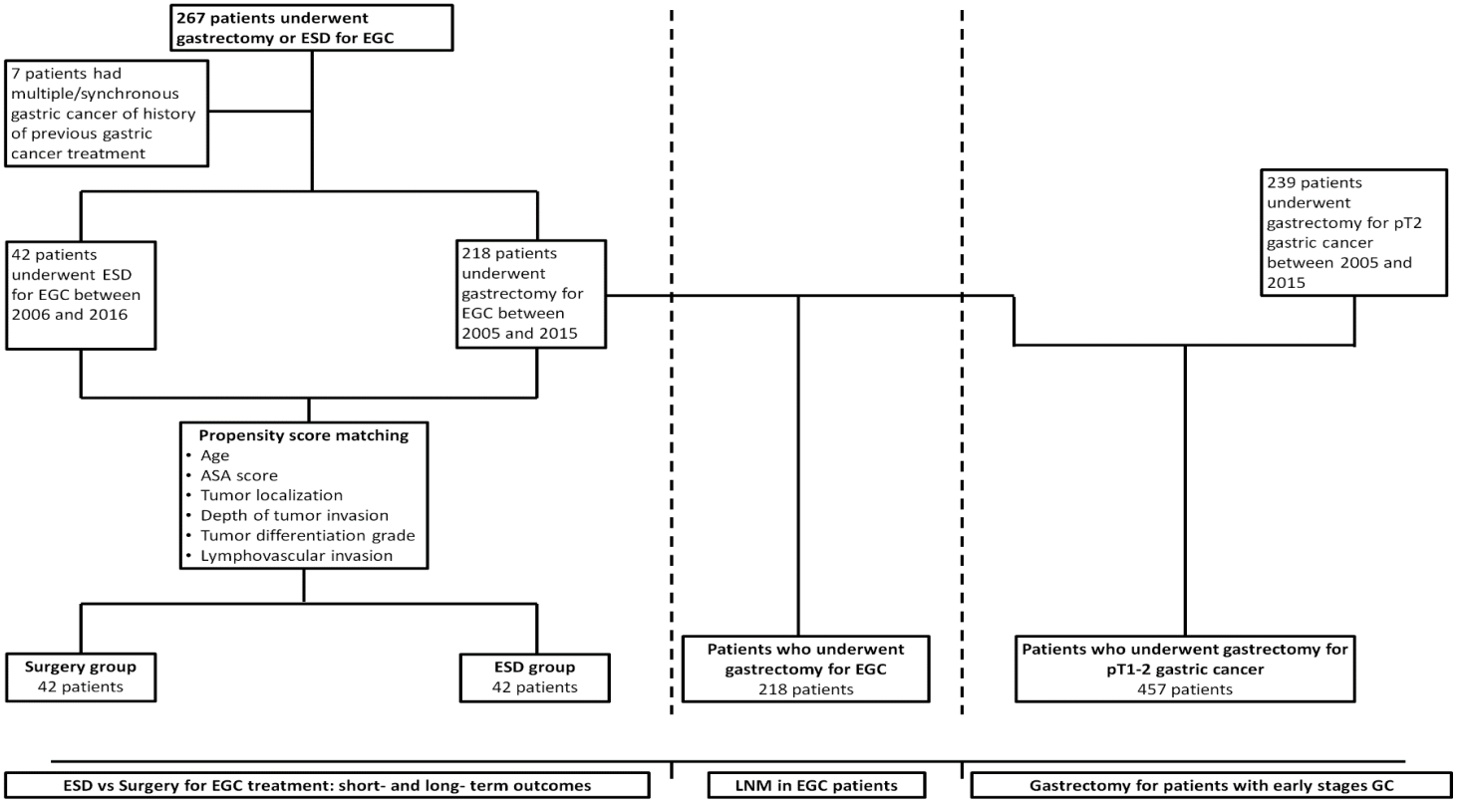
4.1 Ethics

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.

4.2 Patients and study design

A flowchart of patient enrollment is demonstrated in Figure 1.

Figure 1. Flowchart of the study



4.3 ESD vs Surgery for EGC treatment: short- and long- term outcomes

This retrospective design study included all EGC patients who underwent ESD for EGC at Vilnius University hospital Santaros Clinics between January 2006 and December 2016 or surgery at National Cancer Institute between January 2005 and December 2015. ESD for EGC program was implemented in Vilnius University hospital Santaros Clinics in 2006 and slightly different study periods were selected to maintain 10 years study period. Choice of treatment center was made by personal patients' decisions. All patients were Caucasian. The exclusion criteria were: 1) multiple or synchronous EGC and 2) history of gastric cancer treatment including neo-adjuvant chemotherapy. After exclusion of 7 patients who met at least one exclusion criteria, 260 patients were included in the study and were divided into surgery (218 patients) and ESD (42 patients) groups. Propensity score matching analysis was performed to reduce the selection bias and to compare clinical outcomes between these groups. 42 patients in each group were matched by propensity score. The primary endpoint of the study was 5-year disease-free survival (DFS) rate. The secondary endpoints included 5-year overall survival (OS) rate, postoperative complication rate, operation time and postoperative hospitalization time. OS was estimated from the date of surgery until death. DFS was defined as survival from the date of surgery to local, regional or distant recurrence (33).

4.4 LNM in EGC patients

Above mentioned 218 patients who underwent traditional gastrectomy with lymphonodectomy for EGC were analyzed to determine the risk factors for LNM. Patients age, gender, tumor localization, depth of invasion, tumor differentiation grade, lymphovascular invasion, Lauren type, tumor size, ulceration and component of signet ring cells were considered as a potential risk factors and included to the analysis; the rate of LNM between patients who fall under the standard/expanded indications for ESD or exceed them was examined.

4.5 Gastrectomy for patients with early stages GC

To determine the factors for postoperative morbidity and mortality following traditional surgical treatment of early stages gastric cancer patients

who underwent surgery for pT1 (EGC) and pT2 gastric cancer between January 2005 and December 2015 at National Cancer Institute were included to the analysis. It was considered that surgery for pT1 and pT2 tumors are technically very similar, therefore patients with tumors invading *muscularis propria* layer (pT2) were additionally included to the analysis to improve the power of this part of the study. In total 457 patients were included in the analysis (218 patients with pT1 (EGC) and 239 patients with pT2 tumors). To determine postoperative morbidity and mortality following early stages gastric cancer surgery patients were divided into elderly (E; ≥ 70 years) and non-elderly (NE; < 70 years) groups according to the age at the time of surgery (34).

4.6 Patient characteristics and clinical data

All patient characteristics were obtained from their medical records and prospectively collected database. Tumor stage was coded according to the TNM system as described in the Union Internationale Contre le Cancer/American Joint Committee on Cancer 7th edition. Demographic characteristics included age and sex. Clinicopathological characteristics included smoking status, BMI, comorbidity, American Society of Anesthesiology (ASA) score, hospitalization and intensive care unit (ICU) time, type of surgery and lymphadenectomy, length of surgery, blood loss, tumor location, tumor size, differentiation, depth of invasion, lymphovascular invasion, retrieved and metastatic lymph node count. Postoperative complications were defined as any deviations from a normal postoperative course during the hospitalization time. The severity of postoperative morbidity was classified according to Clavien-Dindo classification.

4.7 Preoperative evaluation and surgical procedures

All patients underwent esophagogastroduodenoscopy (EGD) with biopsy sampling before surgery or ESD. Chest and abdomen CT scan was performed for the staging of the disease in most cases. Additionally, most patients underwent an endoscopic ultrasound before ESD for more accurate evaluation of tumor invasion.

ESD was performed under general intravenous anesthesia. The standard ESD procedure at our institution begins with marking the lesion margins and injecting a saline solution containing epinephrine and methylene blue into the

submucosal layer. A circumferential incision is made into the mucosa, and the submucosal layer is dissected. After specimen removal, endoscopic hemostasis is performed with hemoclips or hot biopsy forceps whenever bleeding or an exposed vessel is observed. An en bloc resection is defined as a single-piece resection. Histologically, complete resection included en bloc resection with microscopically negative horizontal and vertical margins. Curative resection was considered as proposed by Japanese gastric cancer treatment guidelines (histologically complete resection of a lesion not exceeding the expanded criteria for curative resection) (16).

The extent of gastrectomy depended on cancer localization in the stomach. Subtotal gastrectomy was performed whenever a sufficient proximal resection margin could be ensured; in other cases, total gastrectomy was performed. The standard lymphadenectomy was a D2 lymph node dissection which was performed as described in the 4th version of Japanese gastric cancer treatment guidelines (16). D1 lymphonodectomy was performed in separate cases based on the individual decision of the operating surgeon. R0 resection, defined by no macroscopically and microscopically remaining tumor, was achieved in all cases (33).

4.8 Pathologic evaluation

Pathologic evaluation was performed at the National Center of Pathology, Vilnius, Lithuania. Pathologist specialized in gastric cancer analyzed all the specimens. Histological type of tumor was classified according to the World Health Organization and Lauren classifications. Slides were stained with hematoxylin-eosin for general evaluation. Tumor size, depth of invasion, lymphovascular involvement together with lateral and vertical margins were evaluated. The maximum diameter was used to determine tumor size. Lymphovascular invasion was defined as observable tumor spread through lymphatic vessels. Lymph nodes were identified in surgical samples and the status of the nodes was evaluated after each node was examined microscopically (33).

4.9 Follow-up schedule

EGD was performed at 3, 6 and 12 months post-ESD and then annually for five years. Patients who underwent surgery received EGD twice a year for the first two years and then annually. Chest and abdominal CT were conducted

annually in both groups. 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 last follow-up data on death and recurrence were collected in December 2017. Two patients from the ESD group and one patient from surgery group were lost to follow-up (33).

4.10 Statistical analysis

All statistical analyses were conducted using the statistical program SPSS 22.0 (SPSS, Chicago, IL, USA). Continuous variables are presented as the mean ± standard deviation or median with interquartile range. Categorical variables are shown as proportions.

To compare the short- and long-term outcomes of EGC treatment by surgery or ESD propensity scores were determined by logistic regression model of covariates using six baseline variables: age, American Society of Anesthesiologists (ASA) score, tumor localization, depth of tumor invasion, grade of tumor differentiation and lymphovascular invasion. After propensity scores were calculated, patients in the ESD group were matched in a 1:1 ratio with the nearest neighbor from the surgery group. Comparison analysis of clinicopathological characteristics between ESD and surgery groups were analyzed by a 2-tailed t-test, Chi-square test or Fisher exact test. Overall and disease-free survival rates were analyzed by the Kaplan–Meier method and were compared by the log-rank test. Cox proportional hazard regression analysis was used to calculate multivariate-adjusted hazards ratios (HRs) and 95% confidence intervals (CIs) for DFS. In all statistical analyses, a p-value of <0.05 was considered to be significant (33).

To determine risk factors for LNM clinicopathological characteristics were analyzed by a 2-tailed t-test, one-way ANOVA test, Chi-square test, or Fisher exact test. The risk factors found to be significant in univariate analysis were included in subsequent multivariate logistic regression analyses to identify the independent variables associated with lymph node metastasis in patients with gastric cancer. Binary logistic regression was performed to identify independent risk factors for lymph node metastasis in the group of patients who exceed the extended indications for endoscopic early gastric cancer treatment (35).

To determine postoperative morbidity and mortality groups were compared by a two-tailed t-test, one-way ANOVA test, chi-square test, Fisher exact test, or non-parametric tests. All potential risk factors for postoperative

mortality and morbidity were included in subsequent multivariate logistic regression analyses. Independent variables associated with postoperative morbidity and mortality were identified (34).

5 RESULTS

5.1 ESD vs Surgery for EGC treatment

5.1.1 Patients and baseline clinicopathologic characteristics

Table 1 presents the baseline characteristics of the patients before and after propensity score matching. Significant differences between the ESD and surgery groups existed before the pairing. Patients in the surgery group were younger with a lower proportion of severe co-morbidities. A higher proportion of patients in ESD group had tumors located in the upper third of the stomach, while submucosal tumor invasion, poor differentiation, diffuse type cancer, ulceration, and wider tumors were more common in the surgery group. After propensity score matching groups were more balanced. Mean propensity scores were 0.39±0.22 and 0.34±0.18 in ESD and surgery groups respectively, p=0.290. However, even after propensity score matching, tumors exceeding 2 cm in diameter were more common in the surgery group (33).

Table 1. Baseline clinicopathological characteristics in ESD and surgery groups before and after propensity score matching. (Reprinted with permission from Surgical Endoscopy)

		Before matching			After matching		
		ESD group (n=42)	Surgery group (n=218)	p	ESD group (n=42)	Surgery group (n=42)	p
Age (mean±SD)		72.0±10.9	65.5±12.3	0.001*	72.0±10.9	72.3±8.0	0.874
Sex, n (%)	Male	24 (57.1 %)	117 (53.7 %)	0.737	24 (57.1 %)	24 (57.1 %)	0.999
	Female	18 (42.9 %)	101 (46.3 %)		18 (42.9 %)	18 (42.9 %)	
BMI (mean±SD)		27.6±7.6	25.9±4.9	0.534	27.6±7.6	26.3±5.4	0.541
ASA score, n (%)	1-2	15 (35.7 %)	128 (58.7 %)	0.006*	15 (35.7 %)	17 (40.5 %)	0.653
	3-4	27 (64.3 %)	90 (41.3 %)		27 (64.3 %)	25 (59.5 %)	
Tumor localization, n (%)	Upper 3rd	11 (26.2 %)	14 (6.4 %)	0.001*	11 (26.2 %)	4 (9.5 %)	0.050
	Middle 3rd	11 (26.2 %)	125 (57.3 %)		11 (26.2 %)	20 (47.6 %)	
	Lower 3rd	20 (47.6 %)	79 (36.2 %)		20 (47.6 %)	18 (42.9 %)	
Tumor invasion, n (%)	Mucosal	35 (83.3 %)	99 (45.4 %)	0.001*	35 (83.3 %)	36 (85.7 %)	0.999
	Submucosal	7 (16.7 %)	119 (54.6 %)		7 (16.7 %)	6 (14.3 %)	

Lauren classification, n (%)	Intestinal type	35 (94.6 %)	123 (59.7 %)	0.001*	35 (94.6 %)	35 (97.2 %)	0.225
	Mixed type	2 (5.4 %)	19 (9.2 %)		2 (5.4 %)	0 (0.0 %)	
	Diffuse type	0 (0.0 %)	64 (31.1 %)		0 (0.0 %)	1 (2.8 %)	
Tumor differentiation grade, n (%)	Well differentiated	25 (59.5 %)	44 (20.2 %)	0.001*	25 (59.5 %)	22 (52.4 %)	0.369
	Moderately differentiated	16 (38.1 %)	70 (32.1 %)		16 (38.1 %)	16 (38.1 %)	
	Poorly differentiated	1 (2.4 %)	104 (47.7 %)		1 (2.4 %)	4 (9.5 %)	
Ulceration, n (%)	Present	8 (19.5 %)	78 (35.9 %)	0.001*	8 (19.5 %)	3 (7.1 %)	0.116
	Absent	33 (80.5 %)	139 (64.1 %)		33 (80.5 %)	39 (92.9 %)	
Lymphovascular invasion, n (%)	Present	2 (4.8 %)	30 (13.8 %)	0.127	2 (4.8 %)	1 (2.4 %)	0.999
	Absent	40 (95.2 %)	188 (86.2 %)		40 (95.2 %)	41 (97.6 %)	
Tumor size, n (%)	<2 cm	39 (92.9 %)	105 (48.4 %)	0.001*	39 (92.9 %)	19 (46.3 %)	0.001*
	2 - 3 cm	3 (7.1 %)	52 (24.0 %)		3 (7.1 %)	9 (22.0 %)	
	>3 cm	0 (0.0 %)	60 (27.6 %)		0 (0.0 %)	13 (31.7 %)	

5.1.2 Treatment and short-term outcomes

Table 2 shows short-term outcomes after surgery or ESD for EGC. In the surgery group, 10 (23.8 %) patients underwent total gastrectomy and 32 (76.2 %) subtotal gastrectomy. Operation and postoperative hospitalization times were significantly shorter in the ESD group. Postoperative complications occurred for 7 (16.7 %) patients in each group. In the ESD group, 2 (4.8 %) patients had infectious complications, 3 (7.1 %) patients had postoperative bleeding, and 2 (4.8 %) patients had a perforation. Endoscopic hemostasis was successful in all hemorrhagic episodes. Both cases of perforation were treated with open or laparoscopic surgery. Four of 7 complications in the surgery group were mild and classified as grade II complications according to Clavien-Dindo. 2 (4.8 %) patients were re-operated due to fecal or biliary peritonitis. One patient (2.4 %) died during the postoperative course as a result of acute cardiopulmonary insufficiency. All patients in the surgery group underwent radical (R0) surgery. In the ESD group, en bloc and histologically complete resection were achieved in 38 (92.7 %) and 32 (78.0 %) cases respectively. However, after the histological examination of specimens, only 30 (71.4 %) procedures were classified as curative. Four of 12 patients who underwent non-curative ESD underwent additional gastrectomy, 1 underwent additional ESD, 5 patients were followed up, 1 patient was lost to follow-up and 1 patient was diagnosed with distant metastasis and carcinomatosis and underwent palliative treatment (33).

Table 2. Short-term outcomes of ESD and Surgery groups after propensity matching. (Reprinted with permission from Surgical Endoscopy)

		ESD group (n=42)	Surgery group (n=42)	P
Operation time (min±SD)		83±47	151±47	0.001*
Postoperative hospitalization time (days±SD)		5.4±3.1	13.4±6.6	0.001*
Postoperative complication rate, n (%)		7 (16.7 %)	7 (16.7 %)	0.999
Clavien-Dindo, n (%)	I-II	2 (4.8 %)	4 (9.5 %)	
	III-IV	5 (11.9 %)	2 (4.8 %)	
	V	0 (0.0 %)	1 (2.4 %)	

Surgical treatment efficacy	Radical (R0) surgery, n (%)	-	42, (100 %)	
	Retrieved lymph nodes (mean±SD)	-	19.31±7.57	
	Lymph node metastasis, n (%)		2, (4.8 %)	
	En bloc resection, n (%)	38, (92.7 %)	-	
	Histologically complete resection	32, (78.0%)	-	
	Curative resection	30, (71.4 %)	-	

5.1.3 Survival outcomes

The mean and median length of follow up was 38±34 and 28 (Q3:60 – Q1:9) months for the ESD group and 52±36 and 42 (Q3:74 – Q1:30) months for the surgery group. Figure 2 represents disease-free and overall survival comparison between the study groups. Patients in the surgery group had significantly higher 5-year DFS (97.6 % vs. 77.5 %, p=0.002) (Figure 2a). Exclusion of patients with non-curative ESD reduced the difference of DFS between the surgery and ESD groups. 5-year DFS was 89.7 % in the curative ESD group and 97.6 % in the surgery group, p=0.099 (Figure 2c). In total, 9 (21.4 %) patients from the ESD group and 1 (2.4 %) patient from the surgery group (p=0.014) had a recurrence of gastric cancer during the follow-up period. 8 (19.0 %) patients from the ESD group and 1 (2.4 %) patient from the surgery group had local recurrences, which were successfully treated with repeated ESD or surgery. One (2.4 %) patient from the ESD group was diagnosed with distant metastasis and carcinomatosis. Overall, 8 of 10 patients who experienced recurrence did so within 36 months after initial treatment. The rate of recurrence after non-curative ESD 5/11 (45.5 %) was significantly higher compared to the rate after curative ESD 3/29 (10.3 %), p=0.007. Furthermore, Cox proportional hazards regression model showed non-curative ESD as an independent risk factor for the decline of DFS (Table 3). Despite the differences between ESD and surgery groups according to the DFS, OS did not differ significantly between the study groups. 5-year OS was

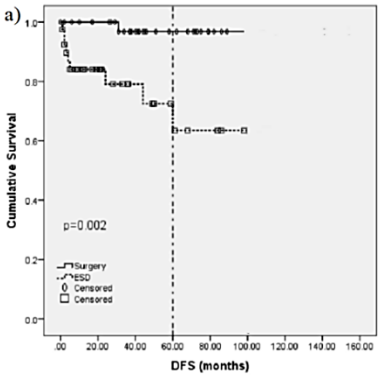
73.8 % and 69.0 % (p=0.599) in the ESD and surgery groups respectively (Figure 2b). Furthermore, we did not find significantly different 5-year OS rate even when we compared groups of patients who underwent curative and non-curative ESD (66.7 % vs. 76.7 %, p=0.581) (Figure 3e) (33).

Table 3. Multivariate Cox regression analysis for disease-free survival in patients with EGC. (Reprinted with permission from Surgical Endoscopy)

Factor		HR (95 % CI)	p value
Age		0.96 (0.89 - 1.04)	0.380
Gender	Female	1	0.126
	Male	0.27 (0.05 -1.44)	
Tumor characteristics	pT1a, differentiated-type, ≤2 cm, Ul-	1	0.940
	1) pT1a, differentiated-type, >2 cm, Ul- 2) pT1a, differentiated-type, ≤3 cm, Ul+ 3) pT1a, undifferentiated-type, ≤2 cm, Ul- 4) pT1b (SM1), differentiated-type, ≤2 cm, Ul-	1.29 (0.14 – 11.74)	
	Exceeding above-mentioned criterias	1.00 (0.08 – 11.97)	
Treatment	Radical surgery or curative ESD	1	0.001*
	Non-curative ESD	41.79 (7.21 – 242.17)	

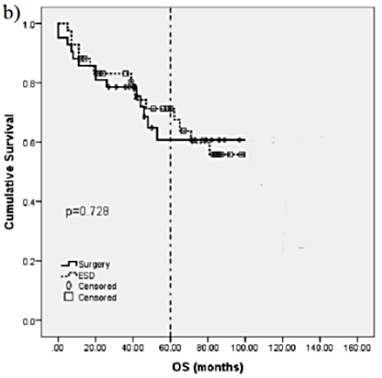
Figure 2. Comparison of long-term outcomes in propensity-matched groups. A) DFS in ESD and surgery groups. B) OS in ESD and surgery groups. C) DFS in curative-ESD and surgery groups. D) OS in curative ESD and surgery groups. E) OS in curative ESD and non-curative ESD groups. (Reprinted with permission from Surgical Endoscopy)

a)



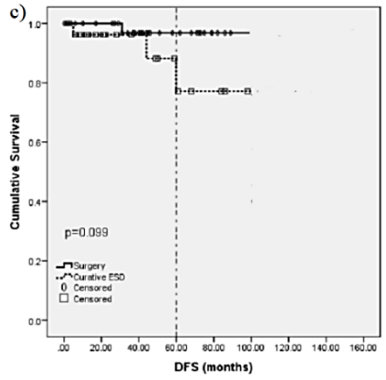
No. at risk								
Surgery	40	34	23	15	7	4	3	2
ESD	40	20	12	7	5	2	1	0

b)



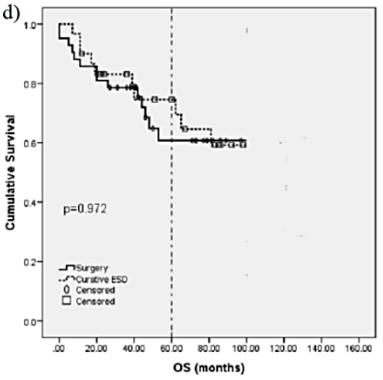
No. at risk								
Surgery	40	34	28	15	9	3	2	
ESD	42	33	26	19	15	2	0	

c)



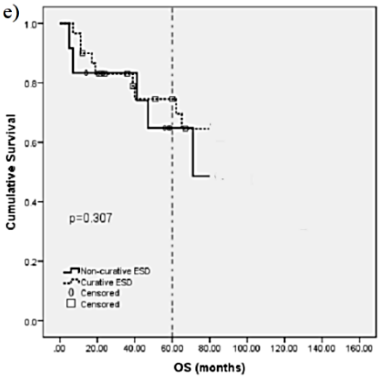
No. at risk								
Surgery	40	34	23	15	7	4	3	2
Curative ESD	29	17	12	7	5	2	1	0

d)



No. at risk								
Surgery	40	34	15	9	4	3	2	
Curative ESD	30	24	15	12	6	2	0	

e)



No. at risk							
Non-curative ESD	12	9	9	4	3	1	0
Curative ESD	30	24	17	15	12	6	2

5.2 LNM in EGC patients

5.2.1 The risk factors for LNM in EGC patients

Two-hundred eighteen patients who underwent surgery with lymphonodectomy were included in the analysis of risk factors for LNM. There were 117 (53.7 %) men and 101 (46.3 %) women, with a mean age of 65.58±12.33 years. Total gastrectomy was performed in 38 cases and subtotal gastrectomy in 180 cases. Majority of the patients underwent a D2 lymphadenectomy – 195 (89.4 %). The average number of removed lymph nodes was 19.89±9.69. After performing the histological examination of operative material, LNM were revealed in 43 (19.7 %) cases. Factors associated with LNM were evaluated by univariate analysis. There was a significantly higher risk for LNM in tumors with submucosal layer infiltration (compared to mucosal infiltration, p=0.001), lymphovascular invasion (LV+ vs LV-, p=0.001), high grade differentiation (G3 vs G1&G2, p=0.047), diffuse or mix type according to Lauren classification (compared to intestinal type, p=0.012), and diameter exceeding 2 cm (compared to tumors≤2 cm, p=0.026). Age, gender, tumor localization, ulceration, and signet ring cell carcinoma had no significance in the presence of LNM (Table 4) (35).

Table 4. Clinicopathological data of patients with EGC and univariate analysis of risk factors for lymph node metastasis (Reprinted with permission from BMC Surgery)

		LNM-	LNM+	p	Odds ratio (95 % CI)
Gender	Male	99 (84.6 %)	18 (15.4 %)	p=0.090	1.80 (0.92 - 3.55)
	Female	76 (75.2 %)	25 (24.8 %)		
Age		65.26±12.17	66.91±13.03	p=0.433	-
Tumor localization	Lower 1/3	62 (78.5 %)	17 (21.5 %)	p=0.457	-
	Middle1/3	100 (80.0 %)	25 (20.0 %)		
	Upper 1/3	13 (92.9 %)	1 (7.1 %)		
Tumor invasion	T1a	94 (94.9 %)	5 (5.1 %)	p=0.001	8.82 (3.31 – 23.46)
	T1b	81 (68.1 %)	38 (31.9 %)		
Tumor differentiation	G1 & G2	100 (87.7 %)	14 (12.3 %)	p=0.006	2.76 (1.36 – 8.57)
	G3	75 (72.1 %)	29 (22.4%)		
Lymphovascular invasion	LV+	12 (40 %)	18 (60 %)	p=0.001	9.78 (4.20 – 22.72)
	LV-	163 (86.7 %)	25 (13.3 %)		
Lauren classification	Diffuse & mix	59 (71.1 %)	24 (28.9 %)	p=0.012	2.09 (1.20 – 3.64)
	Intestinal	106 (86.2 %)	17 (13.8 %)		

Tumor size	≤2cm	91 (86.7%)	14 (13.3 %)	p=0.026	2.27 (1.12 – 4.59)
	>2cm	83 (74.1 %)	29 (25.9 %)		
Ulceration	Ulcerated	58 (74.4 %)	20 (25.6 %)	p=0.114	1.73 (0.88 – 3.42)
	Non-ulcerated	116 (83.5 %	23 (16.5 %)		
Signet ring cell	Yes	11 (73.3 %)	4 (26.7 %)	p=0.513	1.46 (0.44 – 4.86)
	No	149 (80.1 %)	37 (19.9 %)		

The multivariate analysis showed that submucosal tumor invasion, lymphovascular invasion, and high tumor differentiation grade were independent risk factors for lymph node metastasis (Table 5) (35).

Table 5. Multivariate analysis of risk factors for lymph node metastasis. (Reprinted with permission from BMC Surgery)

Factor	p-value	Odds Ratio (95 % CI)
Submucosal tumor invasion (T1b)	p=0.001	6.55 (2.28 – 18.81)
Tumor differentiation grade G3	p=0.045	2.01 (1.03 – 14.66)
Lymphovascular invasion	p=0.001	6.06 (2.28 – 16.07)
Tumor size > 2cm	p=0.155	1.82 (0.79 – 4.19)
Diffuse type according to Lauren classification	p=0.693	1.29 (0.35 – 4.69)

5.2.2 LNM in patients who meet or exceed the standard/extended indication for ESD

Of 58 cancer who met extended criteria, one (1.7 %) had lymph node metastasis in 2 of 22 retrieved lymph nodes. It was not ulcerated, moderately differentiated mucosal cancer with greater than 2 cm diameter (2.2 x 1.8 x 1.5 cm). LNM was found in 42 (30.2 %) of 139 tumors who exceeded the extended criteria (36).

5.3 Surgical treatment outcomes of patients who underwent surgery for early stages GC

5.3.1 Patients and baseline clinicopathologic characteristics

At the time of surgery 267/457 (58.4 %), patients were younger than 70 years. 190 (41.6 %) patients were 70 or older. Table 6 summarizes the clinicopathological findings of the two study groups.

Table 6. Comparison of patient characteristics. (Reprinted with permission from World Journal of Surgical Oncology).

		Group NE (<70 years)		Group E (≥70 years)		p-value
		n	%	n	%	
Sex	Male	150	56.2 %	111	58.4 %	0.701
	Female	117	43.8 %	79	41.6 %	
Age		58.18±8.86		76.43±4.35		0.001
BMI		26.2±5.72		25.9±4.90		0.700
ASA score	1-2	177	68.3 %	71	38.6 %	0.001
	3-4	82	31.7 %	113	61.4 %	
Tumor localization (third)	Upper 1/3	51	19.1 %	26	16.8 %	0.147
	Middle 1/3	119	44.6 %	80	42.1 %	
	Lower 1/3	97	36.3 %	84	44.2 %	
Gastrectomy	Total	83	31.1 %	47	24.7 %	
	Subtotal	184	68.9 %	143	75.3 %	0.143
Lymphanodectomy	D1	13	5.0 %	18	9.8 %	0.059
	D2	246	95.0 %	165	90.2 %	
Multivisceral surgery	Yes	19	7.3 %	15	8.2 %	0.721
	No	241	92.7 %	168	91.8 %	
Tumor invasion	T1a	64	24.0 %	35	18.4 %	0.217

	T1b	63	23.6 %	56	29.5 %	
	T2	140	52.4 %	99	52.1 %	
Lymph node metastasis	Yes	101	37.8 %	74	38,9 %	0.845
	No	166	62.2 %	116	61,1 %	
N categories	N0	166	62.2 %	116	61.1 %	0.778
	N1	65	24.3 %	49	25.8 %	
	N2	19	7.1 %	17	8.9 %	
	N3	17	6.3 %	8	4.3 %	
Distant metastasis	Yes	5	1.9 %	3	1.6 %	0.999
	No	262	98.1 %	187	98.4 %	
Lauren classification	Diffuse	112	42.3 %	17	21.8 %	0.001
	Mix	31	11.7 %	6	8.9 %	
	Intestinal	121	45.8 %	63	69.3 %	
Tumor differentiation grade	G1	27	10.1 %	25	13.2 %	0.001
	G2	69	25.8 %	84	44.2 %	
	G3	171	64.0 %	81	42.6 %	
Tumor size	<2 cm	88	34.2 %	56	30.6 %	0.471
	≥2cm	169	65.8 %	127	69.4 %	

Significant differences were found between the groups in terms of physical status (ASA score), histological type of tumor and tumor differentiation grade. Significantly larger proportion of elderly patients had severe systemic diseases (ASA 3-4) (61.4 % vs. 31.7 %, p=0.001) and intestinal type tumors according to Lauren classification (69.3 % vs 45.8 %, p=0.001). Poorly differentiated tumors were more common in the NE group (G3: 64.0 % vs 42.6 %, p=0.001) (34).

5.3.2 Postoperative morbidity and mortality

The short-term surgical outcomes are shown in Table 7. There was no significant difference in the rate of the total number, the number of severe (3rd or 4th grade according to Clavien-Dindo classification) or the number of surgical postoperative complications between the two groups, but the rate of medical complications was significantly higher in E group (9.7 % vs. 16.3 %, p=0.035). Furthermore, fatal complications which led to postoperative deaths were observed only in elderly patients and the mortality rate was significantly higher in this group (0 % vs. 5.7 %, p=0.001). Even higher differences were observed when 30- and 90-day mortality rates were compared. First deaths in the NE group were observed between 30th and 90th postoperative days with the 90-day mortality rate reaching 2.6 %. During the same time period, the mortality rate in the E group increased from 7.4 % to 12.6 % and remained significantly higher when compared to the NE group (34).

Table 7. Short-term surgical outcomes of NE and E patients who underwent gastrectomy for pT1-T2 gastric cancer. (Reprinted with permission from World Journal of Surgical Oncology).

Factors		Group NE (<70 years)	Group E (≥70 years)	p-value
Operation time: min (mean±SD; min-max)		146.9±41.58	143.72±44.53	0.432
Blood loss: ml (mean±SD; min-max)		171.82±137.11	169.50±136.50	0.879
ICU stay: days (mean±SD; min-max)		1.24±1.24	2.23±6.30	0.014
Postoperative hospital stay: days (mean±SD; min-max)		13.07±5.86	14.05±8.24	0.145
Dissected lymph nodes (mean±SD)		22.18±10.28	19.50±9.43	0.005
Curability	R0	259 (97.0 %)	182 (95.8 %)	0.484
	R1,2	8 (3.0 %)	8 (4.2 %)	
Postoperative complications: n (%)		55/267 (20.5 %)	51/190 (26.8 %)	0.144
Surgical complications		29/267 (10.8 %)	20/190 (10.5 %)	0.909
Anastomotic leakage		2/267 (0.7 %)	5/190 (2.6 %)	0.133
Postoperative bleeding		6/267 (2.2 %)	4/190 (2.1 %)	0.999
Peritonitis/ intraabdominal abscess		5/267 (1.8 %)	3/190 (1.5 %)	0.999
Ileus		3/267 (1.1 %)	0/190 (0.0 %)	0.269

Incisional surgical site infection and (or) eventration		5/267 (1.8 %)	4/190 (2.1 %)	0.999
Postoperative pancreatitis		5/267 (1.8 %)	2/190 (1.0 %)	0.704
Pancreatic/ Biliary/ Enterocutaneuos fistula		3/267 (1.1 %)	2/190 (1.0 %)	0.999
Medical complications		26/267 (9.7 %)	31/190 (16.3 %)	0.043
Cardiac insufficiency		0/267 (0.0 %)	3/190 (1.5 %)	0.071
Pneumonia		11/267 (4.1 %)	4/190 (2.1 %)	0.292
Sepsis		0/267 (0.0 %)	3/190 (1.5 %)	0.071
PATE		0/267 (0.0 %)	2/190 (1.0 %)	0.172
Other		15/267 (5.6 %)	19/190 (10.0 %)	0.102
Clavien-Dindo	1-2	39 (14.6 %)	30 (15.8 %)	0.195
	3-4	16 (6.0 %)	10 (5.3 %)	
Postoperative mortality: n (%)		0 (0.0 %)	11 (5.7 %)	0.001

5.3.3 Risk factors for postoperative complications in NE and E groups

At univariate analysis, ASA III/IV (p=0.006), total gastrectomy (p=0.022) and multivisceral surgery (0.031) were identified as factors that were associated with postoperative complications in E group (Table 8.). At multivariate analysis, only ASA III/IV was independently associated with postoperative complications (OR=6.47; 95 % CI 2.09-20.06, p=0.021).

Table 8. Univariate analysis of risk factors for postoperative complications in NE and E groups. (Reprinted with permission from World Journal of Surgical Oncology).

		Group NE (<70 years)	%	p Value	Group E (≥70 years)	%	p Value
Sex	Male	30/150	20.8 %	0.879	30/111	27.0 %	0.999
	Female	25/117	21.4 %		21/79	26.6 %	
BMI	<30	30/130	23.1 %	0.999	9/30	30.0 %	0.814
	≥30	11/47	23.4 %		24/91	26.4 %	
ASA score	1-2	33/177	18.6 %	0.144	11/71	15.5 %	0.006
	3-4	22/82	26.8 %		39/113	34.5 %	
Gastrectomy	Total	22/83	26.5 %	0.141	19/47	40.4 %	0.022
	Subtotal	33/184	17.9 %		32/143	22.4 %	

Tumor localization (third)	Upper 1/3	15/51	29.4 %	0.077	11/26	42.3 %	0.157
	Middle 1/3	24/119	20.2 %		19/80	23.8 %	
	Lower 1/3	16/97	16.5 %		21/84	25.0 %	
Multivisceral surgery	Yes	2/19	10.5 %	0.381	8/15	53.3 %	0.031
	No	53/241	22.0 %		42/168	25.0 %	
Lymphanodectomy	D1	5/13	38.5 %	0.157	5/18	27.8 %	0.999
	D2	50/246	20.3 %		46/165	27.9 %	
Retrieved lymph nodes (LN)	≤15 LN	6/52	30.8 %	0.058	17/61	27.9 %	0.860
	>15 LN	39/211	18.5 %		33/127	26.0 %	

In NE group none of the analyzed factors were significantly associated with a total number of postoperative complications, but tumor localization in the upper third was associated with severe postoperative complications (≥ 3 grade according to Clavien-Dindo), 14.9 % vs. 4.3 %, p=0.014 (34).

5.3.4 Risk factors for postoperative mortality in NE and E groups

While there were no deaths in the NE group during the first 30 postoperative days, factors associated with 90-day mortality rates were analyzed. At univariate analysis, ASA 3/4 (p=0.034) and tumor localization in the upper third (p=0.013) were associated with 90-day mortality in the NE group.

In the E group, univariate analysis revealed ASA 3/4 (p=0.038) and multivisceral surgery (p=0.017) as factors associated with death during the first 90 postoperative days. With multivariate analysis, only severe complications during hospitalization were found as independent factors associated with a higher 90-day mortality rate (OR=12.82; 95 % CI 1.01-169.21, p=0.049) (34).

6 DISCUSSION

The main findings of our study are: 1) ESD is feasible for EGC treatment in Lithuanian population with comparable long-term outcomes and shorter operation and hospitalization time, but only in case of curative ESD; 2) Non-curative ESD is associated with poor DFS and high rate of recurrence; 3) Submucosal tumor invasion, lymphovascular invasion, and high-grade tumor differentiation are the risk factors for LNM in Lithuanian population of EGC; 4) LNM are present in 1.7 % of EGC patients who meet the expanded indications for ESD; 5) Elderly age is not associated with increased postoperative morbidity, but the higher mortality rate. ASA score may be useful for predicting surgical treatment outcomes in elderly patients undergoing surgery.

The LNM is the key limiting factor for ER of EGC. Therefore, the current concept to select the patients available for ER is based on the identification of those who have a negligible risk of LNM by the prediction based on the

clinicopathologic characteristics of the tumor. Table 9 summarize 17 recent studies, which investigated risk factors for LNM in EGC.

Table 9. Lymph node metastasis in early gastric cancer – a literature review and our results. (Reprinted with permission from BMC Surgery)

Author	Country	Year	No. of patients	LNM+ in T1a cancer patients	LNM+ in T1b cancer patients	Risk factors for LNM
Studies from Asian countries						
Lim MS. et al. (37)	South Korea	2011	376	2.8 %	18.4 %	T1a: tumor size> 2 cm and lymphovascular invasion T1b: macroscopic type (elevated) and lymphovascular invasion
Ren G. el al. (38)	China	2013	202	9.0 %	22.5 %	Depth of invasion
Wang L. et al. (39)	China	2013	242	5.5 %	20.0 %	Depth of invasion, lymphovascular invasion.
Nakagawa M. et al. (40)	South Korea	2015	1042	Not available	Not available	Depth of invasion, tumor size, ulceration, age and positive nodal status by CT.
Wang Y. (41)	China	2015	198	6.0 %	56.2 %	Depth of invasion. tumor size. ulceration. histological type and venous invasion.

Park JH. et al. (42)	South Korea	2015	2270	2.8 %	19.0 %	Depth of invasion, tumor size > 3 cm and lymphovascular invasion
Fang WL. et al. (43)	Taiwan	2015	391	4.9 %	21.4 %	T1a: Lauren's diffuse type and lymphatic invasion T1b: lymphatic invasion
Zhao LY. et al. (44)	China	2016	687	15.5%	35.9 %	Depth of invasion. tumor size>2cm, ulceration, lymphovascular invasion, differentiation
Wang YW. et al. (45)	China	2016	230	8.5 %	28.6 %	Depth of invasion, tumor size≥2 cm and P53 overexpression
Sekiguchi M. et al. (46)	Japan	2016	3131	4.2 %	20.2 %	Depth of invasion, tumor size≥2 cm, ulceration, lymphovascular invasion, differentiation
Zheng Z. et al. (47)	China	2016	597	3.0 %	18.3 %	Depth of invasion, ulceration, lymphovascular invasion, age, differentiation.
Studies from Western countries						

Milhomem LM. et al. (48)	Brazil	2012	126	7.8 %	22.6 %	Depth of invasion, tumor size>5 cm, ulceration and lymphatic invasion.
Bravo Neto GP. et al. (49)	Brazil	2014	26	16.7 %	42.9 %	Not available
Fukuhara S. et al. (31)	USA	2014	104	7.1 %	35.4 %	Lymphovascular invasion, non-Asian race, and younger age.
Haist T. et al. (50)	Germany	2016	124	1.9 %	22.5 %	Depth of invasion, lymphovascular invasion.
Ahmad R. et al. (51)	USA	2016	67	4.3 %	31.8 %	Lymphovascular invasion and positive nodal status by endoscopic ultrasound.
Ronellenfitsch U. et al. (52)	Germany	2016	275	3.9 %	18.2 %	Depth of invasion, lymphovascular invasion, diffuse- and mixed-type according to Lauren.
Our study	Lithuania	2017	218	5.1 %	31.9 %	Depth of invasion, lymphovascular invasion and tumor differentiation grade

The reported rates of LNM in EGC from various Asian and Western countries were varying. In Asia, LNM rates ranged from 2.8 % to 15.5 % for patients with tumors invading only the mucosal layer (37,44) and from 18.3 % to 56.2 % for patients with tumors invading the submucosal layer (35,37,41). Respectively, in Western countries, rates of LNM varied from 1.9 % to 16.7 % when the tumor was localized to the mucosa and from 18.2 % to 42.9 % when the tumor invaded the submucosal layer (35,49,50). Our study results were similar; the rates of LNM for patients with T1a and T1b cancer were 5.1 % and 22.4 %, respectively. Risk factors for LNM determined in various studies were also differing. In Asian studies, the most frequently mentioned factors were the depth of invasion (9 of 11 studies), tumor size (7 of 11 studies), and lymphatic or lymphovascular invasion (7 of 11 studies). In Western studies, the lymphovascular invasion has been of recent focus in 5 of 6 studies with our results also confirming lymphovascular invasion as a risk factor for LNM (35). Another risk factor which was studied in our data, submucosal tumor invasion, was mentioned in 3 of 6 previously published Western studies. Tumor differentiation was only mentioned as a risk factor for LMN in reports from Asian nations (44,46,47). To our best knowledge, our study is the first report of Western countries which confirms tumor differentiation as an independent risk factor for LNM (35).

Despite the variation between Asian and Western regions, the use of EMR/ESD as a treatment option for ECG is increasing in the West (53). However, still, only a small proportion of EGC patients fall under the standard criteria for ESD. The expansion of the standard criteria has been proposed in Japan from clinical observations that too strict indication leads to unnecessary surgery (36,53,54). From the dataset of 5265 patients who underwent gastrectomy for EGC Gotoda et al. identified four additional groups of tumors, which have a very low possibility of LNM when they are not accompanied with lymphovascular infiltration (36,55,56). These criteria are described as expanded indications in Japanese Gastric Cancer guideline: 1) differentiated-type mucosal cancer without ulceration and greater than 2 cm in diameter; 2) differentiated-type mucosal cancer with ulceration and up to 3 cm in diameter; 3) undifferentiated-type mucosal cancer without ulceration and up to 2 cm in diameter and 4) differentiated-type submucosal cancer (SM1, <500 microns from the *muscularis mucosae*) up to 3 cm in diameter (16).

Avoidance of unnecessary surgery for appropriately selected EGC patients would lead to treatment improvement, especially in elderly patients having higher ASA score, since our study showed a higher risk of

postoperative mortality in these patients. However, extending the indications for endoscopic EGC treatment remains controversial because the long-term outcomes of these procedures have not been adequately documented (36,57). A study published by Jee et al. (58) confirmed this uncertainty when reported 2.8 % LNM rate in a cohort of patients who underwent gastrectomy for ECG which met the extended indications for ER. Alike, data from our present study showed a 1.7 % LNM rate in a similar cohort. Interestingly, Jee et al. (58) showed the risk of LNM in three of four expanded criteria, but not in differentiated-type mucosal cancer, without ulceration, greater than 2 cm in diameter. Therefore, the authors proposed to consider this indication as safe (58). In contrast, our study showed that this criterion also carries the risk of LNM. Thus, our result together with findings indicates that the possibility of LNM exists in every extended criterion.

While LNM risk in patients who meets expanded indications for ER is relatively low, patients who exceed these criteria are at high risk. We founded LNM in 30.2 % of tumors who exceeded the expanded criteria (36). Nowadays ER for those tumors is considered as a non-curative treatment. However, some authors discuss that even non-curative ER could lead to satisfactory clinical outcomes. A large multi-center study published by Hatta et al. (59) compared long-term outcomes of patients who underwent either additional radical surgery or only follow-up after non-curative endoscopic resection. Results of the study showed that patients who underwent additional radical surgery had better 3- and 5-year OS and DSS rates. Obviously, it should be declared, that the difference in DSS rates was rather small (99.4 % vs. 98.7 %) compared to the difference in OS rates (96.7 % vs. 84.0 %). Also, the rates of recurrence were significantly different, although in both groups they were low - 1.3 % and 3.1 % in the radical surgery group and the follow-up group, respectively. However, good outcomes in the follow-up group according to DSS and recurrence rates should be treated carefully due to different background characteristics of the study groups. Some major risk factors for LNM (lymphatic invasion or deeper submucosal invasion) were significantly more frequent in the additional radical surgery group (35,59), and these differences may influence the study results. Furthermore, Suzuki et al. (20) recently published results from a similar study and showed a clear superiority of additional surgery after non-curative ESD compared to follow-up. After propensity score matching analysis, they founded significantly higher rates of 5-year DSS rate (99.0 % vs 96.8 %) and 5-year OS (91.0% vs. 75.5 %) in the additional surgery group [19]. Results of those two studies and

a high rate of LNM revealed in our study indicate, that EGC which exceeds expanded criteria for ER should be treated with gastrectomy and appropriate lymphadenectomy. Our results of ESD and surgery comparison by propensity score matching analysis also confirms the need of surgery after non-curative ESD, since we found a major difference in the recurrence rate after non-curative ESD (5/11, 45.5 %) compared to curative ESD (3/29, 10.3 %). Moreover, one patient receiving only follow-up after non-curative ESD was diagnosed with distant metastasis and carcinomatosis (33).

In short-term outcome analysis, we found that ESD achieved significantly better perioperative outcomes compared to surgery regarding shorter operative time and shorter postoperative hospitalization (33). The mean procedure duration of ESD was 83 minutes and was closely comparable to times reported in large Western studies as well as those in Eastern regions (61,62). The superiority of ESD according to shorter operative time and postoperative hospital stay has previously been shown by Chiu et al. (17), where authors retrospectively compared 74 patients with severe dysplasia or EGC treated by ESD to 40 patients treated by gastrectomy in China. In contrast to this study and findings of a systematic review (62), we did not find a lower rate of postoperative complications after ESD. In our study, the postoperative complications occurred for 7/42 (16.7 %) patients in each group. The severity of complications in both groups was also comparable. Complications requiring only pharmacological treatment were observed in 4/42 (9.5 %) and 2/42 (4.8 %) patients in the surgery and ESD groups respectively. An endoscopic intervention for management of complications was necessary only for postoperative bleeding, which occurred after 3 (7.1 %) ESDs. The postoperative bleeding rate found in our study is close to rates reported in various Asian and Western studies reporting delayed bleeding rates between 1.6% and 7% (61,63,64). 2 (4.8 %) patients from each group had complications requiring surgical treatment. In the surgery group, both patients underwent re-operation for postoperative peritonitis, while in the ESD group, surgery was necessary for management of perforations. Likewise, the perforation rate after ESD in our study is also comparable to findings in other studies. According to recent reports, perforation follows 2.2 % to 9.7 % of ESD's in Eastern cohorts and 1.8 % to 10 % in Western cohorts (61–63). Therefore, we believe that the discrepancy in postoperative complications between our findings and Asian studies are influenced by the relatively low rates of postoperative morbidity after surgery and a relatively high proportion

of complications requiring only pharmacological treatment in the ESD group of our study (33).

Postoperative death was registered only in the surgery group of our study in which 1/42 (2.4 %) patient died during the postoperative period. The postoperative mortality rate in the propensity-matched surgery group represents the entire cohort very well since our previous report demonstrated a 1.8 % mortality rate after surgery for EGC in the non-matched cohort (33,35). We failed to show the risk of postoperative mortality after ESD. However, it should be taken into consideration, that our study cohort was relatively small and mortality risk could have been underestimated, as previous reports have shown mortality rates reaching up to 3.3 % (33,65).

We found that all patients who underwent surgical treatment for EGC had radical surgery. This finding confirms the results published in many Asian studies, where the reported rate of radical resection after surgery was 100 % (33,62). In contrast to excellent results of surgery according to radicality, en bloc resection was achieved in 38/42 (92.7 %) and histologically complete resection in 32/42 (78.0 %) patients in the ESD group. The en bloc and histologically complete resection rates of our study were comparable with previous reports from different regions of the world (33,61,63–66). After histological examination of the specimens, 2 (4.8 %) patients had an EGC which exceeded expanded criteria for curative ER and only 30/42 (71.4 %) ESD‘s were classified as curative resections. In a multivariate Cox regression analysis, we revealed non-curative ESD as a risk factor for a decline in DFS. We believe that the relatively high rate of non-curative ESDs explains our finding of significantly higher 5-year DFS in the surgery group (33). In contrast to our results, a total of 1331 Asian patients were summarized in a systematic review comparing ER and surgery for EGC, and no differences regarding recurrence were found between the surgery and ER groups (62). Therefore, we analyzed DFS in ESD and surgery groups after exclusion of the patients who underwent non-curative ESD. As expected, exclusion blunted the significant differences. Although DFS was significantly better in the surgery group, OS did not differ between the two groups in this study. Unexpectedly, even the non-curative ESD group did not show considerably worse OS. Several factors might be responsible for these results. First, the non-curative ESD group was rather small, and a significant number of patients (5/12, 41.6 %) from this group underwent additional surgery during the first six months after initial ESD. Second, 8 of 9 patients who were diagnosed with the recurrent disease after primary ESD were radically treated either with

repeated ESD or surgery. Radical treatment or recurrence resulted in complete cure of cancer, and probably later EGC did not have an impact on OS. Third, according to the latest World Health Organization report published in 2015, life expectancy in Lithuania is 73.6 years, and the mean age of patients in both groups exceeded 72 years. Therefore, we can assume that OS is mainly affected by general health status and natural mortality rates of the cohort (33). This feature of our cohort also explains the differences between OS rates found in our study and those reported in Asia, where 5-year OS after ER and surgery for EGC is 97.5 % and 97.0 % respectively (24).

7 LIMITATIONS

The present study has several limitations. First, it is a retrospective design study in which patients were not randomly assigned to ESD or surgery groups It should be noted, that ESD and surgery has never been tested in a randomized controlled trial and the limitations for constructing such a trial has been already described: significant differences in treatment invasiveness and already widespread acceptance of ESD cause ethical issues, while the need for an enormous sample size because of a low rate of lymph node metastasis, results in an enormous costs of the trial (67). To reduce the selection bias for different treatment methods comparison, we performed propensity score matching analysis, which is considered as an excellent alternative in this case (67). Even with the use of this statistical method, a significant difference remained between the two groups in regards to tumor size. Wider tumors were more frequent in the surgery group, and this difference may have negatively biased outcomes against the surgery group. Nevertheless, the surgery group showed significantly higher 5-year DFS rate and comparable OS rate. Second, the number of patients who underwent non-curative ESD in our study was low. Therefore, we could not compare the outcomes of additional surgery or only follow-up in these patients. Third, the total number of patients in our study was relatively low, especially compared to similar studies performed in Asia. However, due to the low prevalence of EGC in Western countries, only large international multicenter studies can overcome this limitation. Despite all flaws, we managed to show differences between the two treatment groups in the first study comparing ESD and surgery for EGC in a Western setting (33).

8 CONCLUSIONS

- LNM occurs in 19.7 % of patients with EGC. Submucosal tumor invasion, lymphovascular invasion, and high-grade tumor differentiation are the risk factors for lymph node metastasis in the Lithuanian population with EGC.
- ESD might be a perfect alternative to surgery for EGC in the Lithuanian population, because of shorter operation and hospitalization time and comparable long-term outcomes.
- Non-curative ESD leads to a poor DFS rate, therefore, additional surgery should be recommended for these patients whenever treatment-associated risk is acceptable.
- Implementation of expanded criteria for ER of EGC in a Western setting is not entirely safe because of the risk of LNM. EGC who exceeds expanded indications has a high risk of LNM, therefore gastrectomy with lymphadenectomy should remain a standard treatment option in these cases.
- Elderly patients carry a similar risk of postoperative morbidity following surgery for early stages GC. However, in cases of complicated postoperative courses, they suffer from high mortality rate. ASA score may be useful in predicting postoperative complications in elderly patients undergoing surgery for early stages GC. This tool can be used to evaluate the surgery-related risk. Radical surgery with at least limited lymph node dissection should be considered, even for elderly patients.

9 SUMMARY

Santrumpos

ASV – ankstyvas skrandžio vėžys
SV – skrandžio vėžys
LMM – limfinių mazgų metastazės
IBL – išgyvenamumas be ligos atkryčio
LSI – ligai-specifiškas išgyvenamumas
BI – bendras išgyvenamumas
ER – endoskopinė rezekcija
RS – rizikos santykis
ŠS – šansų santykis
ESD – endoskopinė submukozinė disekcija
EGR – endoskopinė gleivinės rezekcija
EGDS – Esofagogastroduodenoskopija
KT – kompiuterinė tomografija
pT1 – navikas augantis į *lamina propria, muscularis mucosae,* ar *pogleivį*
pT2 – navikas augantis į *muscularis propria* sluoksnį
95 % PI – 95 % pasikliautinis intervalas

1. ĮVADAS

1.1 Literatūros apžvalga

Skrandžio vėžys (SV) yra vienas iš labiausiai paplitusių piktybinių navikų pasaulyje. Chirurginis gydymas išlieka pagrindiniu ir vieninteliu visiško pasveikimo leidžiančiu tikėtis šios ligos gydymo metodu (1). Reikšmingai daliai pacientų sergančių SV jau diagnozės nustatymo metu ar iškart po chirurginio gydymo atlikus histologinį pašalinto preparato vertinimą nustatomos metastazės limfiniuose mazguose (LMM) (2). Žinoma, jog LMM yra susijusios su blogesne pacientų prognoze, o chirurginis gydymas gali būti laikomas radikaliu tik tuo atveju, kai po jo nelieka nei makroskopiškai nei mikroskopiškai matomos ligos, taigi radikalus gydymas įmanomas tik chirurgiškai pašalinant visas LMM (3). Todėl auksiniu bet kurios stadijos rezektabilaus SV gydymo standartu išlieka radikalus chirurginis gydymas – gastrektomija ar skrandžio rezekcija kartu su pakankamos apimties limfonodektomija (4,5).

Ankstyvas skrandžio vėžys (ASV) apibrėžiamas kaip SV, kuriame naviko invazija siekia tik gleivinę ar pogleivį, nepriklausomai nuo to, ar yra LMM (pT1). ASV atveju tradicinis chirurginis gydymas leidžia pasiekti puikius onkologinius rezultatus - 5 metų bendrasis išgyvenamumas (BI) siekia nemažiau 90 % (6,7). Deja, tradicinis chirurginis ASV gydymas yra susijęs su ženkliu pooperacinių komplikacijų dažniu, pooperaciniu mirštamumu bei su suprastėjusia paciento gyvenimo kokybe (8-10). Ilgėjant tikėtinai gyvenimo trukmei bei gerėjant su senatve susijusių gretutinių ligų gydymui SV vis dažniau serga ženkliai vyresnio amžiaus pacientai. Chirurginis SV gydymas tapo standartu gydant geros ar patenkinamos klinikinės būklės pacientus, tačiau tokio gydymo rezultatai nėra visiškai aiškūs gydant vyresnius pacientus, ypač tuos, kurie pasižymi gausia gretutine patologija (11-13).

Teoriškai SV chirurgijos apimtis galėtų būti reikšmingai sumažinama iki lokalios naviko ekscizijos ar rezekcinės operacijos be limfonodektomijos, jei jau iki operacijos būtų galima patikimai nustatyti ar yra LMM. Deja, visame pasaulyje priešoperaciniam ligos stadijavimui rutiniškai naudojama kompiuterinė tomografija (KT) ar magnetinis branduolinis rezonansas (MBR) nėra pakankamai jautrūs ir specifiški tyrimai identifikuojant LMM (14,15). Po klinikinių pastebėjimų, kad tam tikrais ASV atvejais LMM rizikos nėra ar ji yra itin maža, kaip alternatyva tradiciniam chirurginiam gydymui buvo pasiūlyta lokali endoskopinė naviko rezekcija (ER): endoskopinė gleivinės rezekcija (EGR) ar endoskopinė submukozinė disekcija (ESD). Manoma, jog lokali ER yra pakankama neišplitusio į limfinius mazgus ASV gydymui. Kadangi KT/MBR neleidžia patikimai nustatyti LMM, ASV atvejai turintys minimalią LMM riziką bei tinkami lokaliai ER pradėti nustatyti remiantis histologinėmis ir morfologinėmis pirminio naviko savybėmis. Šiuolaikiniai endoskopinio ASV gydymo kriterijai nurodomi Japonų Skrandžio Vėžio Gydymo Gairėse (16) kaip standartiniai jei tai yra diferencijuota adenokarcinoma be išopėjimo požymių, navikas yra intramukozinis, o jo diametras ≤2 cm. Ši indikacija buvo pirmoji ir ilgą laiką vienintelė kuomet siūlyta taikyti endoskopinį gydymą. Tačiau, bėgant laikui bei Azijos šalyse sukaupus klinikinės patirties, buvo pastebėta, kad ir kai kurie navikai viršijantys šias labai siauras indikacijas galėtų būti gydomi ER. Todėl šiuolaikinės gairės papildytos išplėstiniais kriterijais: 1) diferencijuoto tipo intramukozinė adenokarcinoma be išopėjimo požymių, kurios diametras viršija 2 cm; 2) diferencijuoto tipo intramukozinė adenokarcinoma su išopėjimo požymiais, kurios diametras neviršija 3 cm; 3) nediferencijuoto tipo intramukozinė adenokarcinoma be išopėjimo požymių neviršijanti 2 cm

diametro; 4) diferencijuoto tipo pogleivinė (SM1, <500 μm nuo muscularis mucosae) adenokarcinoma neviršijanti 3 cm diametro. Būtina pažymėti, jog išplėstinių kriterijų naudojimas vertinamas kaip eksperimentinis gydymo metodas, todėl kad nėra tvirtų įrodymų apie atokiuosius šio gydymo rezultatus.

Pastaraisiais metais pasirodė keletas studijų pateikiančių atokiuosius chirurginio ir endoskopinio ASV gydymo rezultatus, kurie yra panašūs. Taip pat pažymima, jog pooperacinis komplikacijų dažnis bei mirštamumas yra yra mažesnis po ER, taip pat ši procedūra yra pranašesnė dėl tikėtina geresnės pacientų gyvenimo kokybės (17-24). Visos šios klinikinės studijos, kaip ir pats ER konceptas, buvo sukurtos išskirtinai Azijos šalyse, o šių rezultatų atkartojimas vakarietiškoje populiacijoje šiuo metu kelia aršias diskusijas. Jos kyla dėl kelių svarbių priežasčių. Visų pirma, Vakarų ir Azijos šalyse skiriasi histologiniai SV diagnostikos kriterijai (25), o šie skirtumai yra itin svarbūs ASV atveju. Japonijoje ir kai kuriose kitose Azijos šalyse histologinė diagnozė yra paremta struktūrinių ir naviko liaukų ląstelių nukrypimo nuo normos laipsniu (25-27) kuomet Vakarų šalyse histologinei SV diagnozei yra būtinas naviko ląstelių invazijos komponentas (25,28). Dėl tokių skirtingų interpretacijų Vakarų šalyse nustatyta aukšto laipsnio displazija Japonijoje jau yra vertinama kaip ASV (25,29). Antra, vakariečiai sergantys SV skiriasi nuo tokių pat pacientų iš Azijos šalių tuo, kad jų tarpe ženkliai dažniau sutinkamas proksimalinės skrandžio dalies vėžys, daugiau difuzinio tipo vėžio, taip pat vakariečiai pasižymi didesniu kūno masės indeksu bei vyresniu amžiumi (30). Esant šiems skirtumams nesutariama ar SV etiopatogenezė šiuose regionuose yra ta pati. Dar daugiau sumaišties į šią diskusiją įnešė dvi nesenai paskelbtos studijos, nurodančios, kad neazijietiška rasė savaime yra LMM rizikos veiksnys (31,32).

Dėl šių išvardintų priežasčių išlieka neaišku ar ASV gydymo ER koncepcija atsiradusi ir išvystyta Azijos šalyse gali būti sėkmingai perkeliama ir taikoma Vakarų šalyse, įskaitant ir Lietuvą.

1.2 Tyrimo hipotezė

ASV gydymas ER yra saugus ir priimtinas Lietuvos populiacijoje.

1.3 Tyrimo tikslas

Nustatyti, ar ASV gydymas ER yra saugus ir priimtinas Lietuvos populiacijoje, kuri gali būti laikoma vakarietiško tipo populiacija.

1.4 Tyrimo uždaviniai

1. Palyginti artimuosius ir atokiuosius pacientų sergančių ASV gydymo rezultatus taikant tradicinį chirurginį gydymą ar ER Lietuvos populiacijoje.
2. Nustatyti LMM rizikos veiksnius pacientams sergantiems ASV Lietuvos populiacijoje.
3. Nustatyti LMM dažnį Lietuvos pacientų sergančių ASV bei atitinkančių standartinius ir išplėstinius endoskopinio gydymo kriterijus grupėje.
4. Nustatyti LMM dažnį Lietuvos pacientų sergančių ASV bei viršijančių standartinius ir išplėstinius endoskopinio gydymo kriterijus grupėje.
5. Nustatyti pooperacinių komplikacijų ir pooperacinio mirštamumo rizikos veiksnius taikant standartinį chirurginį gydymą pacientams sergantiems ankstyvų stadijų SV.

1.5 Tyrimo naujumas

Mūsų žiniomis, tai yra pirmasis tyrimas, lyginantis tradicinio chirurginio ir minimaliai invazyvaus - endoskopinio ASV gydymo rezultatus vakarietiškoje populiacijoje.

2. METODAI

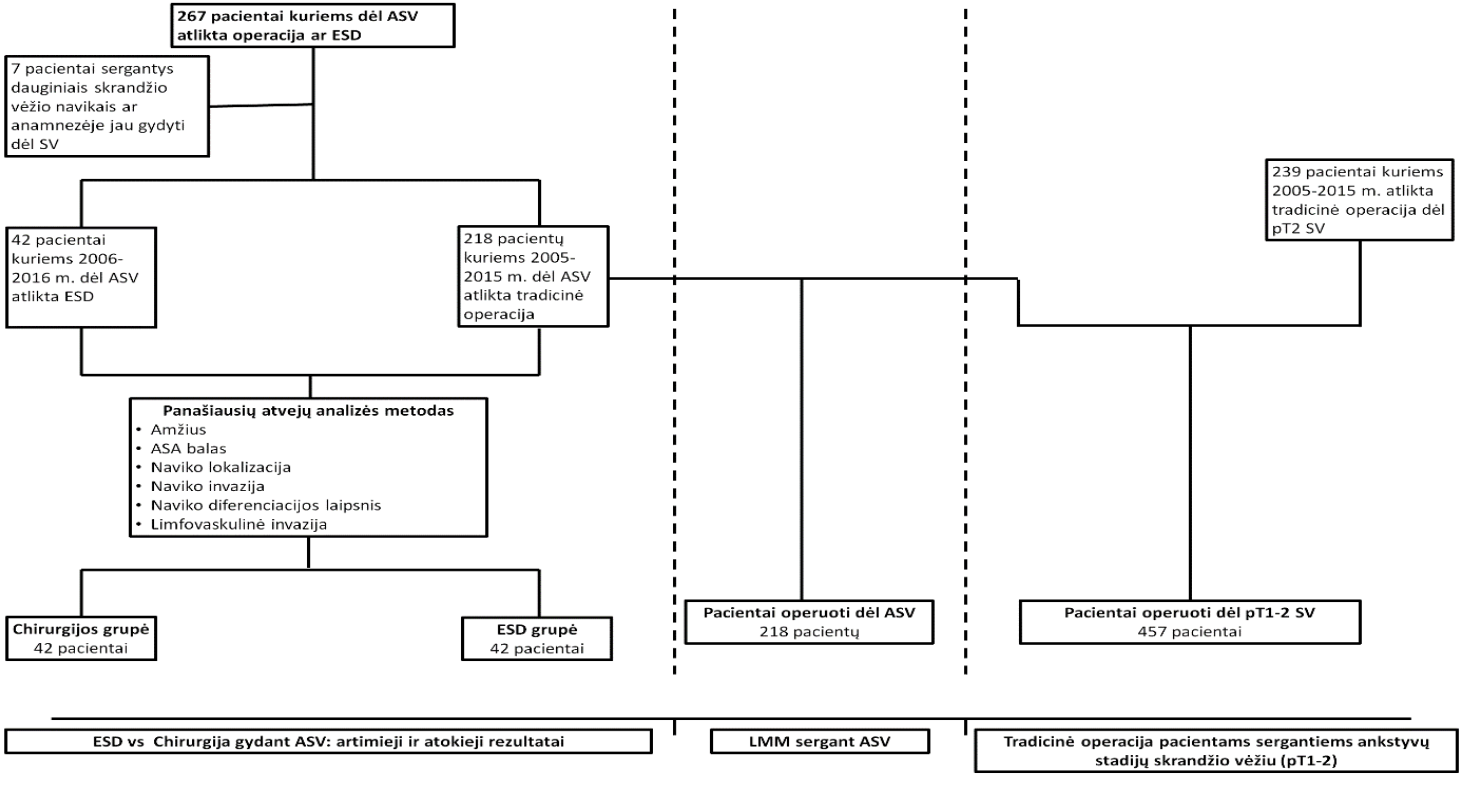
2.1 Etika

Prieš pradedant tyrimą buvo gautas Vilniaus regioninio biomedicininių tyrimų etikos komiteto leidimas.

2.2 Pacientai ir tyrimo dizainas

Pacientų įtraukimas į tyrimą pavaizduotas 1-ame paveiksliuke.

Paveikslėlis 1. Struktūrinė pacientų įtraukimo į tyrimą schema.



2.2.1 ESD ir chirurginio ASV gydymo palyginimas: artimieji ir tolimieji gydymo rezultatai

Į šį retrospektyvaus dizaino tyrimą įtraukti visi pacientai, kurie dėl ASV gydyti Vilniaus Universiteto ligoninės Santaros Klinikose nuo 2006 m. sausio mėn. iki 2016 m. gruodžio mėn. taikant jiems ER ir pacientai, kurie operuoti dėl ASV Nacionaliniame Vėžio Institute nuo 2005 m. sausio mėn. iki 2015 m. gruodžio mėn. ER programa pacientams sergantiems ASV Vilniaus Universiteto ligoninės Santaros Klinikose buvo pradėta 2006 m., todėl nežymiai skiriasi pacientų įtraukimo periodai abiejose institucijose, kurie taip pasirinkti, norint išlaikyti vienodą 10 m. periodą. Pacientai patys rinkosi gydymo centrą. Visi į tyrima įtraukti pacientai buvo europidų rasės. Pacientų neįtraukimo į tyrimą kriterijai: 1) daugybinis arba sinchroninis ASV; 2) ankstesnis SV gydymas, įskaitant ir neoadjuvantinę chemoterapiją.

Taikant įtraukimo ir neįtraukimo į tyrimą kriterijus atrinkta 260 pacientų, kurie suskirstyti į chirurgijos (218 pacientų) ir ESD (42 pacientai) grupes. Abiejų grupių gydymo rezultatai buvo lyginami naudojant panašiausių atvejų analizės metodą (*angl. propensity score matching*). Pirminis šios tyrimo dalies tikslas buvo nustatyti 5 metų išgyvenamumą be ligos atkryčio (IBL) taikant kiekvieną iš šių gydymo metodų. Antriniai tikslai – bendras 5 metų išgyvenamumas (BI), pooperacinių komplikacijų dažnis, operacijos trukmė ir hospitalizacijos laikas. BI buvo skaičiuojamas nuo operacijos datos iki mirties, IBL - nuo operacijos datos iki lokalaus arba atokaus ligos atkryčio.

2.2.2 LMM pacientų sergančių ASV tarpe

Siekiant nustatyti LMM sergančiųjų ASV tarpe buvo tirti aukščiau minėti 218 pacientų, kuriems dėl ASV atlikta tradicinė operacija kartu su limfonodektomija. Kaip potencialūs rizikos veiksniai buvo vertinami: pacientų amžius, lytis, naviko lokalizacija, naviko invazijos gylis, naviko diferenciacijos laipsnis, limfovaskulinė invazija, naviko tipas pagal Lauren, naviko dydis, naviko išopėjimas ir žiedinių ląstelių komponentas. Nustatytas LMM dažnis tarp pacientų atitinkančių bei viršijančių standartinius/išplėstinius kriterijus ER dėl ASV.

2.2.3 Tradicinis chirurginis pacientų sergančių ankstyvųjų stadijų SV gydymas

Tirti pacientai operuoti dėl ankstyvų stadijų (pT1 (ASV) ir pT2) SV Nacionaliniame Vėžio Institute nuo 2005 m. sausio mėn. iki 2015 m. gruodžio mėn. (Paveikslėlis 1), siekiant nustatyti pooperacinių komplikacijų ir mirštamumo dažnį bei tai lemiančius veiksnius. Operacijos technika operuojant dėl pT1 ir pT2 navikų beveik nesiskiria, todėl siekiant didesnės pacientų imties ir tyrimo galios į šią tyrimo dalį įtraukti ir pacientai su pT2 navikais infiltruojančiais *muscularis propria*. Į šią tyrimo dalį iš viso įtraukti 457 pacientai: 218 pacientų su pT1 (ASV) ir 239 pacientai su pT2 navikais. Siekiant išaiškinti vyresnio amžiaus pacientų gydymo rezultatus pacientai buvo suskirstyti į dvi grupes atsižvelgiant į jų amžių: vyresnieji (V; ≥70 metų) ir jaunesnieji (J; <70 metų) (34).

2.3 Pacientų savybės ir klinikiniai duomenys

Visų pacientų duomenys buvo surinkti iš ligoninėje esančių duomenų bazių kaupiančių medicininę dokumentaciją bei iš perspektyviai surinktos ASV atvejus registruojančios duomenų bazės. SV ligos stadijavimui naudota 7-oji AJCC/UICC TNM sistemos klasifikacija. Vertinti pacientų demografiniai duomenys: lytis ir amžius. Taip pat klinikiniai ir demografiniai duomenys: rūkymas, KMI, gretutiniai susirgimai, fizinė būklė pagal Amerikos Anesteziologų Draugijos (ASA) klasifikaciją, hospitalizacijos trukmė, operacijos ir limfonodektomijos apimtis, operacijos trukmė, operacinė kraujo netektis, naviko lokalizacija, jo dydis, naviko invazijos gylis, naviko diferenciacijos laipsnis, limfovaskulinė invazija, pašalintų ir metastatinių limfinių mazgų skaičius. Pooperacinės komplikacijos klasifikuotos remiantis Clavien-Dindo klasifikacija.

2.4 Priešoperacinis pacientų ištyrimas ir chirurginės procedūros

Iki operacijos/ESD visiems pacientams atlikta ezofagogastroduodenoskopija (EGDS) su naviko biopsija. Daugumai pacientų prieš ESD papildomai atlikta endoskopinė sonoskopija naviko invazijos gyliui patikslinti. Priešoperaciniam ligos stadijavimui atliktas krūtinės ląstos ir pilvo organų KT tyrimas.

ESD buvo atliekama bendrinėje intraveninėje nejautroje. Procedūra pradedama pažymint naviko ribas, kai į pogleivį suleidžiamas adrenalino ir metileno mėlio tirpalas. Tuomet cirkuliariai apipjaunama gleivinė ir atliekama pogleivio disekcija siekiant pašalinti naviką vienu bloku (*en bloc*). Pašalinus naviką atliekama hemostazė koaguliuojant arba naudojant hemoklipus. Rezekcija buvo laikoma pilnaverte (*angl. complete resection*) tais atvejais, kai navikas pašalintas vienu bloku (*en bloc),* o histologiškai patvirtinama, jog horizontalus ir vertikalus rezekcijos kraštai yra be naviko. Gydomąja rezekcija (*angl. curative resection)* laikyta tuomet, kai atlikta pilnavertė rezekcija (*complete resection),* o pašalintas navikas neviršijo standartinių ar išplėstinių indikacijų ER nurodomų Japonų Skrandžio Vėžio Gydymo Gairėse (16).

Tradicinio chirurginio gydymo apimtis – gastrektomija ar skrandžio rezekcija, buvo pasirenkama atižvelgiant į naviko lokalizaciją skrandyje. Skrandžio rezekcija buvo atliekama, kai buvo įmanoma užtikrinti pakankamą proksimalinį rezekcijos kraštą. Visais kitais atvejais buvo atliekama gastrektomija. Šalinant skrandį ar jo dalį su naviku kartu atliktos D2 apimties limfonodektomijos kaip nurodoma Japonų Skrandžio Vėžio Gydymo Gairėse (16). Kai kuriais atvejais operuojančio chirurgo sprendimu buvo atliekamos mažesnės apimties D1 limfonodektomijos. Visais atvejais atliktos R0 tipo (mikroskopiškai ir makroskopiškai nėra likutinio naviko) operacijos (33).

2.5 Histologinis naviko vertinimas

Patologinis preparato ištyrimas visais atvejais atliktas Valstybiniame patologijos centre, Vilniuje. Naviko histologinis tipas buvo klasifikuojamas pagal Pasaulio sveikatos organizacijos (PSO) ir Lauren klasifikacijas. Mėginiai buvo dažomi hematoksilinu ir eozinu bendram vertinimui. Makroskopiškai tirtas naviko dydis, vertinant didžiausią diametrą. Mikroskopiškai - invazijos gylis, limfovaskulinė invazija bei rezekcijos kraštai. Iš pašalintų chirurginių preparatų buvo išrenkami visi pašalinti limfiniai mazgai, jie paruošti pagal standartinį protokolą ir tirti gydytojo patologo mikroskpiškai, tokiu būdu nustaytos LMM (33).

2.6 Pacientų stebėsena

Sekant pacientus po ESD pirmaisiais metais esofagogastroduodenoskopija (EGDS) buvo atliekama po 3, 6 ir 12 mėn., vėliau kasmet viso penkerius metus. Po standartinių operacijų EGDS buvo atliekama kas 6 mėn. pirmuosius du metus, vėliau kasmet viso penkerius metus. Abiejų grupių pacientams kasmet buvo atliekamas krūtinės ląstos ir pilvo organų KT tyrimas. Jei pacientų stebėsena buvo atliekama kitose gydymo įstaigose nedalyvaujančiose tyrime, duomenys apie sekimo metu atliktų tyrimų rezultatus buvo renkami susisiekiant su pacientu ar jo šeimos gydytoju. Paskutiniai pacientų sekimo duomenys buvo surinkti 2017 m. gruodžio mėn. Du pacientai iš ESD grupės ir vienas iš chirurginės nebuvo sekti (33).

2.7 Statistinė analizė

Visi statistiniai skaičiavimai atlikti naudojantis SPSS 22.0 (SPSS, Čikaga, JAV) programa. Kiekybiniai kintamieji pateikiami kaip vidurkis su standartiniu nuokrypiu arba kaip mediana su interkvartiliu. Kategoriniai kintamieji nurodomi kaip proporcijos.

Siekiant palyginti artimus ir tolimus gydymo rezultatus po ESD ir tradicinio chirurginio gydymo buvo panaudotas panašiausių atvejų analizės metodas, įtraukiant šešis pagrindinius kintamuosius: amžių, fizinę būklę pagal Amerikos anesteziologų draugijos (ASA) klasifikaciją, naviko lokalizaciją ir invazijos gylį, diferenciacijos laipsnį ir limfovaskulinę invaziją. Suskaičiavus panašumo įvertį pacientai iš ESD grupės buvo suporuoti su artimiausią įvertį turinčiu pacientu iš chirurgijos grupės santykiu 1:1. Klinikiniai ir patologiniai rodikliai palyginti naudojant Chi-kvadrato testą, Fišerio testą bei t-testą. BI ir IBL vertinti Kaplano-Mejerio metodu bei palyginti naudojant Log-rank testą. Visuose skaičiavimuose p reikšmė < 0.05 buvo laikoma statistiškai reikšminga (33).

LMM rizikos veiksniai nustatyti naudojant vienpusį ANOVA testą, Chi-kvadrato testą, Fišerio testą ir dvipusį t-testą. Univariacinės analizės metu nustatyti reikšmingi rizikos veiksniai buvo įtraukti į multivariacinę logistinės regresijos analizę leidusią nustatyti nepriklausomus rizikos veiksnius (35).

Pooperacinės komplikacijos ir mirštamumas palygintos naudojant Chi-kvadrato testą, Fišerio testą, t-testą, vienpusės ANOVA testą bei neparametrinius testus (34).

3. REZULTATAI

3.1 ESD ir tradicinio chirurginio gydymo palyginimas gydant ASV

3.1.1 Pacientai, jų pagrindinės klinikinės ir patologinės savybės

Palyginus ESD ir chirurginio gydymo grupes iki taikant panašiausių atvejų analizės metodą, jos reikšmingai skyrėsi. Chirurginio gydymo grupėje pacientai buvo jaunesni, turėjo mažiau lydinčių susirgimų. Taip pat šioje grupėje reikšmingai didesnė dalis navikų pasižymėjo invazija į pogleivį, bloga diferenciacija, difuziniu tipu pagal Lauren, išopėjimu bei didesniu naviko dydžiu. ESD grupėje pacientai reikšmingai dažniau sirgo viršutinio skrandžio trečdalio navikais. Pritaikius panašiausių atvejų analizės metodą abi grupės tapo panašios. Vidutinis atvejų panašumo įvertis siekė 0.39±0.22 ir 0.34±0.18 atitinkamai ESD ir chirurgijos grupėje (p=0.290), tačiau net ir pritaikius šį statistinį metodą didesnio nei 2 cm diametro navikai reikšmingai dažniau pasitaikė chirurgijos grupėje (33).

3.1.2 Artimieji ASV gydymo rezultatai taikant tradicinį chirurginį gydymą ir ESD

Chirurgijos grupėje 10 (23.8 %) pacientų atlikta gastrektomija, 32 (76.2 %) pacientams - skrandžio rezekcija. Lyginant gydymo rezultatus tarp chirurgijos ir ESD grupių, nustatyta, kad reikšmingai skyrėsi operacijos trukmė ir hospitalizacijos laikas – jie buvo trumpesni ESD grupėje. Kiekvienoje grupėje 7 (16.7 %) iš 42 pacientų patyrė pooperacinių komplikacijų. ESD grupėje 2 (4.8 %) pacientams stebėtos infekcinės kilmės komplikacijos, 3 (7.1 %) pacientams pooperacinis kraujavimas ir 2 (4.8 %) pacientams skrandžio perforacija. Visais atvejais kraujavimas po ESD sustabdytas taikant endoskopines intervencijas. Abiem perforacijų atvejais reikėjo chirurginės intervencijos – vienu atveju atlikta laparaskopinė, kitu atviro tipo operacija.

Didžioji dalis komplikacijų po chirurginio gydymo buvo klasifikuojamos kaip nedidelės (4 iš 7 ≤II laipsnio pagal Clavien-Dindo klasifikaciją). Du (4.8 %) pacientai buvo operuoti pakartotinai dėl sterkoralinio ir tulžingo peritonito. Vienas pacientas (2.4 %) pooperaciniu periodu mirė dėl ūminio širdies ir kvėpavimo sistemų nepakankamumo.

Visiems pacientams chirurgijos grupėje buvo atlikta radikali (R0) operacija. ESD grupėje *en bloc* ir pilnavertė rezekcija atlikta atitinkamai 38

(92.7 %) ir 32 (78 %) atvejais. Tačiau po galutinio morfologinio ištyrimo tik 30 (71.4 %) atvejų buvo įvertinti kaip gydomoji rezekcija. Dvylika pacientų kuriems atlikta ne-gydomoji rezekcija (*angl. Non-curative resection*) toliau gydyti taip: keturiems pacientams taikytas tradicinis chirurginis gydymas, vienam - pakartotinė ESD, penki pacientai stebėti, vienas pacientas nestebėtas, nes iškrito iš sekimo, o vienam pacientui jį sekant nustatytos atokios metastazės ir tuomet skirtas paliatyvus gydymas (33).

3.1.3 Atokieji ASV gydymo rezultatai taikant tradicinį chirurginį gydymą ir ESD

Vidutinis pacientų stebėsenos laikas po ESD buvo 38±34 mėn., mediana – 28 (Q1:9-Q3:60) mėn., atitinkamai chirurgijos grupėje - 52±36 mėn. ir 42 (Q1:30-Q3:74) mėn. Lyginant atokiuosius gydymo rezultatus pastebėta, kad 5 metų IBL buvo reikšmingai didesnis chirurgijos grupėje - 97.6 % prieš 77.5 %, p=0.002. Į analizę traukiant tik tuos pacientus kuriems ESD metu atlikta gydomoji rezekcija reikšmingo skirtumo tarp grupių nebeliko - 5 metų IBL ESD grupėje siekė 89.7 %, o chirurgijos grupėje 97.6 %, p=0.099. 9 (21.4 %) pacientams ESD grupėje ir vienam (2.4 %) pacientui chirurgijos grupėje (p=0.014) stebėtas skrandžio vėžio ligos atkrytis. 8 (19.0 %) pacientams ESD grupėje ir vienam (2.4 %) pacientui chirurgijos grupėje stebėti lokalūs recidyvai, kurie sėkmingai gydyti pakartotina ESD ar įprasta operacija. Vienam (2.4 %) pacientui ESD grupėje nustatytos atokios metastazės ir karcinomatozė. 8 iš 10 pacientų ligos atkrytis stebėtas per pirmuosius 36 mėnesius nuo gydymo pradžios. ESD grupėje ligos atkrytis reikšmingai rečiau stebėtas tais atvejais kai atlikta gydomoji rezekcija - 10.3 % prieš 45.5 %, p=0.007. Ne-gydomoji rezekcija identifikuota kaip nepriklausomas rizikos veiksnys ligos atkryčiui (RS: 41.79; 95 % PI:7.21 – 242.17)

Nors IBL abiejose grupėse reikšmingai skyrėsi, BI rodiklis nesiskyrė. 5 metų BI chirurgijos ir ESD grupėse atitinkamai siekė 69.0 % ir 73.8 %, p=0.599. 5 metų BI išgyvenamumas reikšmingai nesiskyrė ir lyginant jį ESD grupėje po gydomųjų ir ne-gydomųjų rezekcijų (66.7 % vs. 76.7 %, p=0.581) (33).

3.2 Metastazės limfiniuose mazguose ASV atveju

3.2.1 LMM rizikos veiksniai ASV pacientams

Nustatant LMM rizikos veiksnius į analizę įtraukti 218 pacientų, kuriems atlikta tradicinė operacija kartu su limfonodektomija. Operuoti 117 (53.7 %) vyrų ir 101 (46.3 %) moteris, vidutinis pacientų amžius siekė 65.58±12.33 metus. Gastrektomija atlikta 38 pacientams, skrandžio rezekcija – 180 pacientų. Didžiajai daliai pacientų -195 (89.4 %) atlikta D2 limfonodektomija. Limfonodektomijų metu vidutiniškai pašalinti 19.89±9.69 limfmazgių. LMM nustatytos 43 (19.7 %) pacientams sergantiems ASV. Univariacine analize nustatyti LMM rizikos veiksniai: pogleivinė naviko invazija, limfovaskulinė invazija, bloga naviko diferenciacija, difuzinis arba mišrus naviko tipas pagal Lauren klasifikaciją bei naviko diametras viršijantis 2 cm. Amžius, lytis, naviko lokalizacija, išopėjimas ir žiedinių ląstelių komponentas neturėjo reikšmės LMM (35). Multivariacinė analizė parodė, kad naviko invazija į pogleivį, limfovaskulinė invazija ir bloga diferenciacija yra nepriklausomi LMM rizikos veiksniai (35).

3.2.2 LMM dažnis pacientų atitinkančių ar viršijančių standartines/išplėstines indikacijas endoskopiniam ASV gydymui grupėje

Iš 58 ASV atvejų, kurie atitiko išplėstines ESD indikacijas, bet buvo operuoti, 1 (1.7 %) pacientas turėjo metastazes 2-juose iš 22 pašalintų limfinių mazgų. Šiuo atveju navikas buvo intramukozinis, neišopėjęs, vidutiniškai diferencijuotas ir didesnis nei 2 cm diametro (2.2 cm x1.8 cm x1.5 cm). Iš 139 pacientų, kurie sirgo ASV viršijančiu išplėstines indikacijas ER, 42 (30.2 %) pacientams nustatytos LMM (36).

3.3 Tradicinio chirurginio gydymo rezultatai pacientų grupėje, kurie operuoti dėl ankstyvų stadijų skrandžio vėžio

3.3.1 Pacientai ir jų pagrindinės klinikinės ir patologinės savybės

267 iš 457 pacientų (58.4 %) operuotų dėl ankstyvų stadijų skrandžio vėžio (pT1-T2) buvo jaunesni nei 70 metų, 190 (41.6 %) pacientų – vyresni. Jaunesnių ir vyresnių pacientų grupės reikšmingai skyrėsi vertinant pacientų fizinę būklę (ASA balas), naviko histologinį tipą ir diferenciacijos laipsnį. Vyresnių pacientų grupėje didesnė dalis pacientų sirgo sunkiomis

gretutinėmis ligomis (ASA III-IV) (61.4 % vs. 31.7 %, p=0.001) ir žarninio tipo vėžiu pagal Lauren klasifikaciją (69.3 % vs. 45.8 %, p=0.001). Jaunesnių pacientų grupėje dažniau nustatytas blogai diferencijuotas vėžys (G3: 64.0 % vs. 42.6 %, p=0.001) (34).

3.3.2 Pooperacinės komplikacijos ir mirštamumas operuojant dėl ankstyvų stadijų skrandžio vėžio

Lyginant chirurginio gydymo rezultatus vyresnių ir jaunesnių pacientų grupėse bendras komplikacijų, sunkių komplikacijų (III-IV laipsnio pagal Clavien-Dindo klasifikaciją) ar chirurginių pooperacinių komplikacijų dažnis reikšmingai nesiskyrė. Vyresnių grupėje stebėtas didesnis nechirurginių komplikacijų dažnis (9.7 % vs. 16.3 %, p=0.035). Pooperacinės komplikacijos sąlygojančios pacientų mirtį stebėtos tik vyresnių grupėje. Intrahospitalinis pooperacinis mirštamumas jaunesnių ir vyresnių pacientų grupėse atitinkamai siekė 0 % ir 5.7 %, p=0.001. Dar didesni pooperacinio mirštamumo skirtumai stebėti, kai buvo palyginti 30 ir 90 dienų pooperacinio mirštamumo rodikliai. 90 dienų mirštamumas jaunesnių grupėje siekė 2.6 %, o vyresnių – 12.6 %, $p<0.05$ (34).

3.3.3 Pooperacinių komplikacijų rizikos veiksniai jaunesnių ir vyresnių pacientų operuojamų dėl ankstyvų stadijų skrandžio vėžio grupėse

Univariacinės analizės metu nustatyta, kad aukštas ASA (III/IV) įvertis, didesnė operacijos apimtis (gastrektomija) ir multi-organinė rezekcija yra veiksniai susiję su didesniu pooperacinių komplikacijų dažniu vyresnių pacientų grupėje. Multivariacinė analizė parodė, kad tik aukštas ASA įvertis (III/IV) yra nepriklausomas pooperacinių komplikacijų rizikos veiksnys (ŠS=6.47; 95 % PI 2.09-20.06, p=0.021).

Jaunesnių pacientų grupėje nė vienas iš analizuotų faktorių nebuvo statistiškai reikšmingai susijęs su bendru pooperacinių komplikacijų dažniu, tačiau naviko lokalizacija viršutiniame skrandžio trečdalyje buvo susijusi su dažnesnėmis sunkiomis pooperacinėmis komplikacijomis (≥3 laipsnio pagal Clavien-Dindo klasifikaciją) (14.9 % vs. 4.3 %, p=0.014) (34).

3.3.4 Pooperacinio mirštamumo rizikos veiksniai jaunesnių ir vyresnių pacientų operuojamų dėl ankstyvų stadijų skrandžio vėžio grupėse

Kadangi jaunesnių pacientų grupėje per pirmas 30 dienų po operacijos mirusių nebuvo, analizuoti tik 90 dienų mirštamumo veiksniai. Univariacinė analizė parodė, kad aukštas ASA (III/IV) įvertis ir naviko lokalizacija viršutiniame skrandžio trečdalyje yra susijusi su 90 dienų mirštamumu jaunesnių pacientų grupėje.

Vyresnių pacientų grupėje 90 dienų pooperacinis mirštamumas buvo susijęs su aukštu ASA (III/IV) įverčiu ir multiorganine rezekcija. Multivariacinė analizė parodė, kad tik sunkios komplikacijos (≥3 laipsnio pagal Clavien-Dindo klasifikaciją) patirtos hospitalizacijos metu yra nepriklausomas rizikos veiksnys devyniasdešimties dienų pooperaciniam mirštamumui (ŠS=12.82; 95 % PI 1.01-169.21, p=0.049) (34).

4. DISKUSIJA

Pagrindiniai mūsų studijos radiniai buvo tokie: 1) Lietuvos pacientus, sergančius ASV, galima gydyti taikant ESD, nes atokieji gydymo rezultatai yra panašūs į tradicinio chirurginio gydymo rezultatus, tačiau operacijos ir hospitalizacijos laikas yra trumpesni. Tai galioja tais atvejais, kai įmanoma atlikti gydomąją rezekciją; 2) Atlikus negydomąją rezekciją yra didelė ligos atkryčio tikimybė bei tikėtini prasti IBL rezultatai; 3) Naviko invazija į pogleivį, limfovaskulinė invazija ir bloga naviko diferenciacija yra LMM rizikos veiksniai Lietuvos pacientų sergančių ASV populiacijoje; 4) LMM yra nustatomos 1.7 % pacientų, kurie serga ASV atitinkančiu išplėstinius endoskopinio gydymo kriterijus; 5) Taikant tradicinį chirurginį gydymą dėl ankstyvų stadijų SV vyresnis amžius nėra susijęs su didesniu pooperacinių komplikacijų dažniu, tačiau yra susijęs su išaugusiu pooperaciniu mirštamumu. ASA fizinės būklės vertinimas yra naudingas, prognozuojant vyresnių pacientų chirurginio gydymo išeitis.

LMM yra pagrindinis veiksnys ribojantis endoskopinio gydymo galimybes pacientams sergantiems ASV. Todėl šiuolaikinė endoskopinė ASV gydymo koncepcija remiasi tiksliu tinkamų pacientų (be LMM) atrinkimu atsižvelgiant į klinikines ir patologines naviko savybes. Atlikus išsamią literatūros apžvalgą rasta 17 studijų nagrinėjančių rizikos veiksnius LMM sergant ASV. 6 iš jų atliktos Vakarų šalyse, 11 Azijos šalyse. Studijose iš Azijos LMM dažnis

sergant ASV siekia nuo 2.8 % iki 15.5 % kai navikas infiltruoja tik gleivinę (37,44) ir nuo 18.3 % iki 56.2 % kai infiltruoja ir pogleivį (35,37,41). Atitinkamai Vakarų šalyse LMM buvo randamos nuo 1.9 % iki 16.7 % atvejų navikui infiltruojant tik gleivinę ir nuo 18.2 % iki 42.9 % atvejų navikui siekiant ir pogleivį (35,49,50). Mūsų studijos rezultatai yra panašūs, LMM dažnis esant T1a navikams siekia 5.1 %, esant T1b navikams - 22.4 %.

Įvariose studijose nurodomi LMM rizikos veiksniai irgi skiriasi. Azijos šalių studijose dažniausiai minimas invazijos gylis (9 iš 11 studijų), naviko dydis (7 iš 11 studijų) ir limfovaskulinė invazija (7 iš 11 studijų). Vakarų šalių studijose limfovaskulinė invazija kaip rizikos veiksnys LMM minima 5 iš 6 studijų, tą patvirtino ir mūsų studija (35). Naviko invazija į pogleivį kuri nustatyta kaip rizikos veiksnys LMM mūsų studijoje, paminėta 3 iš 6 anksčiau publikuotų studijų. Naviko diferenciacijos laipsnis kaip rizikos veiksnys LMM minimas tik Azijos šalių studijose (44,46,47). Mūsų žiniomis, mūsų studija yra pirmoji Vakarų šalyse, patvirtinusi, kad naviko diferenciacija yra nepriklausomas LMM rizikos faktorius (35).

EGR ir ESD kaip ASV gydymo metodas vis plačiau taikomos ne tik Azijoje, bet ir Vakarų šalyse (53). Deja, tik nedidelė dalis pacientų, sergančių ASV, atitinka standartinius ESD gydymo kriterijus. Remiantis klinikiniais pastebėjimais, kad pernelyg griežtos standartinės indikacijos didina nebūtinų tradicinių operacijų skaičių, buvo pasiūlyti išplėstiniai kriterijai (36,53,54). Gotoda et al., išanalizavęs 5265 operuotų dėl ASV pacientų duomenis, nustatė 4 papildomus navikų tipus, kurie nesant limfovaskulinės invazijos, labai retai metastazuoja į limfinius mazgus (36,55,56). Šie kriterijai Japonų Skrandžio Vėžio Gydymo Gairėse yra apibrėžiami kaip išplėstiniai kriterijai: 1) diferencijuoto tipo intramukozinė adenokarcinoma be išopėjimo požymių, kurios diametras viršija 2 cm; 2) diferencijuoto tipo intramukozinė adenokarcinoma su išopėjimo požymiais, kurios diametras neviršija 3 cm; 3) nediferencijuoto tipo intramukozinė adenokarcinoma be išopėjimo požymių neviršijanti 2 cm diametro; 4) diferencijuoto tipo pogleivinė (SM1, <500 μm nuo *muscularis mucosae*) adenokarcinoma, iki 3 cm diametro (16).

Tinkamai atrinkus pacientus tinkančius endoskopiniam gydymui galima išvengti nebūtinų didelės apimties tradicinių operacijų. Tai leistų pagerinti ASV gydymo rezultatus ypač vyresnio amžiaus pacientų, sergančių gausia gretutine patologija (ASA III/IV), grupėje, kurią mūsų studija identifikavo kaip didesnės rizikos dėl ženklaus pooperacinio mirštamumo. Tačiau išplėstinių kriterijų ER naudojimas kasdieninėje praktijoje išlieka kontroversiškas, nes nepakanka įrodymų dėl ilgalaikių gydymo rezultatų

sekmės (36,57). Tokį nuogastavimą stiprina Jee et al. (58) publikuota studija, nurodanti, kad atlikus tradicinę operaciją su limfonodektomija pacientams sergantiems ASV, kuris atitinka išplėstines indikacijas ER, 2.8 % pacientų nustatomos LMM. Mūsų studija patvirtina tokius radinius, kuomet tokioje pat pacientų grupėje nustatytas LMM dažnis siekia 1.7 %. Įdomu tai, kad Jee et al. (58) nustatė LMM riziką trims iš keturių išplėstinių kriterijų, bet ne diferencijuoto tipo intramukozinei adenokarcinomai be išopėjimo požymių, kurios diametras viršija 2 cm. Todėl iki mūsų studijos ši indikacija laikyta visiškai saugia (58). Mūsų studijoje LMM rastos būtent tokio tipo ASV. Todėl apibendrindami mūsų radinius ir ankstesnių studijų duomenis galime teigti, jog navikai atitinkantys išplėstinius kriterijus visuomet neša metastazių limfiniuose mazguose riziką.

Nors taikant išplėstinius kriterijus LMM rizika ir yra, ji santykinai nedidelė. Ši rizika labai ženkliai išauga, jei yra viršijami išplėstiniai kriterijai. Mūsų studijos duomenimis LMM tuomet randamos iki 30.2 % pacientų (36), todėl tokiems pacientams neabejotinai turėtų būti taikomas tradicinis chirurginis gydymas.

Kai kurie autoriai diskutuoja, kad net ir ne-gydomoji ESD lemia patenkinamus ASV gydymo rezultatus. Hatta et al. (59) savo multicentrinėje studijoje palygino gydymo rezultatus tarp pacientų kurie po ne-gydomosios ESD tik stebėti bei tų, kurie iškart papildomai radikaliai operuoti. Radikaliai operuotų pacientų 3 ir 5 metų BI ir LSI buvo geresnis. Reikia pažymėti, kad LSI skirtumas buvo nedidelis (99.4 % vs. 98.7 %) lyginant su BI skirtumu (96.7 % ir 84.0 %). Nors ligos recidyvo dažnis tarp stebėtų ir iškart operuotų pacientų skyrėsi reikšmingai, tačiau abiejose grupėse jis buvo nedidelis - 1.3 % radikaliai operuotų pacientų grupėje ir 3.1 % stebėtų pacientų grupėje. Vis dėlto gerą LSI rodiklį ir mažą ligos recidyvų skaičių stebimų pacientų grupėje reikėtų vertinti kritiškai dėl tarp tyrimo grupes sudarančių pacientų klinikinių ir patologinių savybių skirtumų. Žinomi LMM rizikos veiksniai (limfovaskulinė invazija, gilesnė invazija į pogleivį) buvo reikšmingai dažniau sutinkami operuotų pacientų grupėje (35,59), todėl grupių nevienalytiškumas galėjo daryti įtaką studijos rezultatams. Suzuki et al. neseniai publikavo panašią studiją, kurioje nurodo, kad pacientai kurie radikaliai operuoti po ne-gydomosios ESD pasiekia geresnius gydymo rezultatus. Pritaikius panašiausių atvejų analizę išaiškėjo, jog operuotų pacientų 5 metų LSI ir BI yra reikšmingai geresni, bei atitinkamai siekia 99.0 % prieš 96.8 % ir 91.0 % prieš 75.5 % (19). Apibendrinant šių dviejų Azijos šalių tyrimų ir mūsų studijos rezultatus galime patvirtinti, kad pacientai, kurie

serga ASV viršijančiu išplėstinius ER kriterijus turi būti gydomi tradiciniu chirurginiu būdu iškart arba nedelsiant po to kai išaiškinama, kad atlikta negydomoji ESD, dėl didelės ligos atkryčio ar progresavimo tikimybės (33).

Vertindami ankstyvuosius gydymo rezultatus nustatėme, kad ESD turi pranašumą prieš chirurgiją dėl trumpesnės procedūros trukmės ir trumpesnės hospitalizacijos (33). Vidutinė ESD trukmė buvo 83 minutės ir šis rezultatas yra artimas laikui, skelbiamam didelėse Vakarų ir Rytų šalių studijose (61,62). Chiu et al. (17) studija iš Kinijos retrospektyviai tyrė 74 pacientus, kuriems atlikta ESD dėl aukšto laipsnio displazijos arba ASV bei lygino juos su 40 pacientų, kuriems atlikta tradicinė operacija. Kaip ir mes, šis autorius nurodo, jog ESD grupėje pačios operacijos ir hospitalizacijos trukmė yra trumpesnė. Priešingai nei Chiu et al. studijoje ar kitose panašiose apžvalgose (62), savo studijoje mes nenustatėme, kad ESD grupėje būtų mažiau pooperacinių komplikacijų. Abiejose grupėse pooperacinių komplikacijų dažnis buvo vienodas ir siekė 16.7 %. Pooperacinės komplikacijos buvo panašios ir vertinant jų sunkumą. Medikamentinio gydymo pakako atitinkamai 4/42 (9.5 %) ir 2/42 (4.8 %) pacientams iš chirurgijos ir ESD grupių. Endoskopinės intervencijos buvo reikalingos tik po ESD, kuomet 3 (7.1 %) pacientams atliktas kraujavimo stabdymas. Kraujavimų dažnis po ESD pateikiamas literatūroje yra panašus ir siekia 1.6 % - 7.0 % (61,63,64). 2 (4.8 %) pacientams iš kiekvienos mūsų tyrimo grupės išsivystė komplikacijos, kurių gydymui reikėjo chirurginės intervencijos. Chirurgijos grupėje abu pacientai buvo operuoti dėl peritonito, o ESD grupėje – dėl skrandžio perforacijos. Kitų autorių duomenimis perforacijų dažnis po ESD svyruoja nuo 2.2 % iki 9.7 % Rytų šalyse ir nuo 1.8 % iki 10 % Vakarų šalyse (61-63). Manome, kad skirtingai nuo Azijos studijų, mūsų studijoje bendro pooperacinių komplikacijų skirtumo po ESD ir chirurginio gydymo nebuvimą lėmė santykinai mažas pooperacinių komplikacijų dažnis po tradicinių operacijų ir santykinai didelis nesunkių komplikacijų skaičius (Clavien-Dindo≤2) po ESD (33).

Chirurgijos grupėje po pritaikyto panašiausių atvejų analizės metodo pooperacinis mirštamumas siekė 2.4 %. Ši grupė gerai atspindi visą dėl ASV operuojamų pacientų grupę, nes ankstesniuose darbuose nustatėme, kad mirštamumas po tradicinių chirurginių operacijų dėl ASV siekia 1.8 % (33,35). ESD grupėje mirusių pacientų nebuvo, tačiau reikia įvertinti tai, kad ši grupė buvo santykinai maža todėl galima egzistuojanti rizika neįvertinta. Įvairių autorių duomenimis pooperacinis mirštamumas po ESD gali siekti iki 3.3 % (33,65).

Visiems pacientams, operuotiems dėl ASV, buvo atliktos radikalios operacijos. Azijos šalių studijose pateikiamas radikalių operacijų dažnis yra toks pats – 100 % (33,62). Tačiau ESD grupėje, priešingai nei chirurgijos, *en bloc* rezekcija atlikta tik 38/42 (92.7 %), o pilnavertė rezekcija tik 32/42 (78.0 %) pacientų. Šie rezultatai yra panašūs į literatūroje sutinkamus rezultatus (33,61,63-66). Po pašalinto naviko morfologinio ištyrimo 2 (4.8 %) atvejais nustatyta, jog pašalintas ASV navikas viršija išplėstinius ER kriterijus ir tik 30/42 (71.4 %) ESD atvejų buvo klasifikuoti kaip gydomoji rezekcija. Mūsų tyrimas parodė, jog ne-gydomoji ESD yra rizikos veiksnys ligos atkryčiui. Manome, jog santykinai didelis ne-gydomųjų rezekcijų dažnis ESD grupėje lėmė tai, kad 5 metų IBL chirurgijos grupėje buvo reikšmingai geresnis (33). Priešingai nei mūsų studijoje, sisteminėje apžvalgoje iš Azijos šalių apimančioje 1331 pacientus toks skirtumas nenustatytas (62). Dėl to palyginome 5 metų IBL rezultatus chirurgijos ir ESD grupėje neįtraukdami į analizę pacientų, kuriems atlikta ne-gydomoji rezekcija. Kaip ir tikėtasi tokiu atveju reikšmingo skirtumo tarp grupių vertinant atokiuosius gydymo rezultatus nebeliko. Nors laikas iki ligos atkryčio statistiškai reikšmingai skyrėsi ir buvo ilgesnis chirurgijos grupėje, BI abiejose grupėse nesiskyrė. Netikėta, bet net ir ne-gydomoji ESD neturėjo įtakos bendram išgyvenamumui. Taip galėjo nutikti dėl kelių skirtingų priežasčių. Pirma, pacientų, kuriems atlikta ne-gydomoji ESD, grupė buvo nedidelė, o 5 iš 12 (41.6 %) šios grupės pacientų taikytas papildomas gydymas atliekant tradicinę operaciją jau per pirmus 6 mėn. po endoskopinio gydymo. Antra, 8 iš 9 pacientų, kuriems nustatytas ligos atkrytis, buvo operuoti arba jiems atlikta pakartotina ESD. Radikalus ligos atkryčio gydymas lėmė gerus gydymo rezultatus, todėl pirmasis nesėkmingas ESD epizodas neturėjo įtakos BI. Trečia, Pasaulinės sveikatos organizacijos 2015 metų duomenimis, tikėtina gyvenimo trukmė Lietuvoje siekė 73.6 metų, o vidutinis mūsų studijos pacientų amžius abiejose grupėse buvo 72 metai. Todėl galime manyti, kad BI sergančių ASV tarpe labiau lemia bendra sveikatos būklė ir natūralus populiacinis mirštamumas, o ne mirštamumas tiesiogiai įtakotas ASV (33).

5. TYRIMO APRIBOJIMAI

Mūsų studija turi keletą apribojimų, kuriuos būtina paminėti. Pirma, tai retrospektyvinis tyrimas, kuriame pacientai nebuvo randomizuoti į ESD ar chirurgijos grupes. Būtina pabrėžti, kad ESD ir tradicinis chirurginis gydymas niekada nebuvo palyginti prospektyvinėse randomizuotose kontrolinėse studijose, kurios yra laikomos auksiniu standartu lyginant gydymo metodus. Tam yra keletas priežasčių: skirtingo gydymo intervencijos apimtis ir sudėtingumas labai reikšmingai skiriasi, o ESD šiuo metu jau yra plačiai paplitusi ir taikoma kasdienėje praktikoje, taip pat egzistuoja nemažai kitais būdais sukauptų įrodymų apie šio metodo saugumą, todėl randomizuotos kontrolinės studijos pradėjimas šiuo metu keltų didelę etinę dilemą. Taip pat, nors LMM rizika sergant ASV atitinkančiu ER kriterijus egzistuoja, ji yra labai maža, todėl siekiant užtikrinti pakankamą randomizuoto kontrolinio tyrimo galią tektų įtraukti labai didelį pacientų kiekį ir tyrimo kaštai taptų nepakeliami (67). Tam, kad būtų galima sumažinti retrospektyviniams tyrimams lyginantiems du gydymo metodus būdingą pacientų atrankos klaidą mes taikėme panašiausių atvejų analizės metodą (angl. propensity score matching). Ši technika yra laikoma puikia alternatyva tokiais kaip šis atvejais, kai randomizuotas kontrolinis tyrimas yra neįmanomas ir dažnai taikoma chirurginiuose tyrimuose (67). Turime pripažinti, kad net ir naudojant šį statistinį metodą tarp ESD ir chirurgijos grupių išliko reikšmingas skirtumas, kai didesnio diametro navikai buvo dažnesni chirurgijos grupėje. Išliekantis skirtumas galėjo lemti prastesnius gydymo rezultatus chirurgijos grupėje. Antra, pacientų skaičius, kuriems atlikta ne-gydomoji ESD mūsų studijoje buvo nedidelis, todėl negalėjome palyginti rezultatų taikant papildomą chirurginį gydymą ar tik stebėseną po ne-gydomosios ESD. Trečia, bendra mūsų tyrimo imtis buvo santykinai maža, ypač lyginant su panašiomis studijomis, atliktomis Azijos šalyse. Kadangi ESD dėl ASV Vakarų šalyse atliekama rečiau, o bendras sergamumas ASV Vakaruose taip pat yra ženkliai mažesnis, šį trūkumą būtų galima įveikti tik atliekant didelės imties tarptautines, multicentrines studijas. Nepaisant visų čia išvardintų trūkumų, šioje studijoje mes sugebėjome parodyti ESD ir chirurginio gydymo skirtumus gydant pacientus sergančius ASV. Mūsų žiniomis, tai yra pirmoji pasaulyje studija lyginanti ASV gydymą chirurgija ar ESD vakarietiškoje populiacijoje (33).

6. IŠVADOS

- LMM nustatomos 19.7 % pacientų, sergančių ASV. Naviko invazija į pogleivį, limfovaskulinė invazija ir bloga naviko diferenciacija yra LMM rizikos veiksniai pacientams, sergantiems ASV Lietuvos populiacijoje.
- ESD gali būti puikia alternatyva chirurginiam ASV gydymui Lietuvos populiacijoje dėl trumpesnės operacijos ir hospitalizacijos trukmės bei adekvačių atokių gydymo rezultatų jei pavyksta pasiekti gydomąją rezekciją.
- Ne-gydomoji ESD yra susijusi su didele ligos atkryčio rizika bei nepatenkinamais atokiaisiais rezultatais, todėl po tokių ESD turėtų būti taikomas papildomas tradicinis chirurginis gydymas visais atvejais, kai su juo susijusi rizika yra priimtina.
- Išplėstinių indikacijų endoskopiniam ASV gydymui naudojimas Lietuvos populiacijoje nėra visiškai saugus dėl egzistuojančios nedidelės LMM rizikos. Jei išplėstinės indikacijos endoskopiniam ASV gydymui viršijamos LMM rizika yra didelė, todėl standartinis tokių pacientų gydymas turėtų susidėti iš rezekcinio tipo operacijos kartu atliekant pakankamą limfonodektomiją.
- Pooperacinių komplikacijų skaičius vyresnių ir jaunesnių pacientų grupėje operuojant dėl ankstyvų stadijų SV nesiskiria. Tačiau išsivysčius komplikacijoms vyresnių asmenų grupėje jie dažniau miršta. Aukštesnis ASA balas leidžia prognozuoti, kad vyresnis pacientas operuojamas dėl ankstyvų stadijų SV turi didesnę pooperacinių komplikacijų riziką. Šis rodiklis gali būti naudojamas vertinant su operacija susijusią riziką. Vyresnis amžius neturėtų sulaikyti nuo radikalaus chirurginio gydymo bent su mažesnės apimties limfonodektomija.

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11 LIST OF PUBLICATIONS

1. **Bausys R**, Bausys A, Vysniauskaite I, Maneikis K, Klimas D, Luksta M, Strupas K, Stratilatovas E. Risk factors for lymph node metastasis in early gastric cancer patients: Report from Eastern Europe country-Lithuania. BMC Surg. 2017 23;17(1):108.

2. **Bausys R**, Bausys A, Maneikis K, Belogorceva V, Stratilatovas E, Strupas K. Safety of expanded criteria for endoscopic resection of early gastric cancer in a Western cohort. BMC Surg. 2018 25;18(1):79.

3. **Bausys R**, Bausys A, Vysniauskaite I, Maneikis K, Stratilatovas E, Strupas K. Surgical treatment outcomes of patients with T1-T2 gastric cancer: does the age matter when excellent treatment results are expected? World J Surg Oncol. 2018 16;16(1):79.

4. **Bausys R**, Bausys A, Stanaitis J, Vysniauskaite I, Maneikis K, Bausys B, Stratilatovas E, Strupas K. Propensity score-matched comparison of short-term and long-term outcomes between endoscopic submucosal dissection and surgery for treatment of early gastric cancer in a Western setting. Surg Endosc. 2018 Dec 3; doi: 10.1007/s00464-018-06609-6

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Risk factors for lymph node metastasis in early gastric cancer patients: Report from Eastern Europe country- Lithuania

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Risk factors for lymph node metastasis in early gastric cancer patients: Report from Eastern Europe country– Lithuania

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Abstract

Background: Current risk factors for lymph node metastasis in early gastric cancer have been primarily determined in Asian countries; however their applicability to Western nations is under discussion. The aim of our study was to identify risk factors associated with lymph node metastasis in Western cohort patients from the Eastern European country - Lithuania.

Methods: A total of 218 patients who underwent open gastrectomy for early gastric cancer were included in this retrospective study. After histolopathological examination, risk factors for lymph node metastasis were evaluated. Overall survival was evaluated and factors associated with long-term outcomes were analyzed.

Results: Lymph node metastases were present in 19.7% of early gastric cancer cases. The rates were 5/99 (4.95%) for pT1a tumors and 38/119 (31.9%) for pT1b tumors. Submucosal tumor invasion, lymphovascular invasion, and high grade tumor differentiation were identified as independent risk factors for lymph node metastasis. Submucosal tumor invasion and lymphovascular invasion were also associated with worse 5-year survival results.

Conclusion: Our study established submucosal tumor invasion, lymphovascular invasion, and high grade tumor differentiation as risk factors for lymph node metastasis.

Keywords: Early gastric cancer, Lymph node metastasis, Risk factors, Mucosal tumor, T1a

Background

Gastric cancer is one of the leading causes of cancer death worldwide. It is believed that early detection and appropriate treatment can reduce mortality caused by gastric cancer. After the detection of cancer, preoperative disease staging must be performed to plan an ideal treatment for each individual patient. Next, the absence or presence of lymph node metastasis (LNM) must be confirmed to apply the treatment strategy. Lymph node status has great significance to the path of care chosen in early gastric cancer (EGC). It is not only important for proper treatment, but also for the prognosis of survival [1, 2]. Additionally, confirmation of LNM is crucial when an endoscopic approach is considered, because such a procedure does not cure the disease in lymph nodes. One obstacle in determining lymph node status has been the uncertainty of radiological tests. Staging of gastric cancer typically utilizes a variety of imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasounds and combined positron tomography, as well as, laparoscopic staging and cytogenetic analysis of peritoneal fluid in appropriate patients [3, 4]. The evaluation of metastatic infiltration of lymph nodes is mostly based on CT and MRI imaging. However, neither have the correct high sensitivity and specificity for the detection of LNM in gastric cancer [5, 6]. The lack of accurate radiological imaging calls for research of risk factors for LNM in EGC, which are used when endoscopic treatments of EGC are considered. According to the European Society for Medical Oncology (ESMO) guidelines, gastric

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adenocarcinomas staged as T1a, well-differentiated, less than 2 cm diameter and not ulcerated have very low or no risks for LNM. Those that fall under such standard criteria are eligible for endoscopic mucosal resection (EMR)/ endoscopic submucosal dissection (ESD) [7–10]. These guidelines are based on known risk factors for LNM, which have been determined in Asia. However, recently published data has revealed race as an independent risk factor for LNM, raising concern whether such risk factors can be considered in Western countries [11, 12].

The aim of our study was to integrate our experience of treating early gastric cancer with open gastrectomy to identify risk factors for LNM in EGC in Western populations.

Methods

This retrospective study included 218 patients who underwent surgical treatment for EGC in the Department of General and Abdominal Surgery and Oncology, National Cancer Institute, Vilnius, Lithuania between January 2005 and December 2015. In total, 1654 patients with gastric adenocarcinoma were operated on at the institution during the study period. 1436 (86,8%) patients underwent surgery for advanced gastric cancer and 218 (13,2%) for EGC.EGC was defined as a cancer that does not invade past the submucosa, irrespective of regional lymph node metastasis (T1 any N). None of the patients received neoadjuvant chemotherapy or radiotherapy prior to surgery. All patients had morphological gastric cancer verification before surgery, except in a few cases when it was not possible due to technical feasibility. Depending on cancer localization in the stomach and histological characteristics of the tumor, the type of surgery - total or subtotal gastrectomy- was determined before the operation. Reconstruction after a total gastrectomy was performed with esophagojejunostomy using a jejunal loop and Braun's side-to-side enteroanastomosis (m.Omega). Reconstruction after subtotal gastrectomy consisted of an antecolic end-to-side gastrojejunostomy with Braun's jejunojejunostomy (m.Balfur).The standard lymphanodectomy in our institution was a D2 lymph node dissection and was performed in accordance with the guidelines of the Japanese Research Society for Gastric Cancer. D1 lymphanodectomy was an alternative option based on the surgeon's individual decision. R0 resection was defined as no tumor remaining macroscopically and microscopically, and was achieved in all cases. Specimens' histological examination was performed in the National Center of Pathology, Vilnius, Lithuania. Standard histological examination protocol included entire lesion examination with 5 mm wide slices. All of the dissected lymph nodes were analyzed, each lymph node was embedded in paraffin, and at least two sections were prepared and visualized. Immunohistochemistry was performed using an anti-podoplanin antibody (D2–40) and CD34 antibody to identify and distinguish the lymphatic endothelium. The rate of LNM was calculated after histological evaluation. Various clinicopathological parameters such as gender, age, primary tumor invasion, tumor differentiation grade, lymphatic and vascular invasion, tumor type according to Lauren classification, ulceration, tumor size and localization were evaluated as possible risk factors for LNM. Analysis of postoperative morbidity and intra-hospital 30- and 90-day mortality rates were performed. Surgical complications were classified by Clavien-Dindo classification.

Outcomes of interest included the overall survival (OS) rates. OS was defined as the duration from the date of surgery to the date of death. Data on survival and death were obtained from Lithuania's Cancer register and Lithuania's death register. The date of the last follow up was 31 December 2016. 6 (2.7%) patients were lost during the follow-up period. Mean and median follow-up periods were 68 and 63 months (range from 0 to 142) respectively.

Statistical analysis

All statistical analyses were conducted using the statistical program SPSS 16.0 (SPSS, Chicago, IL, USA). Clinicopathological characteristics were analyzed by a 2-tailed t test, one-way ANOVA test, Chi-square test, or Fisher exact test. The risk factors found to be significant in univariate analysis were included in subsequent multivariate logistic regression analyses to identify the independent variables associated with lymph node metastasis in patients with gastric cancer. Overall survival was analyzed by the Kaplan–Meier method, and the curves drawn were compared by the log-rank test. Multivariate survival analysis was performed using the Cox proportional-hazards model (hazard ratio and 95% confidence intervals). In all statistical analyses, a p value of <0.05 was considered to be significant.

Results

From January 2005 to December 2015, 218 patients undergoing total or subtotal gastrectomy for EGC were included in this study. All of the patients were of Caucasoid race. Baseline characteristics of all patients are shown in Table 1.

There were 117 (53.7%) men and 101 (46.3%) women, with a mean age of 65.58 ± 12.33 years. Total gastrectomy was performed in 38 cases and subtotal gastrectomy in 180 cases. Forty-five of 220 patients had postoperative complications, with four of them lethal. Postoperative mortality and morbidity rates were 1.8 and

Table 1 Baseline characteristics of all patients

Variable		
Age (mean ± SD, range) (min.-max. Years)		65.58 ± 12.33 (27–88)
BMI (mean ± SD, range) (kg/m^2)		26.31 ± 5.41
Count of retrieved lymph nodes (mean ± SD, range) (min.-max.)		19.89 ± 9.69 (3–70)
Gender	Male	117 (53.7%)
	Female	101 (46.3%)
ASA score	I	23 (10.6%)
	II	105 (48.2%)
	III	87 (39.9%)
	IV	3 (1.4%)
Tumor localization	Lower third	79 (36.2%)
	Middle third	125 (57.3%)
	Upper third	14 (6.4%)
Tumor invasion	Mucosal	99 (45.4%)
	Sub-mucosal	119 (54.6%)
Lymph node status	Positive	43 (19.7%)
	Negative	175 (80.3%)
Tumor differentiation grade	G1	44 (20.2%)
	G2	70 (32.1%)
	G3	104 (47.7%)
Type of surgery	Total gastrectomy	38 (17.4%)
	Subtotal gastrectomy	180 (82.6%)
Type of lymphanodectomy	D1	23 (10.6%)
	D2	195 (89.4%)

20.6% respectively. The vast majority of complications (29 of 45, 64.4%) were not life threatening and did not require any surgical, endoscopic, or radiological interventions. According to Clavien-Dindo classification they were either grade I or II complications. Grade III complications occurred in 8 cases (3.6%), and reoperation was indicated for 5 (2.3%) patients. Complications requiring intensive care unit management (grade IV) were rare – 4 cases (1.8%). Four patients (1.8%) died during the intra-hospital period after postoperative complications had occurred. Causes of death for these patients were as follows. One patient had anastomotic leakage and peritonitis, while three patients died from non-surgical complications: pulmonary embolism – 1 case, pneumonia and sepsis - 1 case and acute cardiovascular insufficiency – 1 case. Mean hospitalization time was 17.34 ± 5.90 days and mean postoperative period was 13.00 ± 5.39 days. 30 day mortality rates were higher when compared to intra-hospital mortality rates and involved 6 (2,8%) cases. Three additional deaths were registered between the 31st and 90th postoperative day. 90 day postoperative mortality rates reached 4.1%. Higher 90 days mortality rates were associated with elderly age (≥75 years; 12.5% vs 1.2%, $p = 0.010$). Other factors such as gender, smoking status, obesity (BMI > 30), ASA score, extent of lymphanodectomy, type of surgery, and tumor localization did not impact mortality rate, $p > 0.05$.

Majority of the patients underwent a D2 lymphadenectomy – 195 (89.4%). The average number of removed lymph nodes was 19.89 ± 9.69. After performing histological examination of operative material, LNM were revealed in 43 (19.7%) cases. Factors associated with LNM were evaluated by univariate analysis. There was a significantly higher risk for LNM in tumors with submucosal layer infiltration (compared to mucosal infiltration, $p = 0.001$), lymphovascular invasion (LV+ vs LV-, $p = 0.001$), high grade differentiation (G3 vs G1&G2, $p = 0.047$), diffuse or mix type according to Lauren classification (compared to intestinal type, $p = 0.012$), and diameter exceeding 2 cm (compared to tumors ≤ 2 cm, $p = 0.026$). Age, gender, tumor localization, ulceration, and signet ring cell carcinoma had no significance in the presence of LNM (Table 2).

The multivariate analysis showed that submucosal tumor invasion, lymphovascular invasion, and high tumor differentiation grade were independent risk factors for lymph node metastasis (Table 3).

Survival analysis

5-year overall survival was 83.3% in patients without LNM and 54.2% in patients with LNM, $p = 0.001$ (Fig. 1). In the univariate analysis, LNM (p = 0.001), higher ASA classification (ASA III/IV p = 0.001), D1 lymphanodectomy ($p = 0.049$), and lymphovascular invasion (p = 0.001) had a negative effect on 5-year survival (Fig. 2). In multivariate analysis, lymphovascular invasion ($p = 0.028$; HR 2.19; 95% CI 1.08–4.42) and age ($p = 0.020$; HR 1.04; 95% CI 1.01–1.08) were discovered as independent factors with negative influences on the postoperative overall survival rate.

Discussion

The definition of EGC was established by the Japanese Gastroenterological Endoscopic Society in 1962, originally characterizing EGC as gastric cancer that invades no deeper than the submucosa regardless of lymph node metastasis. EGC is more commonly diagnosed in Asia compared with Western countries. In Japan, EGC comprises approximately 60% of all diagnosed gastric cancers, whereas in Western countries the incidence of EGC varies from 10% to 20%. Such differences could be explained by the presence of more screening programs in Asian countries and also by different interpretations of histological changes. Western pathologists consider

Table 2 Clinicopathological data of patients with EGC and univariate analysis of risk factors for lymph node metastasis

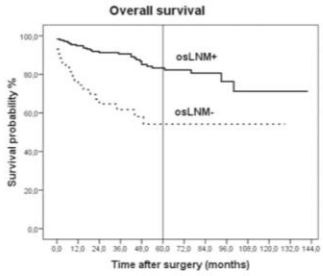
		LNM-	LNM+	p	Odds ratio (95% CI)
Gender	Male	99 (84.6%)	18 (15.4%)	$p = 0.090$	1.80 (0.92–3.55)
	Female	76 (75.2%)	25 (24.8%)		
Age		65.26 ± 12.17	66.91 ± 13.03	$p = 0.433$	–
Tumor localization	Lower 1/3	62 (78.5%)	17 (21.5%)	$p = 0.457$	–
	Middle1/3	100 (80.0%)	25 (20.0%)		
	Upper 1/3	13 (92.9%)	1 (7.1%)		
Tumor invasion	T1a	94 (94.9%)	5 (5.1%)	$p = 0.001$	8.82 (3.31–23.46)
	T1b	81 (68.1%)	38 (31.9%)		
Tumor differentiation	G1 & G2	100 (87.7%)	14 (12.3%)	$p = 0.006$	2.76 (1.36–8.57)
	G3	75 (72.1%)	29 (22.4%)		
Lymphovascular invasion	LV+	12 (40%)	18 (60%)	$p = 0.001$	9.78 (4.20–22.72)
	LV-	163 (86.7%)	25 (13.3%)		
Lauren classification	Diffuse & mix	59 (71.1%)	24 (28.9%)	$p = 0.012$	2.09 (1.20–3.64)
	Intestinal	106 (86.2%)	17 (13.8%)		
Tumor size	≤2 cm	91 (86.7%)	14 (13.3%)	$p = 0.026$	2.27 (1.12–4.59)
	>2 cm	83 (74.1%)	29 (25.9%)		
Ulceration	Ulcerated	58 (74.4%)	20 (25.6%)	$p = 0.114$	1.73 (0.88–3.42)
	Non-ulcerated	116 (83.5%	23 (16.5%)		
Signet ring cell	Yes	11 (73.3%)	4 (26.7%)	$p = 0.513$	1.46 (0.44–4.86)
	No	149 (80.1%)	37 (19.9%)		

invasion into the lamina propria of the mucosa mandatory characteristics for the diagnosis of carcinoma, whereas nuclear and structural features are more important in Japan. Therefore, EGC lesions diagnosed in Japan are potentially diagnosed as high grade dysplasia in Western countries. This distinction could partly explain the higher incidence of EGC in the Asian population and be responsible for better patient prognoses when compared to Western counterparts [11]. Several studies in Asian countries have declared excellent 5-year survival rates for EGC patients with overall survival exceeding 90%. Comparatively, our study presents worse results with the 5-year overall survival rate reaching only 77,6%. Since there is a disparity in histological interpretations and a difference in average life expectancy amongst distinct regions, it is difficult to compare data of several studies using the same statistical indicators [2, 13]. Disagreement between Asian and Western interpretations of pre-cancerous lesions and EGC could also influence results of studies analyzing risk factors and rate of LNM in EGC patients. During the last 5 years, 17 studies investigating factors associated with LNM in EGC were published. Eleven studies came from Asian countries and six from Western countries (Table 4).

Table 3 Multivariate analysis of risk factors for lymph node metastasis

Factor	p value	Odds Ratio (95% CI)
Submucosal tumor invasion (T1b)	$p = 0.001$	6.55 (2.28–18.81)
Tumor differentiation grade G3	$p = 0.045$	2.01 (1.03–14.66)
Lymphovascular invasion	$p = 0.001$	6.06 (2.28–16.07)
Tumor size >2 cm	$p = 0.155$	1.82 (0.79–4.19)
Diffuse type according to Lauren classification	$p = 0.693$	1.29 (0.35–4.69)

Rates of LNM reported in various Asian and Western countries were varying. In Asia LNM rates ranged from 2.8% to 15.5% for patients with tumors invading only the mucosal layer [14, 15] and from 18.3% to 56.2% for patients with tumors invading the submucosal layer [16, 17]. Respectively, in Western countries, rates of LNM varied from 1.9% to 16.7% when the tumor was localized to the mucosa and from 18.2% to 42.9% when the tumor invaded the submucosal layer [17, 18]. Our study results were similar; rates of LNM for patients with T1a and T1b cancer were 5.1 and 22.4%, respectively. Risk factors for LNM determined in various studies were also differing. In Asian studies, the most frequently mentioned factors were depth of invasion (9 of 11 studies), tumor size (7 of 11 studies), and lymphatic or lymphovascular invasion (7 of 11 studies). In Western studies, lymphovascular invasion has been of recent focus in five of six studies with our



Number at risk

LNM-	174	163	151	139	127	115
LNM+	42	31	19	7	0	0

Fig. 1 Five-year overall survival rate of patients with EGC according to lymph node status

results also confirming lymphovascular invasion as a risk factor for LNM. Another risk factor which was studied in our data, submucosal tumor invasion, was mentioned in 3 of 6 previously published Western studies. Tumor differentiation was only mentioned as a risk factor for LMN in reports from Asian nations [15, 17, 19]. To our best knowledge, our study is the first report of Western countries which confirms tumor differentiation as an independent risk factor for LNM. Despite the discussed variation between Asian and Western regions, the use of EMR/ESD as a treatment option for ECG is increasing in the West [8]. Western guidelines such as the National Comprehensive Cancer Network (NCCN) guidelines for gastric cancer treatment and ESMO clinical practice guidelines recommend the endoscopic approach as an appropriate option for some cases of intramucosal gastric cancer. Indications for endoscopic treatment reported by these guidelines are very similar but display several discrepancies. While both guidelines note that tumor diameter should not exceed 2 cm, only the NCCN guidelines indicate lymphovascular invasion as a required criteria. On the other hand, the ESMO guidelines are more strict on the limits for differentiation grade. They suggest that only well differentiated tumors should be treated endoscopically. NCCN guidelines are more liberal by indicating that both well and moderately-well differentiated tumors can be treated by the endoscopic approach. Additionally, ESMO guidelines limit indications with ulceration criteria and NCCN guidelines do not. In our cohort of patients, 30 (13.7%) of 218 patients would have met the criteria for endoscopical treatment according to NCCN guidelines. 1 (3.13%) of these 30 patients had histologically confirmed LNM. Fewer patients fit ESMO criteria (13 of 218 patients) and none of them had LNM. While LNM risk is low or equal to zero for patients who match standard endoscopical treatment criteria, implementation of expanded criteria in Western countries has been questioned. Furthermore, suspicions about different tumor behavior have increased after Ikoma et al. and Fukuhara et al. studies recently published that race is a risk factor for lymph node metastasis in gastric cancer [11, 12].

On the other hand, even non-curative endoscopic treatment could lead to satisfactory results. Hatta et al. recently published a large multi-center study, in which they evaluated and compared long term outcomes for patients who underwent non-curative endoscopic treatment of EGC followed by either radical surgery or only follow-up. The study revealed that patients who underwent radical surgery had significantly longer 3- and 5-year overall survival (OS) and disease-specific survival rates (DSS). However, the difference in DSS rates was rather small (99.4% vs. 98.7%) compared to the difference in OS rates (96.7% vs. 84.0%). Estimated rates of recurrence were significantly different, although both were low; 1.3% in the radical surgery group and 3.1% in the follow-up group. Nonetheless, positive results according to DSS and recurrence rates in the follow-up group should be interpreted carefully due to different clinicopathological backgrounds between the two groups. Some risk factors for LNM (lymphatic invasion or deeper submucosal invasion) were significantly more frequent in the radical surgery group [20]. Furthermore, Nakamura et al. provided a direct correlation between lymphatic infiltration and worse survival [21]. Up to this date, evidence of a correlation between lymphatic invasion and worse survival results have been demonstrated only by studies performed in Asia, with Western studies confirming these findings. Haist et al. analyzed lymphatic invasion and survival result correlation in a Western cohort, however they did not display a significant effect

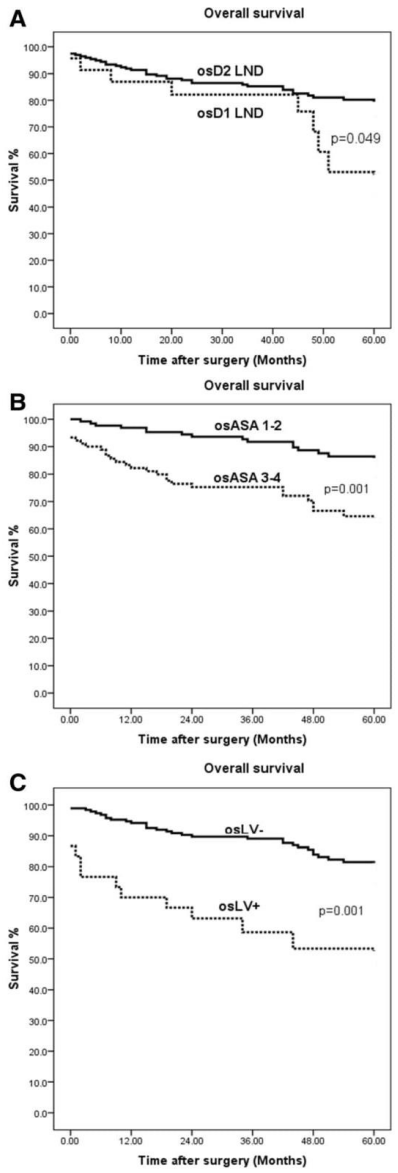


Fig. 2 Five-year overall survival rate of patients with EGC according to lymphanodectomy (**a**), ASA score (**b**) and lymphovascular invasion (**c**)

of lymphatic invasion on longtime survival results [22]. Consequently, our study became the first of such Western reports to present lymphovascular invasion as an independent prognostic factor associated with worse long-term survival results.

Several limitations of our study must be taken into consideration. First, it is a retrospective study originating from a single centre conducted over a long period of time. Second, surgical techniques used were not standardized. Even though the D2 lympahadenectomy remained institutionally standard over the entire study period and the number of examined lymph nodes was sufficient, the extent of resection and confirmation of lymph node removal was not clear in every case. Appropriate lymphadenectomy is important because the risk of lymph node metastasis could be underestimated in cases with incomplete lymphanodectomy. However, we believe that the quality of th obtained histological specimens was accurate and adequate, while the average number of removed lymph nodes was 19.89 ± 9.69. More than 15 lymph nodes were removed for 72% of the patients and only 9% of cases included less than ten dissected lymph nodes. Also, patients with insufficient lymphanodectomy were not excluded from our study to avoid discrepancies as we compared our study results to five other studies from Western countries, where patients with less than 15 examined lymph nodes were included [18, 20, 22–24]. Moreover if only patients with ≥15 resected LN would have been analyzed, the percentage of lymph node metastasis would not be much higher than in the whole series (T1a cancer - 5,1% vs 5,6%, T1b cancer 31,9% vs 36%). Therefore, the entire continuous series was used to avoid selection bias. Third, we were unable to use follow-up records, preventing us from estimating and evaluating recurrence rates, disease free survival and disease specific survival. Fourth, although our study was large enough when compared to other similar Western studies, the absolute number of patients with LNM was still relatively low. This reduces the statistical power of our analyses and the confidence of identifying correct risk factors for LNM.

Conclusion

In our study, LNM occurred in 19,7% of EGC cases. However, depending on varying criteria of several distinct guidelines, the rate of LNM meeting indications for an endoscopic resection was low or equal to zero. Additionally, this study identified submucosal tumor invasion, lympovascular invasion, and high grade tumor differentiation as risk factors for lymph node metastasis. Lymphatic invasion and submucosal tumor invasion were associated with worse 5-year overall survival results. Endoscopical treatment of EGC should be performed within the standard criteria. If risk factors for

Table 4 Lymph node metastasis in early gastric cancer – literature review and our results

Author	Country	Year	No. of patients	LNM+ in T1a cancer patients	LNM+ in T1b cancer patients	Risk factors for LNM
Studies from Asian countries						
Lim MS. et al. [14]	South Korea	2011	376	2.8%	18.4%	T1a: tumor size > 2 cm and lymphovascular invasion T1b: macroscopic type (elevated) and lymphovascular invasion
Ren G. el al. [25]	China	2013	202	9.0%	22.5%	Depth of invasion
Wang L. et al. [26]	China	2013	242	5.5%	20.0%	Depth of invasion, lymphovascular invasion.
Nakagawa M. et al. [27]	South Korea	2015	1042	Not available	Not available	Depth of invasion, tumor size, ulceration, age and positive nodal status by CT.
Wang Y. [16]	China	2015	198	6.0%	56.2%	Depth of invasion. Tumor size. Ulceration. histological type and venous invasion.
Park JH. et al. [28]	South Korea	2015	2270	2.8%	19.0%	Depth of invasion, tumor size >3 cm and lymphovascular invasion
Fang WL. et al. [29]	Taiwan	2015	391	4.9%	21.4%	T1a: Lauren's diffuse type and lymphatic invasion T1b: lymphatic invasion
Zhao LY. et al. [15]	China	2016	687	15.5%	35.9%	Depth of invasion. tumor size > 2 cm, ulceration, lymphovascular invasion, differentiation
Wang YW. et al. [30]	China	2016	230	8.5%	28.6%	Depth of invasion, tumor size ≥ 2 cm and P53 overexpression
Sekiguchi M. et al. [19]	Japan	2016	3131	4.2%	20.2%	Depth of invasion, tumor size ≥ 2 cm, ulceration, lymphovascular invasion, differentiation
Zheng Z. et al. [17]	China	2016	597	3.0%	18.3%	Depth of invasion, ulceration, lymphovascular invasion, age, differentiation.
Studies from Western countries						
Milhomem LM. et al. [31]	Brazil	2012	126	7.8%	22.6%	Depth of invasion, tumor size > 5 cm, ulceration and lymphatic invasion.
Bravo Neto GP. et al. [23]	Brazil	2014	26	16.7%	42.9%	Not available
Fukuhara S. et al. [10]	USA	2014	104	7.1%	35.4%	Lymphovascular invasion, non-Asian race and younger age.
Haist T. et al. [22]	Germany	2016	124	1.9%	22.5%	Depth of invasion, lymphovascular invasion.
Ahmad R. et al. [18]	USA	2016	67	4.3%	31.8%	Lymphovascular invasion and positive nodal status by endoscopic ultrasound.
Ronellenfitsch U. et al. [24]	Germany	2016	275	3.9%	18.2%	Depth of invasion, lymphovascular invasion, diffuse- and mixed-type according to Lauren.
Our study	Lithuania	2017	218	5.1%	31.9%	Depth of invasion, lymphovascular invasion and tumor differentiation grade
Indication for endoscopic treatment of EGC according to different guidelines						
ESMO-ESSO-ESTRO	Well-differentiated, lesion is ≤2 cm in diameter, confined to the mucosa and not ulcerated.					
NCCN	Well or moderately well differentiated, lesion is ≤2 cm in diameter, confined to the mucosa, does not exhibit lymphovascular invasion					

LNM are present in histological specimens, surgery with adequate lymphadenectomy should be followed. To successfully utilize the endoscopical approach in Western countries, criteria need to be expanded and applied to the appropriate population. For safe implementation, further research should be conducted by Western studies.

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The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions
RB and ES were guarantor of the integrity of the study. AB was responsible for literature research. DK, KM, IV and ML were responsible for data collection and statistical analysis. Manuscript was prepared by AB and IV, edited by RB and reviewed by ES and KS. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethics approval and consent to participate was given by institutional Bioethical committee.

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Safety of expanded criteria for endoscopic resection of early gastric cancer in a Western cohort

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Safety of expanded criteria for endoscopic resection of early gastric cancer in a Western cohort

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Abstract

Background: Endoscopic resection is widely accepted treatment option for early gastric cancer if tumors meet the standard or expanded indications. However, the safety of expanded criteria is still under investigation. Furthermore, discussion, if any additional treatment is necessary for patients who underwent endoscopic resection but exceeded expanded criteria, is rising. This study aimed to evaluate the safety of extended indications for endoscopic resection of early gastric cancer in a Western cohort. Also, we aimed to analyze the lymph node metastasis rate in tumors which exceeds the extended criteria.

Methods: Two hundred eighteen patients who underwent surgery for early gastric cancer at National Cancer Institute, Vilnius, Lithuania between 2005 and 2015 were identified from a prospective database. Lymph node status was examined in 197 patients who met or exceeded extended indications for endoscopic resection.

Results: Lymph node metastasis was detected in 1.7% of cancers who met extended indications and in 30.2% of cancers who exceeded expanded indications. Lymphovascular invasion and deeper tumor invasion is associated with lymph node metastasis in cancers exceeding expanded indications.

Conclusions: Expanded criteria for endoscopic resection of early gastric cancer in Western settings is not entirely safe because these tumors carry the risk of lymph node metastasis.

Keywords: Early gastric cancer, Endoscopic resection, Expanded indications, Safety, West

Background

Worldwide, the overall incidence of gastric cancer (GC) has steadily declined over the past 50 years, but in some regions (Asia, South America and Eastern Europe) it remained high [1, 2]. Furthermore, the incidence of early gastric cancer (EGC) in these areas is even rising [3]. According to the Japanese classification of gastric cancer, EGC is defined when tumor invasion is confined to the mucosa or submucosa, irrespective of the presence of lymph node metastasis (LNM) [4]. Surgery remains the only potentially curative treatment option for GC, but the extent of surgery for EGC and advanced GC may differ dramatically. Radical gastrectomy with regional lymphadenectomy remains the gold-standard for advanced GC, while endoscopic resection (ER) is sufficient procedure to treat EGC without LNM. According to studies from different regions, the rate of LNM in tumors confined to the mucosa varies between 2.7 and 6.5% and in submucosal tumors between 22.9 and 26.0%. There is a tendency, that rate of LNM in Western countries is higher compared to Asian countries [1]. Since radiological imaging accuracy for LNM detection is insufficient, indications for ER is based on histological tumor characteristics. The absolute indication for ER includes differentiated-type adenocarcinoma without ulcerative findings, of which the depth of invasion is clinically diagnosed as T1a, and the diameter is ≤2 cm [5]. However, only a small part of EGCs fulfill these criteria. The expansion of the standard criteria has been proposed in Japan from clinical observations that too

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strict indication leads to unnecessary surgery [6, 7]. From the dataset of 5265 patients who underwent gastrectomy for EGC Gotoda et al. identified four additional groups of tumors, which have very low possibility of LNM when they are not accompanied with lymphovascular infiltration [8, 9]. These criteria are described as expanded indications in Japanese Gastric Cancer guideline: 1) differentiated-type mucosal cancer without ulceration and greater than 2 cm in diameter; 2) differentiated-type mucosal cancer with ulceration and up to 3 cm in diameter; 3) undifferentiated-type mucosal cancer without ulceration and up to 2 cm in diameter and 4) differentiated-type submucosal cancer (SM1, < 500 μm from the muscularis mucosae) up to 3 cm in diameter [5] (Table 1).

However, extending the indications for endoscopic EGC treatment remains controversial because the long-term outcomes of these procedures have not been adequately documented [10].

Also, some authors reported LNM in tumors which fulfill extended criteria [3, 10, 11].

Indications for ER of EGC were established in the Asian population. These findings translation to the Western world may be controversial because two recently published studies identified non-Asian race as an independent risk factor for LNM [12, 13]. Furthermore, it is not clear if any additional treatment is necessary for patients who underwent ER, but histological examination showed that tumor exceeds expanded criteria.

Therefore, our study aimed to evaluate the safety of extended indications for ER of EGC in a Western population. Also, we analyzed the LNM rate in tumors which exceeds the extended criteria.

Methods

Regional ethical committee approval was given before study was conducted. Retrospective analysis of prospectively collected GC database was performed. Between January 2005 and December 2015, a total of 1564 patients underwent curative surgery for gastric cancer at the National Cancer Institute, Vilnius, Lithuania. From this cohort, 218 (13.9%) patients underwent open gastrectomy with a D1 or D2 lymph node dissection for early gastric cancer. They were initially enrolled in this study. The clinicopathological characteristics of these patients were reviewed, and 197 patients with tumors who met or exceeded the extended indications for ER were identified and included to further analysis.

Statistical analysis

All statistical analyses were conducted using the statistical program SPSS 22.0 (SPSS, Chicago, IL, USA). Clinicopathological characteristics were analyzed by the 2-tailed t-test, one-way ANOVA test, Chi-square test or Fisher exact test. Binary logistic regression was performed to identify independent risk factors for lymph node metastasis in the group of patients who exceed the extended indications for endoscopic early gastric cancer treatment. In all statistical analyses, a p-value of < 0.05 was considered to be significant.

Results

Table 2 shows the clinicopathological characteristics of the 218 patients with EGC. 99 (45.4%) patients were diagnosed with intramucosal cancers and 119 (54.6%) with submucosal cancers.

The rate of lymph node metastasis, the presence of lymphovascular invasion and rate of tumors with greater diameter were significantly higher in submucosal cancer group. 21 patients had tumors which met standard indications for ER and they were excluded from further analysis. 58 patients met and 139 patients exceeded the extended indications for endoscopic EGC treatment. Table 3 shows clinicopathological data of these two groups.

Groups were comparable only according to age, retrieved lymph node number, and male: female ratio.

Of 58 cancer who met extended criteria, one (1.7%) had lymph node metastasis in 2 of 22 retrieved lymph nodes. It was not ulcerated, moderately differentiated mucosal cancer with greater than 2 cm diameter (2.2 × 1.8 × 1.5 cm).

LNM was found in 42 (30.2%) of 139 tumors who exceeded the extended criteria. Submucosal tumor invasion (36.2% vs. 11.8%, $p = 0.009$) and presence of lymphovascular invasion (61.3% vs. 21.3%, $p = 0.001$) was revealed as risk factors for LNM at univariate analysis (Table 4).

Binary logistic regression confirmed univariate analysis findings and showed submucosal tumor invasion (OR = 5.57, 95% CI: 1.40–22.08, $p = 0.014$) and lymphovascular

Table 1 The standard and expanded indications for endoscopic resection of early gastric cancer

The absolute indication for endoscopic resection of EGC	The expanded indications for endoscopic resection of EGC
Differentiated-type mucosal adenocarcinoma without ulcerative findings and the diameter is ≤2 cm	1) Differentiated-type mucosal cancer without ulceration and greater than 2 cm in diameter 2) Differentiated-type mucosal cancer with ulceration and up to 3 cm in diameter 3) Undifferentiated-type mucosal cancer without ulceration and up to 2 cm in diameter 4) Differentiated-type submucosal cancer (SM1, < 500 μm from the muscularis mucosae) up to 3 cm in diameter

Table 2 Clinicopathological characteristics of patients with mucosal and submucosal early gastric cancer

	Mucosal tumor invasion ($n = 99$)	Submucosal tumor invasion ($n = 119$)	p value
Age (mean ± SD)	63.5 ± 12.9	67.3 ± 11.6	**0.024**
Gender			
Male	44 (44.4%)	73 (61.3%)	**0.014**
Female	55 (55.6%)	46 (38.7%)	
Histology			
Differentiated	53 (53.5%)	61 (51.3%)	0.786
Undifferentiated	46 (46.5%)	58 (48.7%)	
Lauren classification			
Intestinal	54 (58.7%)	69 (60.5%)	0.902
Mix	8 (8.7%)	11 (9.6%)	
Diffuse	30 (32.6%)	34 (29.8%)	
Lymphanodectomy			
D1	11 (11.1%)	12 (10.1%)	0.828
D2	88 (89.9%)	107 (89.9%)	
No. of retrieved lymph nodes (mean ± SD)	19.4 ± 8.3	20.3 ± 10.7	0.454
Lymph node metastasis			
LNM+	5 (5.1%)	38 (31.9%)	**0.001**
LNM-	94 (94.9%)	81 (68.1%)	
Ulceration			
UL+	30 (30.3%)	48 (40.3%)	0.156
UL-	69 (69.7%)	71 (59.7%)	
Lymphovascular invasion			
LV+	3 (3.0%)	28 (23.5%)	**0.001**
LV-	96 (97.0%)	97 (76.5%)	
Tumor size			
< 2 cm	55 (55.6%)	42 (35.3%)	**0.009**
2–3 cm	25 (25.2%)	40 (33.6%)	
> 3 cm	19 (19.2%)	37 (31.1%)	

All the values in bold shows significance

invasion (OR = 7.13, 95% CI: 2.46–20.64, p = 0.001) as independent prognostic factors for LNM.

Discussion

EGC treatment with traditional gastrectomy and lymphadenectomy leads to excellent oncological outcomes. Several studies reported 5-year overall survival rate of up to 99% [14, 15]. However, compared to ER, surgery has some disadvantages. It is more invasive treatment method, associated with higher costs and reduced quality of life [16].

Avoidance of unnecessary surgery for appropriately selected EGC patients would lead to treatment improvement. Ideal selection of candidates for ER or surgery would consist of reliable preoperative radiological imaging and identification of LNM before choosing an appropriate surgical method for the individual patient. Unfortunately, available methods are not sufficiently accurate. Currently used endoscopic ultrasonography and computed tomography can reach only 50–87% accuracy [3, 17]. Therefore, the indications for ER is based on LNM risk presumption based on a set of histological tumor characteristics. As mentioned in the introduction section, several reasons exist to consider if expanded indications are entirely safe, especially in the Western population. A study published by Jee et al. [3] confirmed this uncertainty when reported 2.8% LNM rate in a cohort of patients who underwent gastrectomy for ECG which met the extended indications for ER. Alike, data from our present study showed 1.7% LNM rate in the similar cohort.

Furthermore, Jee et al. [3] showed the risk of LNM in three of four expanded criteria, but not in differentiated-type mucosal cancer, without ulceration, greater than 2 cm in

Table 3 Clinicopathological characteristics of patients who met and exceeded extended indications for endoscopic early gastric cancer treatment

	Extended indications group ($n = 58$)	Exceeding extended indications group ($n = 139$)	p value
Age (mean ± SD)	65.7 ± 11.3	65.2 ± 12.7	0.438
Gender			
Male	34 (58.6%)	71 (51.1%)	0.352
Female	24 (41.4%)	68 (48.9%)	
Histology			
Differentiated	40 (70.2%)	52 (37.4%)	**0.001**
Undifferentiated	17 (29.8%)	87 (62.6%)	
No. of retrieved lymph nodes (mean ± SD)	20.7 ± 10.8	19.0 ± 7.1	0.212
Tumor invasion			
Mucosal	44 (75.5%)	34 (24.5%)	**0.001**
Submucosal	14 (24.1%)	105 (75.5%)	
Lymph node metastasis			
LNM+	1 (1.7%)	42 (30.2%)	**0.001**
LNM-	57 (98.3%)	97 (69.8%)	
Ulceration			
UL+	8 (13.8%)	70 (50.3%)	**0.001**
UL-	50 (86.2%)	69 (49.7%)	
Lymphovascular invasion			
LV+	0 (0%)	31 (22.3%)	**0.001**
LV-	58 (100%)	108 (77.7%)	
Tumor size			
< 2 cm	34 (58.6%)	41 (29.4%)	**0.001**
2–3 cm	16 (27.6%)	49 (35.3%)	
> 3 cm	8 (13.8%)	49 (35.3%)	

All the values in bold shows significance

diameter. Therefore, authors proposed to consider this indication as safe [3]. In contrast, our study showed that this criterion also carries the risk of LNM. Thus, our result together with previous Jee et al. [3] findings indicates that possibility of LNM exists in every extended criterion.

Two recent studies showed the non-Asian race as a risk factor for LNM in gastric cancer [12, 13]. Our study cohort was very homogenous according to race and ethnicity. All patients were a Caucasian race. Despite, we failed to show a higher rate of LNM in tumors who meet extended criteria compared to the rate reported from similar Asian study [3]. These unexpected findings, together with a fact, that GC incidence in Eastern Europe is significantly higher compared to the rest of Western world, perfectly illustrates heterogenicity of the disease between different regions and different populations. Therefore, multicenter studies with large sample sizes from different racial and ethnical populations are needed to understand the risk of nodal involvement in EGC better. Only new and high-quality evidence will let us establish accurate and reliable clinical practice guidelines for EGC management.

While LNM risk in patients who meets expanded indications for ER is relatively low, patients who exceed these criteria are at high risk. We founded LNM in 30.2% of tumors who exceeded the expanded criteria. Nowadays ER for those tumors is considered as a non-curative treatment. However, some authors discuss that even non-curative ER could lead to satisfactory clinical outcomes. A large multi-center study published by Hatta et al. [18] compared long-term outcomes of patients who underwent either additional radical surgery or only follow-up after non-curative endoscopic resection. Results of the study showed that patients who underwent additional radical surgery had better 3- and 5-year overall survival (OS) and disease-specific survival (DSS) rates. Obviously, it should be declared, that the difference in DSS rates was rather small (99.4% vs.

Table 4 Univariate analysis of risk factors for lymph node metastasis in patients who exceed extended indications for endoscopic early gastric cancer treatment

	LNM- ($n = 97$)	LNM+ ($n = 42$)	p value
Age (mean ± SD)	64.6 ± 12.6	66.4 ± 12.8	0.441
Gender			
Male	53 (54.6%)	18 (42.9%)	0.268
Female	44 (45.4%)	24 (57.1%)	
Histology			
Differentiated	39 (40.2%)	13 (31.0%)	0.344
Undifferentiated	58 (59.8%)	29 (69.0%)	
Lauren classification			
Intestinal	50 (51.6%)	18 (42.9%)	0.553
Mix	11 (11.3%)	7 (16.7%)	
Diffuse	36 (37.1%)	17 (40.4%)	
Tumor invasion			
Mucosal	30 (30.9%)	4 (9.5%)	**0.009**
Submucosal	67 (69.1%)	38 (90.5%)	
Ulceration			
UL+	50 (51.6%)	20 (47.6%)	0.670
UL-	47 (48.4%)	22 (52.4%)	
Lymphovascular invasion			
LV+	12 (12.4%)	19 (45.2%)	**0.001**
LV-	85 (87.6%)	23 (54.8%)	
Tumor size			
< 2 cm	30 (30.9%)	11 (26.2%)	0.319
2–3 cm	31 (32.0%)	19 (45.2%)	
> 3 cm	36 (37.1%)	12 (28.6%)	

All the values in bold shows significance

98.7%) compared to the difference in OS rates (96.7% vs. 84.0%). Also, the rates of recurrence were significantly different, although in both groups they were low - 1.3% and 3.1% in the radical surgery group and the follow-up group, respectively. However, good outcomes in the follow-up group according to DSS and recurrence rates should be treated carefully due to different background characteristics of the study groups. Some major risk factors for LNM (lymphatic invasion or deeper submucosal invasion) were significantly more frequent in the additional radical surgery group [18, 19], and these differences may influence the study results. Furthermore, Suzuki et al. [20] recently published results from the similar study and showed a clear superiority of additional surgery after non-curative ESD compared to follow-up. After propensity score matching analysis, they founded significantly higher rates of 5-year DSS rate (99.0% vs 96.8%) and 5-year OS (91.0% vs. 75.5%) in the additional surgery group [19]. Results of those two studies and a high rate of LNM revealed in our study indicate, that EGC which exceeds expanded criteria for ER should be treated with gastrectomy and appropriate lymphadenectomy.

Some limitations of the present study should be mentioned as well. First, 5 (8.6%) of 58 patients with EGC that met expanded indications for ER underwent D1 lymphadenectomy. Because of limited lymphadenectomy, the risk of LNM in this group could be underestimated. Second, our study sample size was small compared to reports from Asian countries. Only 58 patients were in a group of tumors who met extended criteria for ER. However, lack of reports from Western countries increases the scientific value of our paper. Furthermore, despite the small sample size we managed to reach our study goal and showed the risk of LNM in tumors who meet expanded indications for ER.

Conclusion

Implementation of expanded criteria for endoscopic resection of EGC in a Western setting is not entirely safe because cancers who meet these indications carry the risk of LNM.

EGC who exceeds expanded indications has a high risk of LNM, therefore gastrectomy with lymphadenectomy should remain a standard treatment option.

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Availability of data and materials
The data analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
RB, KS, ES and AB were responsible for study concept and design. KM, AB and VB were responsible for data collection and analysis. Manuscript was prepared by AB and KM. RB, VB, ES, KS were major contributors in writing, editing and revising the manuscript. All authors read and approved the final form of manuscript.

Ethics approval and consent to participate
Ethics approval was given by Vilnius Regional Biomedical Research Ethics Committee. This study was retrospective analysis with no direct contact with participants and data were collected anonymously, therefore a waiver of consent was given.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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III

Surgical treatment outcomes of patients with T1-T2 gastric cancer: does the age matter when excellent treatment results are expected?

Bausys R, Bausys A, Vysniauskaite I, Maneikis K, Stratilatovas E, Strupas K

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Surgical treatment outcomes of patients with T1-T2 gastric cancer: does the age matter when excellent treatment results are expected?

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Abstract

Background: The proportion of early gastric cancer stages is increasing, as is the incidence of gastric cancer among the elderly population. Therefore, this study was designed to analyze surgical treatment outcomes of T1-T2 gastric cancer in elderly patients.

Methods: A total of 457 patients with T1-T2 gastric cancer who underwent gastrectomy between 2005 and 2015 were enrolled in this retrospective study. Patients were classified into two groups according to age (< 70 years versus ≥ 70 years). Clinicopathological features, surgical treatment results, and clinical outcomes were compared between the groups.

Results: Higher ASA score (ASA 3/4), differentiated cancer, and intestinal-type tumors were more common in elderly patients. Postoperative complication rates were similar between the two groups; however, postoperative mortality rates were significantly higher in the elderly group. Higher ASA score was independently associated with postoperative complications in the elderly group. Furthermore, severe postoperative complications were found as an independent factor associated with higher 90-day mortality rate. Elderly patients had a significantly poorer 5-year overall survival rate. Two surgery-related factors—total gastrectomy and complicated postoperative course—were revealed as independent prognostic factors for poor overall survival in the elderly group.

Conclusions: Despite higher postoperative mortality rate and poorer overall survival results, elderly patients with gastric cancer should be considered for radical surgery. ASA score may be useful for predicting surgical treatment outcomes in elderly patients undergoing surgery for GC and hence assists clinicians in planning treatment strategies for each individual patient.

Keywords: Gastric cancer, T1, T2, Elderly patients, Early invasion

Background

Even though the incidence of gastric cancer (GC) has decreased over the past decades, it continues to be a major healthcare problem being the fourth most common malignancy and the second cause of death among all cancers [1]. Treatment strategy of gastric cancer has dramatically changed during the last decades mainly as a result of advances in chemotherapy. However, surgery remains the main and only curative treatment option for GC. Survival rates after curative surgery vary depending on several factors, but the stage of disease and the quality of surgery are the two most important predictors [2]. Best results of surgical GC treatment are achieved when patients undergo surgery while the tumor has only limited invasion. Reports from Asian and Western countries show excellent overall survival (OS) results of patients who underwent surgery for early gastric cancer (pT1) with a 5-year OS rate up to 99% [3–6]. Results for patients with pT2 gastric cancer were also high with a 5-year OS reaching

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up to 66% [7]. Despite these advancements, such favorable outcomes will be difficult to maintain in the increasing aging population. The increasing lifetime expectancy and improved treatment of age-related chronic diseases have led to a greater number of older patients suffering from GC, who can be potentially cured by surgical resection. While surgery is standard in patients with a stable clinical condition, the indication for operations in elderly patients, especially in those with comorbidities, remains unclear [8–10]. Therefore, identification of factors affecting short-term and long-term surgical treatment outcomes in elderly is essential for treatment personalization and optimization. This is especially significant for a cohort of patients in which excellent outcomes can be expected. Moreover, because early GC stages are relatively rare in the West, only limited data are available to guide treatment decisions for such a population.

The aim of our study was to analyze the differences in surgical treatment outcomes between elderly and non-elderly patients with early invasion (pT1-T2) gastric cancer.

Methods

Patients selection

A total of 1654 patients diagnosed with gastric adenocarcinoma underwent surgery at the National Cancer Institute, Vilnius, Lithuania, between 2005 and 2015. One thousand one hundred ninety-seven patients who received gastrectomy for pT3-4 gastric cancer or received neoadjuvant chemotherapy prior to surgery were excluded from the study. The remaining 457 patients who underwent gastrectomy for pT1-2 gastric cancer were included into the final analysis.

Surgery

Surgical procedures were performed as described in our previous report [3]. Based on tumor location, a total or distal gastrectomy with regional lymph node dissection (D1 or D2) was performed. In all cases, gastrectomy was performed via an open approach. D1 dissection included perigastric lymph nodes as well as the greater and lesser omenta. D2 dissection included the nodes from the D1 dissection plus those along the celiac axis, common hepatic artery, splenic artery and hilum, and the root of the left gastric artery. Resection was considered R0 when microscopically negative resection margin was achieved without macroscopic or microscopic remaining in primary tumor bed. In most cases (119 of 124), reconstruction after a total gastrectomy was performed with esophagojejunostomy using a jejunal loop and side-to-side entero anastomosis (m.Omega). The most common (240 of 320 cases) method of reconstruction after subtotal gastrectomy consisted of an antecolic end-to-side gastrojejunostomy with side-to-side entero anastomosis (m.Balfur) [3]. For the purpose of this study, all patients were divided into elderly (E; ≥ 70 years) and non-elderly (NE; < 70 years) groups according to the age at the time of surgery. Postoperative chemotherapy was recommended to all patients with pT1N+ or pT2N0/N+ gastric cancer.

Personal characteristics and clinical data

All patient characteristics were obtained from their medical records and prospectively collected database. Tumor stage was coded according to the TNM system as described in the Union Internationale Contre le Cancer/American Joint Committee on Cancer 7th edition. Demographic characteristics included age and sex. Clinicopathological characteristics included smoking status, body mass index (BMI), comorbidities, American Society of Anesthesiology (ASA) score, hospitalization and intensive care unit (ICU) time, type of surgery and lymphanodectomy, length of surgery, blood loss, tumor location, tumor size, differentiation, depth of invasion, lymphovascular invasion, and retrieved and metastatic lymph node count. Postoperative morbidity and mortality were evaluated. All postoperative complications were graded according to Clavien-Dindo classification.

OS analysis was performed. OS was defined as time from surgery to death. Data of survival and date of death were collected from Lithuania's Cancer register and Lithuania's death register [3]. The last follow-up was performed on the 31st of December 2016. Two (0.44%) patients were lost during the follow-up period. Mean and median follow-up periods were 52 and 45 months (range from 0 to 142) respectively.

Statistical analysis

Statistical package SPSS 16.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Groups were compared by a two-tailed t test, one-way ANOVA test, chi-square test, Fisher exact test, or non-parametric tests. All potential risk factors for postoperative mortality and morbidity were included in subsequent multivariate logistic regression analyses. Independent variables associated with postoperative morbidity and mortality were identified. OS analysis was performed by the Kaplan-Meier method. Survival curves were compared by the log-rank test. Multivariate survival analysis was performed using the Cox proportional hazards model (hazard ratio and 95% confidence intervals). In all statistical analyses, a p value of < 0.05 was considered to be significant.

Results

Clinicopathological characteristic of gastric cancer in NE and E groups

At the time of surgery, 267/457 (58.4%) patients were younger than 70 years. One hundred ninety (41.6%) patients were 70 or older. Table 1 summarizes the clinicopathological findings of the two study groups.

Table 1 Comparison of patient characteristics

		Group NE (< 70 years)		Group E (≥ 70 years)		*p* value
		n	%	*n*	%	
Sex	Male	150	56.2	111	58.4	0.701
	Female	117	43.8	79	41.6	
Age		58.18 ± 8.86		76.43 ± 4.35		0.001
BMI		26.2 ± 5.72		25.9 ± 4.90		0.700
ASA score	1–2	177	68.3	71	38.6	0.001
	3–4	82	31.7	113	61.4	
Tumor localization (third)	Upper 1/3	51	19.1	26	16.8	0.147
	Middle 1/3	119	44.6	80	42.1	
	Lower 1/3	97	36.3	84	44.2	
Gastrectomy	Total	83	31.1	47	24.7	0.143
	Subtotal	184	68.9	143	75.3	
Lymphanodectomy	D1	13	5.0	18	9.8	0.059
	D2	246	95.0	165	90.2	
Multivisceral surgery	Yes	19	7.3	15	8.2	0.721
	No	241	92.7	168	91.8	
Tumor invasion	T1a	64	24.0	35	18.4	0.217
	T1b	63	23.6	56	29.5	
	T2	140	52.4	99	52.1	
Lymph node metastasis	Yes	101	37.8	74	38,9	0.845
	No	166	62.2	116	61,1	
N categories	N0	166	62.2	116	61.1	0.778
	N1	65	24.3	49	25.8	
	N2	19	7.1	17	8.9	
	N3	17	6.3	8	4.3	
Distant metastasis	Yes	5	1.9	3	1.6	0.999
	No	262	98.1	187	98.4	
Lauren classification	Diffuse	112	42.3	17	21.8	0.001
	Mix	31	11.7	6	8.9	
	Intestinal	121	45.8	63	69.3	
Tumor differentiation grade	G1	27	10.1	25	13.2	0.001
	G2	69	25.8	84	44.2	
	G3	171	64.0	81	42.6	
Tumor size	< 2 cm	88	34.2	56	30.6	0.471
	≥ 2 cm	169	65.8	127	69.4	

Significant differences were found between the groups in terms of physical status (ASA score), histological type of tumor, and tumor differentiation grade. Significantly larger proportion of elderly patients had severe systemic diseases (ASA 3–4) (61.4 vs. 31.7%, $p = 0.001$) and intestinal type tumors according to Lauren classification (69.3 vs. 45.8%, $p = 0.001$). Poorly differentiated tumors were more common in the NE group (G3: 64.0 vs. 42.6%, $p = 0.001$).

Postoperative morbidity and mortality

The short-term surgical outcomes are shown in Table 2. There was no significant difference in the rate of total, severe (3rd or 4th grade according to Clavien-Dindo classification), or surgical postoperative complications between the two groups, but the rate of medical complications was significantly higher in the E group (9.7 vs. 16.3%, $p = 0.035$). Furthermore, fatal complications which led to postoperative deaths were observed only in elderly

Table 2 Short-term surgical outcomes of NE and E patients who underwent gastrectomy for pT1-T2 gastric cancer

Factors		Group NE (< 70 years)	Group E (≥ 70 years)	*p* value
Operation time: min (mean ± SD; min-max)		146.9 ± 41.58	143.72 ± 44.53	0.432
Blood loss: ml (mean ± SD; min-max)		171.82 ± 137.11	169.50 ± 136.50	0.879
ICU stay: days (mean ± SD; min-max)		1.24 ± 1.24	2.23 ± 6.30	0.014
Postoperative hospital stay: days (mean ± SD; min-max)		13.07 ± 5.86	14.05 ± 8.24	0.145
Dissected lymph nodes (mean ± SD)		22.18 ± 10.28	19.50 ± 9.43	0.005
Curability	R0	259 (97.0%)	182 (95.8%)	0.484
	R1,2	8 (3.0%)	8 (4.2%)	
Postoperative complications: *n* (%)		55/267 (20.5%)	51/190 (26.8%)	0.144
Surgical complications		29/267 (10.8%)	20/190 (10.5%)	0.909
Anastomotic leakage		2/267 (0.7%)	5/190 (2.6%)	0.133
Postoperative bleeding		6/267 (2.2%)	4/190 (2.1%)	0.999
Peritonitis/ intraabdominal abscess		5/267 (1.8%)	3/190 (1.5%)	0.999
Ileus		3/267 (1.1%)	0/190 (0.0%)	0.269
Incisional surgical site infection and (or) eventration		5/267 (1.8%)	4/190 (2.1%)	0.999
Postoperative pancreatitis		5/267 (1.8%)	2/190 (1.0%)	0.704
Pancreatic/biliary/enterocutaneuos fistula		3/267 (1.1%)	2/190 (1.0%)	0.999
Medical complications		26/267 (9.7%)	31/190 (16.3%)	0.043
Cardiac insufficiency		0/267 (0.0%)	3/190 (1.5%)	0.071
Pneumonia		11/267 (4.1%)	4/190 (2.1%)	0.292
Sepsis		0/267 (0.0%)	3/190 (1.5%)	0.071
PATE		0/267 (0.0%)	2/190 (1.0%)	0.172
Other		15/267 (5.6%)	19/190 (10.0%)	0.102
Clavien-Dindo	1–2	39 (14.6%)	30 (15.8%)	0.195
	3–4	16 (6.0%)	10 (5.3%)	
Postoperative mortality: *n* (%)		0 (0.0%)	11 (5.7%)	0.001

patients, and the mortality rate was significantly higher in this group (0 vs. 5.7%, $p = 0.001$). Even higher differences were observed when 30- and 90-day mortality rates were compared. First deaths in NE group were observed between 30th and 90th postoperative days with the 90-day mortality rate reaching 2.6%. During the same time period, mortality rate in the E group increased from 7.4 to 12.6% and remained significantly higher when compared to the NE group.

Risk factors for postoperative complications in NE and E groups

At univariate analysis, ASA III/IV ($p = 0.006$), total gastrectomy ($p = 0.022$), and multivisceral surgery ($p = 0.031$) were identified as factors that were associated with postoperative complications in the E group (Table 3). At multivariate analysis, only ASA III/IV was independently associated with postoperative complications (OR = 6.47; 95% CI 2.09–20.06, $p = 0.021$).

In the NE group, none of the analyzed factors were significantly associated with total number of postoperative complications, but tumor localization in the upper third was associated with severe postoperative complications (≥ 3 grade according to Clavien-Dindo), 14.9 vs. 4.3%, $p = 0.014$.

Risk factors for postoperative mortality in NE and E groups

While there were no deaths in the NE group during first 30 postoperative days, factors associated with 90-day mortality rate were analyzed. At univariate analysis, ASA 3/4 ($p = 0.034$) and tumor localization in the upper third ($p = 0.013$) were associated with 90-day mortality in the NE group.

In the E group, univariate analysis revealed ASA 3/4 ($p = 0.038$) and multivisceral surgery ($p = 0.017$) as factors associated with death during the first 90 postoperative days. With multivariate analysis, only severe complications during hospitalization were found as independent factors associated with higher 90-day mortality rate (OR = 12.82; 95% CI 1.01–169.21, $p = 0.049$).

Table 3 Univariate analysis of risk factors for postoperative complications in NE and E groups

		Group NE (< 70 years)	%	*p* value	Group E (≥ 70 years)	%	*p* value
Sex	Male	30/150	20.8	0.879	30/111	27.0	0.999
	Female	25/117	21.4		21/79	26.6	
BMI	< 30	30/130	23.1	0.999	9/30	30.0	0.814
	≥ 30	11/47	23.4		24/91	26.4	
ASA score	1–2	33/177	18.6	0.144	11/71	15.5	0.006
	3–4	22/82	26.8		39/113	34.5	
Gastrectomy	Total	22/83	26.5	0.141	19/47	40.4	0.022
	Subtotal	33/184	17.9		32/143	22.4	
Tumor localization (third)	Upper 1/3	15/51	29.4	0.077	11/26	42.3	0.157
	Middle 1/3	24/119	20.2		19/80	23.8	
	Lower 1/3	16/97	16.5		21/84	25.0	
Multivisceral surgery	Yes	2/19	10.5	0.381	8/15	53.3	0.031
	No	53/241	22.0		42/168	25.0	
Lympha-nodectomy	D1	5/13	38.5	0.157	5/18	27.8	0.999
	D2	50/246	20.3		46/165	27.9	
Retrieved lymph nodes (LN)	≤ 15 LN	16/52	30.8	0.058	17/61	27.9	0.860
	> 15 LN	39/211	18.5		33/127	26.0	

Furthermore, we found the higher rate of postoperative complications after surgery for upper third tumors in the entire study cohort (Fig. 1a). Analysis of specific complications showed that surgery for upper third cancer leads to higher rate of anastomotic insufficiency (upper third 5/77 (6.4%) vs. middle or lower third 2/380 (0.5%), $p = 0.001$). However, we did not found a significant difference in postoperative complications rate after surgery for upper third tumors between the NE and E groups (Fig. 1b).

Survival analysis

Five-year OS rate after surgical treatment of pT1/2 gastric cancer reached 60.8% in our study cohort. Non-elderly patients had significantly higher OS rate, 67.8 vs. 51.1%, $p = 0.001$ (Fig. 2).

Kaplan-Meier analysis revealed total gastrectomy, multivisceral surgery, T2 tumor invasion, lymph node and distant metastasis, lymphovascular invasion, and tumor size ≥ 2 cm to have a negative effect upon OS in both study groups (Table 4). In the multivariate analysis, male gender, lower BMI, deeper tumor invasion, and diffuse tumor type were found to be independent prognostic factors of OS results in the NE group. However, none of these factors showed a significant impact in the E group. Only total gastrectomy and postoperative complications were independent prognostic factors in this subgroup of patients.

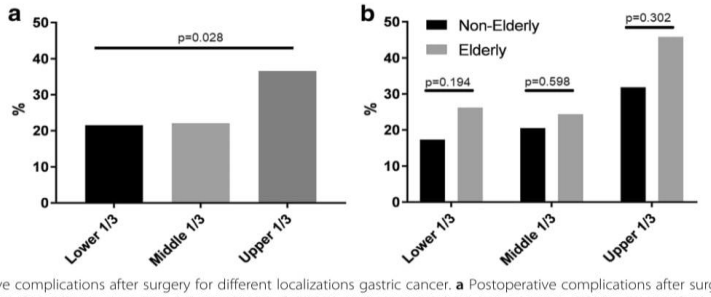

Fig. 1 Postoperative complications after surgery for different localizations gastric cancer. **a** Postoperative complications after surgery for different localization cancer in the entire study cohort. **b** Comparison of postoperative complications between non-elderly and elderly groups according to tumor localization

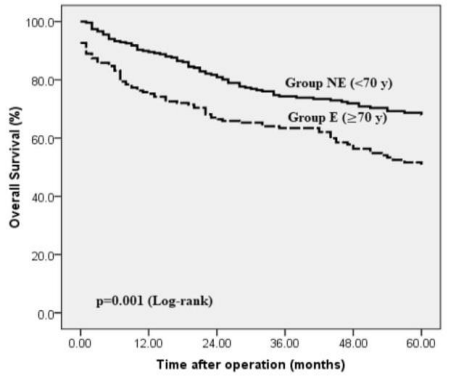

Fig. 2 Overall survival after surgery for T1-T2 gastric cancer in elderly and non-elderly groups. Non-elderly (NE) patients have significantly higher 5-year overall survival rate after surgery for T1/T2 gastric cancer

Discussion

With the population in Europe and Lithuania aging, the proportion of patients with gastric cancer who are elderly at the time of diagnosis is increasing [11]. Naturally, the definition of elderly patients varies in different studies with cutoff values ranging from 65 to 70 years to 75 or even 80 years [11–13]. However, average lifetime expectancy in Lithuania is lower compared to most developed Western or Asian countries. According to WHO report, the average lifetime expectancy in Lithuania in 2015 was 73.6 years. Therefore, we used 70 years as the threshold. With this selection, the elderly group amounted to 41.6% of the total cohort in this study.

Several aspects should be discussed with respect to the clinicopathological differences between the groups of our study. We found two distinct histological features. First, the intestinal type of tumor was more often found in the E group. These results support previously published data [14–17]. Higher frequency of intestinal gastric cancer with increasing age has been explained by studies, which showed intestinal GC development in areas of the stomach where intestinal metaplasia occurs. With chronic atrophic gastritis, a gradual change from normal mucosa to intestinal-type mucosa takes many years to develop. The process peaks in elderly age contributing to an increased risk of intestinal gastric cancer [18, 19]. The second difference that we noted was that the incidence of differentiated cancer (well or moderately differentiated adenocarcinoma) was significantly higher in the E group. Higher incidence of differentiated tumors supports the hypothesis that gastric cancer in an elderly age develops first as a differentiated type of tumor and only later, probably due to long-lasting chronic gastritis, these tumors progress to an undifferentiated one. Both of these unique findings emphasize the major role of chronic gastritis in the GC development and progression in elderly individuals.

There was no significant difference in the overall and surgical postoperative complication rate between the NE and E groups. These results oppose studies published in the early 2000s, where age was shown to be a major predictor of postoperative complications or mortality [20, 21]. Instead, it supports results of more recent studies, demonstrating that advances in surgical and anesthesiological techniques have reduced surgical complications and consequently improved short-term surgical outcomes in elderly patients [22, 23]. One of the differences between gastric cancer surgeries between the different age groups is lymph node dissection, which is usually limited in the elderly. Although the rate of D1 or insufficient (≤ 15 lymph nodes) lymphanodectomy was not significantly higher in the E group, we did find a significant difference when the average number of retrieved lymph nodes was compared between the groups (22.18 vs. 19.50, $p = 0.005$). However, in contrast to most Western and Japanese reports [24–26], we failed to show the association between limited lymphanodectomy and lower postoperative morbidity or mortality. Perhaps, this discrepancy can be explained by the retrospective design of our study and the fact that limited lymphanodectomies were performed for patients with a high morbidity risk.

Other well-known surgical risk factors for postoperative morbidity are the extent of gastric resection (total or subtotal) and multivisceral resection [20, 25, 26]. Our results confirmed the association between these two factors and higher postoperative complication rates in the E group. Generally, according to the principles of surgical oncology, subtotal gastrectomy may be carried out if an adequate proximal margin can be achieved. However, the requirements for proximal margin vary between different guidelines. Our study cohort included only patients with early invasion (pT1-T2) GC in which the recommended proximal margin is 5–8 cm according to the European Society for Medical Oncology guidelines. On the other hand, the Japanese gastric cancer treatment guidelines indicate only 3–5 cm in cases of T2 tumors and 2 cm in cases of T1 tumors. In our opinion, less radical resection margins are preferred to avoid a total gastrectomy, especially for patients with high risk of postoperative complications.

Even though the rate of total complications was comparable between the study groups, we found significantly higher number of medical complications in the E group. Furthermore, 5.7% of elderly patients died after postoperative complications occurred, while there were no deaths in the NE group. Hayashi et al. reported similar results [27], in which elderly patients with complicated

Table 4 Factors affecting overall survival in NE and E patient groups. Kaplan-Meier (univariate) and Cox regression (multivariate) analysis

		Group NE (< 70 years)			Group E (≥ 70 years)		
		Univariate analysis		Multivariate analysis	Univariate analysis		Multivariate analysis
		5-year OS (%)	*p* value	HR (95% CI); *p* value	5-year OS (%)	*p* value	HR (95% CI); *p* value
Sex	Male	66.0	0.263	5.24 (1.26–21.79); 0.023	46.8	0.094	0.64 (0.16–2.50); 0.528
	Female	70.1			57.0		
BMI	< 30	65.5	0.202	7.75 (1.37–43.72); 0.020	61.5	0.678	3.71 (0.69–19.69); 0.124
	≥ 30	73.9			56.7		
ASA score	1–2	70.6	0.190	2.01 (0.59–6.80); 0.261	59.2	0.052	1.88 (0.53–6.70); 0.326
	3–4	64.6			46.0		
Lymphano-dectomy	D1	76.9	0.745	1.21 (0.74–1.86); 0.981	38.9	0.172	3.93 (0.37–40.80); 0.251
	D2	68.7			53.3		
Retrieved lymph nodes	≤ 15	73.1	0.310	1.15 (0.24–5.44); 0.854	45.9	0.443	2.89 (0.60–13.93); 0.186
	> 15	67.3			53.5		
Gastrectomy	Total	49.4	0.001	2.32 (0.59–9.14); 0.227	34.0	0.012	10.14 (2.15–47.77); 0.003
	Subtotal	76.1			56.6		
Multivisceral surgery	Yes	47.4	0.006	1.93 (0.38–9.78); 0.425	53.6	0.019	22.83 (0.39–132.69); 0.131
	No	70.5			33.3		
Postoperative complications	Yes	72.7	0.425	1.57 (0.38–6.43); 0.525	21.6	0.001	3.94 (1.05–14.82); 0.042
	No	66.5			61.9		
Tumor invasion	T1a	89.1	0.001	5.81 (1.14–29.69); 0.034	65.7	0.010	4.29 (0.39–46.19); 0.229
	T1b	85.7			62.5		
	T2	50.0			39.4		
Lymph node metastasis	LNM+	80.7	0.001	2.02 (0.66–6.18); 0.215	36.5	0.001	0.54 (0.09–3.32); 0.512
	LNM-	46.5			60.3		
Distant metastasis	M1	0.0	0.001	4.30 (0.31–58.14); 0.271	51.9	0.001	2.20 (0.09–53.74); 0.628
	M0	69.1			0.0		
Tumor localization (third)	Upper	49.0	0.001	2.02 (0.36–11.21); 0.419	34.6	0.298	1.04 (0.29–3.74); 0.947
	Middle	71.4			55.0		
	Lower	73.2			52.4		
Lauren classification (type)	Diffuse	60.7	0.086	9.72 (1.73–54.53); 0.010	59.0	0.147	4.82 (0.99–17.41); 0.929
	Mix	64.5			68.8		
	Intestinal	74.4			44.4		
Tumor differentiation grade	G1	81.5	0.037	2.21 (0.29–16.93); 0.443	68.0	0.074	3.78 (1.03–24.39); 0.910
	G2	76.8			42.9		
	G3	62.0			54.3		
Ulceration	UL+	67.1	0.901	1.51 (0.55–4.15); 0.415	56.5	0.583	2.37 (0.66–8.51); 0.184
	UL-	69.6			50.7		
Lymphovascular invasion	LV+	45.8	0.001	2.00 (0.61–6.51); 0.250	42.9	0.005	2.50 (0.53–11.72); 0.245
	LV-	79.1			60.9		
Signet ring cell carcinoma	SRC+	67.7	0.601	2.49 (0.64–9.65); 0.186	71.4	0.354	3.92 (0.12–11.99); 0.433
	SRC-	60.6			50.9		
Tumor size	< 2 cm	84.1	0.001	1.27 (0.37–4.31); 0.693	66.1	0.010	4.09 (0.80–20.95); 0.091
	≥ 2 cm	61.5			45.7		

postoperative courses after the gastrectomy had higher mortality rates. Consequentially, elderly patients should receive special attention if postoperative complications occur. Precise surgical risk assessment prior to surgery is crucial when an optimal treatment strategy is being determined for individual patients. As expected, the number of patients with an ASA score of 3 or 4 was significantly higher in the E group (31.7 vs. 61.4%). In contrast to other reports [24, 28–30], we found that higher ASA score is an independent risk factor for postoperative complications in the E group. Moreover, we correlated a higher ASA score to an increase in 90-day mortality rates in the NE group. Therefore, evaluating the physical status of patients using the ASA classification is a reliable tool in predicting the short-term outcomes in both the E and NE groups.

In determining the appropriate treatment for each individual, patient prognosis should also be considered before turning to surgery. Many studies have specifically compared the long term-outcome of GC in elderly patients with non-elderly. Most of these have confirmed that the prognosis for elderly patients was poorer [19, 31, 32]. Our results are consistent with such reports as we found a significantly higher 5-year overall survival rate in the NE group. Additionally, after performing a multivariate Cox regression analysis, we determined different prognostic factors for poor OS results in the two groups. These results indicate different pathways of poor long-term outcomes in non-elderly and elderly patients. In the NE group, two subgroups of determinants were significant. First, patient characteristics—male gender and lower BMI—were correlated to a poorer prognosis. Male gender and worse prognosis were previously shown by Sato et al. [33] and were most likely linked to a shorter lifetime expectancy in the male population. Lower BMI has been known to be associated with specific respiratory postoperative complications and respiratory causes of death, complicating survival rates [11]. The second subgroup corresponds to tumor-related factors, specifically deeper tumor invasion and diffuse tumor type. Similarly, Ikoma and colleagues [7] have published data in which T2 invasion was found to be an independent risk factor for shorter survival. Deeper invasion of the tumor was associated with more advanced disease and to its link of significantly higher rates of lymph node metastasis. Histological tumor type according to Lauren classification also influences OS results. Series of reports have shown that diffuse-type cancer has a worse prognosis [34, 35] as was confirmed by our results.

Contrary to the predictive factors determined in the NE group, we failed to find any patient or tumor-related links to poor OS results in the E group. Although total gastrectomy and postoperative complications were two independent risk factors of decreased OS in the E group, both of them were related to the surgery itself. We hypothesize that with a total gastrectomy, poor OS results are due to the prolonged duration of surgery and more extensive intraabdominal manipulations, which can result in higher risks of postoperative complications and deaths in early postoperative period. Furthermore, Mantovani et al. [36] suggested that prolonged inflammatory responses could promote the proliferation and survival of cancer cells. Based on this report, the association of poor long-term outcomes and postoperative complications can be explained by the idea that residual cancer cells stimulated by inflammatory responses, caused by postoperative complications, result in proliferation and metastasis of cancer cells. Additionally, postoperative complications are associated with adjuvant chemotherapy omission and treatment delays resulting in postpone of residual cancer treatment. Therefore, postoperative complication prevention may play a major role in improving not only short-term but also long-term results in elderly patients with GC.

Conclusion

Elderly patients with early invasion of GC have a similar risk of postoperative complications as the non-elderly population. However, they should receive special attention in cases of complicated postoperative courses because mortality rates in the elderly are significantly higher.

Our study suggests that the ASA score may be useful in predicting postoperative complications in elderly patients undergoing surgery for GC. It offers clinicians another tool in optimizing treatment strategies. Finally, our results suggest that radical surgery with at least limited lymph node dissection should be considered, even for elderly patients.

Availability of data and materials

The data analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RB, KS, and ES were the guarantor of the integrity of the study. AB and IV were responsible for literature research. KM and AB were responsible for the data collection and statistical analysis. The manuscript was prepared by AB and IV, edited by RB, and reviewed by ES and KS. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval and consent to participate was given by the institutional review board in National Cancer Institute, Vilnius, Lithuania.

Competing interests

The authors declare that they have no competing interests.

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IV

Propensity score-matched comparison of short-term and long-term outcomes between endoscopic submucosal dissection and surgery for treatment of early gastric cancer in a Western setting

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Propensity score-matched comparison of short-term and long-term outcomes between endoscopic submucosal dissection and surgery for treatment of early gastric cancer in a Western setting

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Abstract

Background Endoscopic submucosal dissection (ESD) is a standard treatment option for early gastric cancer (EGC) in Asia; however, data about ESD efficacy in Western populations are limited. Furthermore, outcomes of EGC treatment after ESD or surgery have not been compared in Western cohorts. This study aimed to compare short-term and long-term results of ESD and surgery for EGC.

Methods This retrospective case–control study included patients with EGC treated in two largest cancer centers in Eastern Lithuania between 2005 and 2016. Propensity score nearest-neighbor 1:1 matching, based on clinicopathologic characteristics, was performed between patients who underwent ESD and surgery. The primary endpoint of the study was 5-year disease-free survival (DFS).

Results Of 260 eligible patients, 42 (16.1%) underwent ESD. After matching, two well-balanced groups consisting of 42 patients in each were analyzed. The operation time (83 vs. 151 min., $p=0.001$) and postoperative hospitalization stay (5.4 vs. 13.4 days, $p=0.001$) was significantly shorter in the ESD group. 5-year DFS rate was significantly higher in the surgery group (97.6% vs. 77.5%, $p=0.002$). However, this difference was reduced after exclusion of non-curative ESD cases (97.6% vs. 89.7%, $p=0.099$). There was no significant difference in 5-year OS rate between the study groups (73.8% vs. 69.0%, $p=0.599$).

Conclusions ESD might be an excellent alternative to surgery for EGC if curative resection is achieved. Non-curative ESD is associated with poor DFS and high rate of recurrence. Additional surgery should be recommended after non-curative ESD whenever treatment-associated risk is acceptable.

Keywords Early gastric cancer · Endoscopic submucosal dissection · Surgery · West

Early gastric cancer (EGC) is defined as gastric cancer in which tumor invasion is limited to the mucosa or submucosa, irrespective of the presence of lymph node metastasis (LNM). The LNM is a strong negative predictor of patients' prognosis. Therefore, gastrectomy with lymph node dissection has historically been the gold standard treatment for resectable gastric cancer [1, 2]. Surgery for EGC has shown excellent long-term outcomes, with 5-year overall survival exceeding 90% [3, 4]. However, radical surgery is associated with postoperative morbidity, mortality, and impaired quality of life [5–7]. Instead, local endoscopic resection (ER), including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), has been suggested as an alternative treatment option for EGC associated with negligible risk of LNM. Nowadays, the endoscopic approach is accepted and is considered as a standard treatment option

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for EGC meeting indications set by the Japanese gastric cancer treatment guidelines [8]. Many recent studies have compared ER with radical surgery for EGC treatment and have shown similar short-term and long-term outcomes [9–16]. However, all of these studies were conducted in Asian populations where the incidence of gastric cancer, including EGC, is higher than in the West. Additionally, the Western population is characterized by a higher BMI, older age, higher prevalence of proximal tumors and diffuse-type cancer [17]. Hence, while ESD is a widely accepted treatment of EGC in the East, its application and pertinency to Western cohorts is unclear. Furthermore, two recently published studies have suggested non-Asian race as a risk factor for LNM [18, 19]. Thus, the efficacy of ESD compared to surgical treatment of EGC in Western countries is an important issue to investigate.

While randomized controlled trials are the gold standard for comparing treatment outcomes, it is not always feasible to construct such studies due to lack of resources or ethical concerns. Propensity score matching analysis has been used to reduce selection bias in longitudinal observational studies and has been considered to mimic randomized controlled trials in which the effects of treatments are approximately randomized [20]. Therefore, to ensure suitable randomization in the evaluation of short and long-term outcomes in EGC patients who underwent ESD or surgery, we applied propensity score matching to equate the baseline clinicopathological characteristics of both studied groups.

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.

Study design and patients

We reviewed data from 2 prospectively collected databases in two cancer care centers in Eastern Lithuania. ESD program for EGC treatment was implemented in Vilnius University hospital Santaros Clinics at 2006 and patients who underwent ESD for EGC between January 2006 and December 2016 were included in this study. Another center—National Cancer Institute did not have ESD program and all patients with gastric cancer underwent surgery. Since 2016, a significant number of patients who are candidates for ESD are sent to ESD centers. Therefore, to maintain a 10-year study period, patients who underwent surgery for EGC between January 2005 and December 2015 at the National Cancer Institute were included. Choice of treatment center was made by personal patients' decisions. All patients were Caucasian. The exclusion criteria were (1) multiple or synchronous EGC and (2) history of gastric cancer treatment including neo-adjuvant chemotherapy. A flowchart of patient enrollment is demonstrated in Fig. 1. After exclusion of patients who met at least one exclusion criteria, 260 patients were included in the study and were divided into two groups according to the treatment method (surgery vs. ESD). Among these patients, propensity score matching analysis was performed to reduce the selection bias and to compare clinical outcomes between these groups. Forty-two patients in each group were matched by propensity score. The primary endpoint of the study was 5-year disease-free survival (DFS) rate. The secondary endpoints included 5-year overall survival (OS) rate, postoperative complication rate, operation time, and postoperative hospitalization time. OS was estimated from the date of surgery until death. DFS was defined as survival from the date of surgery to local, regional, or distant recurrence. Postoperative complications were defined as any deviations from a normal postoperative course during the hospitalization time. The severity of postoperative morbidity was classified according to Clavien–Dindo classification.

Preoperative evaluation and surgical procedures

Esophagogastroduodenoscopy with biopsy sampling was performed in all patients before surgery or ESD. Standard staging of the disease consisted of chest and abdomen CT scan. Additionally, endoscopic ultrasound was performed before ESD for more accurate evaluation of tumor invasion.

ESD was performed under general intravenous anesthesia. The standard ESD procedure at our institution begins with marking the lesion margins and injecting a saline solution containing epinephrine and methylene blue into the submucosal layer. A circumferential incision is made into the mucosa, and the submucosal layer is dissected. After specimen removal, endoscopic hemostasis is performed with hemoclips or hot biopsy forceps whenever bleeding or an exposed vessel is observed. An en bloc resection is defined as a single-piece resection. Histologically, complete resection included en bloc resection with microscopically negative horizontal and vertical margins. Curative resection was considered as proposed by Japanese gastric cancer treatment guidelines (histologically complete resection of a lesion not exceeding the expanded criteria for curative resection) [8].

The extent of gastrectomy depended on cancer localization in the stomach. In all cases patients underwent open surgery. Subtotal gastrectomy was performed whenever a sufficient proximal resection margin could be ensured; in other cases, total gastrectomy was performed. The standard lymphadenectomy was a D2 lymph node dissection

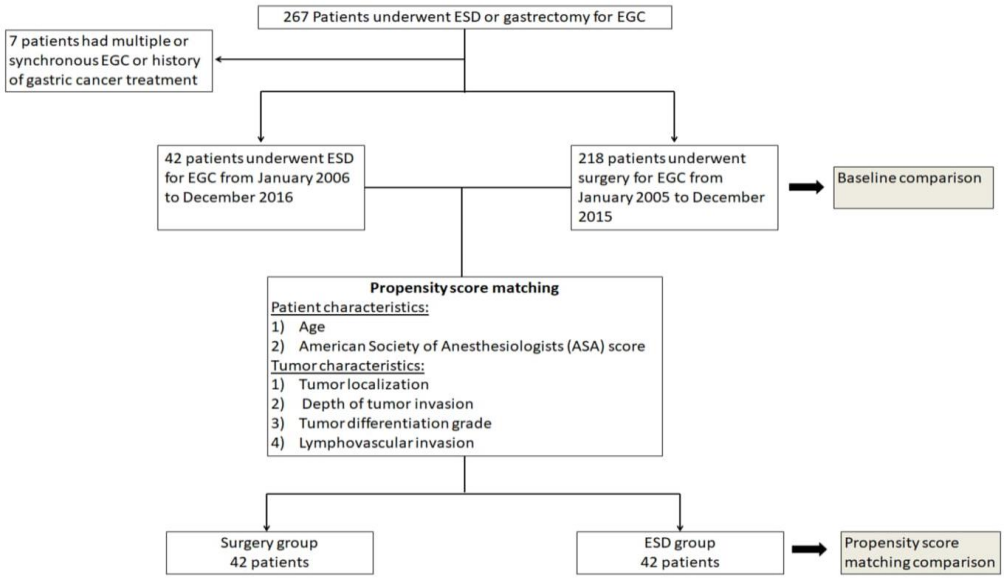

Fig. 1 Flowchart showing the patient selection process

which was performed as described in the 4th version of Japanese gastric cancer treatment guidelines [8]. D1 lymphadenectomy was performed in separate cases based on the individual decision of the operating surgeon. R0 resection, defined by no macroscopically and microscopically remaining tumor, was achieved in all cases.

Pathologic evaluation

Pathologic evaluation was performed at the National Center of Pathology, Vilnius, Lithuania. Pathologists specialized in gastric cancer analyzed all the specimens. Histological type of tumor was classified according to the World Health Organization and Lauren classifications. Slides were stained with hematoxylin-eosin for general evaluation. Tumor size, depth of invasion, lymphovascular involvement together with lateral and vertical margins were evaluated. The maximum diameter was used to determine tumor size. Lymphovascular invasion was defined as observable tumor spread through lymphatic vessels. Lymph nodes were identified in surgical samples and status of the nodes was evaluated after each node was examined microscopically.

Follow-up schedule

Esophagogastroduodenoscopy (EGD) was performed at 3, 6, and 12 months post-ESD and then annually for 5 years. Patients who underwent surgery received EGD twice a year for the first 2 years and then annually. Chest and abdominal CT were conducted annually in both groups. If patients underwent follow-up visits outside of the original study institutions, data were still obtained directly from the patient or their physicians by phone interview. The last follow-up data on death and recurrence were collected in December 2017. Two patients from the ESD group and one patient from surgery group were lost to follow-up.

Statistical analysis

All statistical analyses were conducted using the statistical program SPSS 22.0 (SPSS, Chicago, IL, USA). Continuous variables are presented as the mean ± standard deviation or median with interquartile range. Categorical variables are shown as proportions. Propensity scores were determined by logistic regression model of covariates using six baseline variables: age, American Society of Anesthesiologists (ASA) score, tumor localization, depth of tumor invasion,

grade of tumor differentiation, and lymphovascular invasion. After propensity scores were calculated, patients in the ESD group were matched in a 1:1 ratio with the nearest neighbor from the surgery group. Comparison analysis of clinicopathological characteristics between ESD and surgery groups were analyzed by a 2-tailed t test, χ^2 test, or Fisher exact test. Overall and disease-free survival rates were analyzed by the Kaplan–Meier method and were compared by the log-rank test. Cox proportional hazard regression analysis was used to calculate multivariate-adjusted hazards ratios (HRs) and 95% confidence intervals (CIs) for DFS. In all statistical analyses, a p value of <0.05 was considered to be significant.

Results

Patients and baseline clinicopathologic characteristics

After propensity score matching analysis 42 patients who underwent ESD were matched with 42 patients who underwent surgery for EGC. Table 1 presents the baseline characteristics of the patients before and after propensity score matching. Significant differences between the ESD and surgery groups existed before the pairing. Patients in the surgery group were younger with a lower proportion

Table 1 Baseline clinicopathological characteristics in ESD and surgery groups before and after propensity score matching

	Before matching			After matching		
	ESD group ($n=42$)	Surgery group ($n=218$)	p	ESD group ($n=42$)	Surgery group ($n=42$)	p
Age (mean ± SD)	72.0 ± 10.9	65.5 ± 12.3	**0.001**	72.0 ± 10.9	72.3 ± 8.0	0.874
Sex, n (%)						
Male	24 (57.1%)	117 (53.7%)	0.737	24 (57.1%)	24 (57.1%)	0.999
Female	18 (42.9%)	101 (46.3%)		18 (42.9%)	18 (42.9%)	
BMI (mean ± SD)	27.6 ± 7.6	25.9 ± 4.9	0.534	27.6 ± 7.6	26.3 ± 5.4	0.541
ASA score, n (%)						
1–2	15 (35.7%)	128 (58.7%)	**0.006**	15 (35.7%)	17 (40.5%)	0.653
3–4	27 (64.3%)	90 (41.3%)		27 (64.3%)	25 (59.5%)	
Tumor localization, n (%)						
Upper 3rd	11 (26.2%)	14 (6.4%)	**0.001**	11 (26.2%)	4 (9.5%)	0.050
Middle 3rd	11 (26.2%)	125 (57.3%)		11 (26.2%)	20 (47.6%)	
Lower 3rd	20 (47.6%)	79 (36.2%)		20 (47.6%)	18 (42.9%)	
Tumor invasion, n (%)						
Mucosal	35 (83.3%)	99 (45.4%)	**0.001**	35 (83.3%)	36 (85.7%)	0.999
Submucosal	7 (16.7%)	119 (54.6%)		7 (16.7%)	6 (14.3%)	
Lauren classification, n (%)						
Intestinal type	35 (94.6%)	123 (59.7%)	**0.001**	35 (94.6%)	35 (97.2%)	0.225
Mixed type	2 (5.4%)	19 (9.2%)		2 (5.4%)	0 (0.0%)	
Diffuse type	0 (0.0%)	64 (31.1%)		0 (0.0%)	1 (2.8%)	
Tumor differentiation grade, n (%)						
Well differentiated	25 (59.5%)	44 (20.2%)	**0.001**	25 (59.5%)	22 (52.4%)	0.369
Moderately differentiated	16 (38.1%)	70 (32.1%)		16 (38.1%)	16 (38.1%)	
Poorly differentiated	1 (2.4%)	104 (47.7%)		1 (2.4%)	4 (9.5%)	
Ulceration, n (%)						
Present	8 (19.5%)	78 (35.9%)	**0.001**	8 (19.5%)	3 (7.1%)	0.116
Absent	33 (80.5%)	139 (64.1%)		33 (80.5%)	39 (92.9%)	
Lymphovascular invasion, n (%)						
Present	2 (4.8%)	30 (13.8%)	0.127	2 (4.8%)	1 (2.4%)	0.999
Absent	40 (95.2%)	188 (86.2%)		40 (95.2%)	41 (97.6%)	
Tumor size, n (%)						
< 2 cm	39 (92.9%)	105 (48.4%)	**0.001**	39 (92.9%)	19 (46.3%)	**0.001**
2–3 cm	3 (7.1%)	52 (24.0%)		3 (7.1%)	9 (22.0%)	
> 3 cm	0 (0.0%)	60 (27.6%)		0 (0.0%)	13 (31.7%)	

Significant p values are highlighted in bold

of severe comorbidities. A higher proportion of patients in ESD group had tumors located in the upper third of the stomach, while submucosal tumor invasion, poor differentiation, diffuse-type cancer, ulceration, and wider tumors were more common in the surgery group. After propensity score matching groups were more balanced. Mean propensity scores were 0.39 ± 0.22 and 0.34 ± 0.18 in ESD and surgery groups, respectively, $p = 0.290$. After pairing, patients in both groups were comparable according to various patient-related characteristics such as age, sex, BMI, ASA score, and also, according to multiple tumor-related characteristics: depth of invasion, histological type, differentiation grade of the tumor, ulceration, and lymphovascular invasion. However, even after propensity score matching, tumors exceeding 2 cm in diameter were more common in the surgery group.

Treatment and short-term outcomes

Table 2 shows short-term outcomes after surgery or ESD for EGC. In the surgery group, 10 (23.8%) patients underwent total gastrectomy and 32 (76.2%) subtotal gastrectomy. Operation and postoperative hospitalization times were significantly shorter in the ESD group. Postoperative complications occurred for 7 (16.7%) patients in each group. In the ESD group, 2 (4.8%) patients had infectious complications, 3 (7.1%) patients had postoperative bleeding, and 2 (4.8%) patients had a perforation. Endoscopic hemostasis was successful in all hemorrhagic episodes. Both cases of perforation were treated with open or laparoscopic surgery. Four of 7 complications in the surgery group were mild and classified as grade II complications according to Clavien–Dindo. Two (4.8%) patients were re-operated due to fecal or biliary peritonitis, which in both cases were not associated with anastomotic insufficiency. One patient (2.4%) died during the postoperative course as a result of acute cardiopulmonary insufficiency. All patients in the surgery group underwent radical (R0) surgery. In the ESD group, en bloc and histologically complete resection were achieved in 38 (92.7%) and 32 (78.0%) cases, respectively. However, after the histological examination of specimens, only 30 (71.4%) procedures were classified as curative. Figure 2 shows

Table 2 Short-term outcomes of ESD and surgery groups after propensity matching

	ESD group ($n = 42$)	Surgery group ($n = 42$)	p
Operation time (min ± SD)	83 ± 47	151 ± 47	**0.001**
Postoperative hospitalization time (days ± SD)	5.4 ± 3.1	13.4 ± 6.6	**0.001**
Postoperative complication rate, *n* (%)	7 (16.7%)	7 (16.7%)	0.999
Clavien–Dindo, *n* (%)			
I–II	2 (4.8%)	4 (9.5%)	
III–IV	5 (11.9%)	2 (4.8%)	
V	0 (0.0%)	1 (2.4%)	
Surgical treatment efficacy			
Radical (R0) surgery, *n* (%)	–	42, (100%)	
Retrieved lymph nodes (mean ± SD)	–	19.31 ± 7.57	
Lymph node metastasis, *n* (%)		2, (4.8%)	
En bloc resection, *n* (%)	38, (92.7%)	–	
Histologically complete resection	32, (78.0%)	–	
Curative resection	30, (71.4%)	–	

Significant p values are highlighted in bold

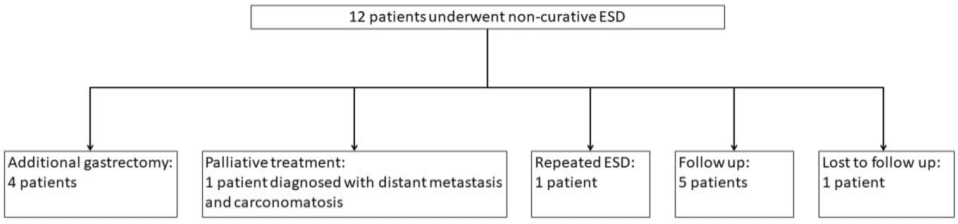

Fig. 2 Flowchart showing additional treatment after non-curative ESD

additional treatment tactics of 12 patients who underwent non-curative ESD.

Survival outcomes

The mean and median length of follow-up was 38 ± 34 and 28 (Q3:60–Q1:9) months for the ESD group and 52 ± 36 and 42 (Q3:74–Q1:30) months for the surgery group. Figure 3 represents disease-free and overall survival comparison between the study groups. Patients in the surgery group had significantly higher 5-year DFS (97.6% vs. 77.5%, $p = 0.002$) (Fig. 3a). Exclusion of patients with non-curative ESD reduced the difference of DFS between the surgery and ESD groups. Five-year DFS was 89.7% in the curative ESD group and 97.6% in the surgery group, $p = 0.099$ (Fig. 3c). In total, 9 (21.4%) patients from the ESD group and 1 (2.4%) patient from the surgery group ($p = 0.014$) had a recurrence of gastric cancer during the follow-up period. Eight (19.0%) patients from the ESD group and 1 (2.4%) patient from the surgery group had local recurrences, which were successfully treated with repeated ESD or surgery. One (2.4%) patient from the ESD group was diagnosed with distant metastasis and carcinomatosis. Overall, 8 of 10 patients who experienced recurrence did so within 36 months after initial treatment. The rate of recurrence after non-curative ESD 5/11 (45.5%) was significantly higher compared to the rate after curative ESD 3/29 (10.3%), $p = 0.007$. Furthermore, Cox proportional hazards regression model showed non-curative ESD as an independent risk factor for the decline of DFS (Table 3). Despite the differences between ESD and surgery groups according to the DFS, OS did not differ significantly between the study groups. Five-year OS was 73.8% and 69.0% ($p = 0.599$) in the ESD and surgery groups, respectively (Fig. 3b). Furthermore, we did not find significantly different 5-year OS rate even when we compared groups of patients who underwent curative and non-curative ESD (66.7% vs. 76.7%, $p = 0.581$) (Fig. 3e).

Discussion

Despite the common use of ER as a treatment option for EGC in the East, Western countries have been slow to accept such an approach. It has been speculated if Western institutions could achieve ESD results comparable to those reported from leading Asian institutions [21]. Besides a few recent studies demonstrating favorable outcomes similar to those achieved in Asia, data on ESD efficacy in Western populations are limited [21–24]. Additionally, these studies have limitations such as lack of data of long-term results or a high percentage of study participants with non-cancerous lesions. Also, all of these studies reported outcomes after ER, but none of them compared ESD with surgery. To our best knowledge, our study is the first study comparing short-term and long-term outcomes of ESD and surgery for EGC in a Western cohort of patients.

In short-term outcome analysis, we found that ESD achieved significantly better perioperative outcomes regarding shorter operative time and shorter postoperative hospitalization. The mean procedure duration of ESD was 83 min and was closely comparable to times reported in large Western studies as well as those in Eastern regions [23, 25]. The superiority of ESD according to shorter operative time and postoperative hospital stay has previously been shown by Chiu et al. [9], where authors retrospectively compared 74 patients with severe dysplasia or EGC treated by ESD to 40 patients treated by gastrectomy in China. In contrast to this study and findings of a systematic review [25], we did not find a lower rate of postoperative complications after ESD. In our study, the postoperative complications occurred for 7/42 (16.7%) patients in each group. The severity of complications in both groups was also comparable. Complications requiring only pharmacological treatment were observed in 4/42 (9.5%) and 2/42 (4.8%) patients in the surgery and ESD groups, respectively. An endoscopic intervention for management of complications was necessary only for postoperative bleeding, which occurred after 3 (7.1%) ESDs. The postoperative bleeding rate found in our study is close to rates reported in various Asian and Western studies reporting delayed bleeding rates between 1.6 and 7% [22, 23, 26]. Two (4.8%) patients from each group had complications requiring surgical treatment. In the surgery group, both patients underwent re-operation for postoperative peritonitis, while in the ESD group, surgery was necessary for management of perforations. In one case, it was intraoperative perforation and the patient underwent surgery after unsuccessful initial endoscopic management, and in another case, it was delayed perforation. Likewise, the perforation rate after ESD in our study is also comparable to findings in other studies. According to recent reports, perforation follows 2.2% to 9.7% of ESDs in Eastern cohorts and 1.8% to 10% in Western cohorts [22, 23, 25]. Therefore, we believe that the discrepancy in postoperative complications between our findings and Asian studies are influenced by the relatively low rates of postoperative morbidity after surgery and relatively high proportion of complications requiring only pharmacological treatment in the ESD group of our study.

Postoperative death was registered only in the surgery group of our study in which 1/42 (2.4%) patient died during the postoperative period. The postoperative mortality rate in the propensity-matched surgery group represents the entire cohort very well since our previous report demonstrated a 1.8% mortality rate after surgery for EGC in the non-matched cohort [27]. We failed to show the risk of postoperative mortality after ESD. However, it should be taken into consideration that our study cohort was relatively

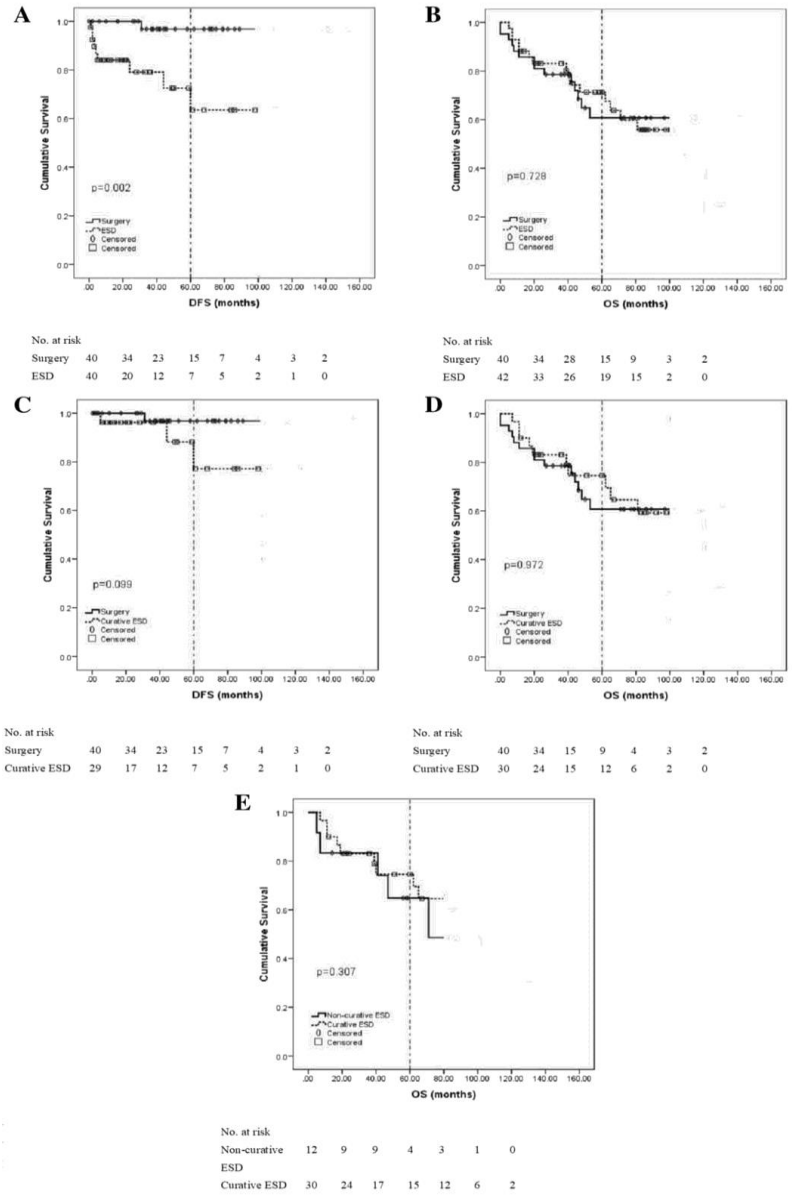

Fig. 3 Comparison of long-term outcomes in propensity-matched groups. **A** DFS in ESD and surgery groups. **B** OS in ESD and surgery groups. **C** DFS in curative ESD and surgery groups. **D** OS in curative ESD and surgery groups. **E** OS in curative ESD and non-curative ESD groups

Table 3 Multivariate Cox regression analysis for disease-free survival in patients with EGC

Factor	HR (95% CI)	*p* value
Age	0.96 (0.89–1.04)	0.380
Gender		
Female	1	0.126
Male	0.27 (0.05–1.44)	
Tumor characteristics		
pT1a, differentiated-type, ≤2 cm, Ul−	1	0.940
(1) pT1a, differentiated-type, >2 cm, Ul− (2) pT1a, differentiated-type, ≤3 cm, Ul+ (3) pT1a, undifferentiated-type, ≤2 cm, Ul− (4) pT1b (SM1), differentiated-type, ≤2 cm, Ul−	1.29 (0.14–11.74)	
Exceeding above-mentioned criteria	1.00 (0.08–11.97)	
Treatment		
Radical surgery or curative ESD	1	**0.001**
Non-curative ESD	41.79 (7.21–242.17)	

Significant *p* value is highlighted in bold

low and mortality risk could have been underestimated, as previous reports have shown mortality rates reaching up to 3.3% [21].

We found that all patients who underwent surgical treatment for EGC had radical surgery. This finding confirms the results published in many Asian studies, where the reported rate of radical resection after surgery was 100% [25]. In contrast to excellent results of surgery according to radicality, en bloc resection was achieved in 38/42 (92.7%) and histologically complete resection in 32/42 (78.0%) patients in the ESD group. The en bloc and histologically complete resection rates of our study were comparable with previous reports from different regions of the world [21–24, 26]. After histological examination of the specimens, 2 (4.8%) patients had an EGC which exceeded expanded criteria for curative ER and only 30/42 (71.4%) ESDs were classified as curative resections. In a multivariate Cox regression analysis, we revealed non-curative ESD as a risk factor for a decline in DFS. We believe that the relatively high rate of non-curative ESDs explains our finding of significantly higher 5-year DFS in the surgery group. In contrast to our results, a total of 1331 Asian patients were summarized in a systematic review comparing ER and surgery for EGC, and no differences regarding recurrence were found between the surgery and ER groups [25]. Therefore, we analyzed DFS in ESD and surgery groups after exclusion of the patients who underwent non-curative ESD. As expected, exclusion blunted the significant differences.

The necessity of additional treatment after non-curative ER for EGC has been widely discussed. Many recent studies have failed to show significant differences in disease-specific survival (DSS) in groups with or without additional surgery after non-curative ESD [28–30]. These previous studies did have limitations such as data from a single institution, a relatively small sample size, and significant clinicopathologic differences between the groups. The clear benefit of additional surgery after non-curative ESD was shown in a large multicenter propensity score-based retrospective analysis published by Suzuki et al. [20]. In this Japanese study, patients who underwent additional surgery showed a significantly higher rate of DSS and OS compared to the patients who only received follow-up care. This study found that additional surgery reduced the risk of gastric cancer-related death by one-third. However, the difference in DSS rates was narrow. Thus, the authors suggested that risk stratification systems to improve the selection of candidates for surgery are necessary to achieve the most favorable outcomes. In our institutions, the decision between additional surgery and follow-up after non-curative ESD is based on patient's age, physical status, and comorbidities. These factors affect the risk of operation and life expectancy. In our study, we were not able to compare the outcomes between patients who underwent additional treatment or received only follow-up care after non-curative ESD, because the total number of non-curative ESDs was low. However, we found a major difference in the recurrence rate after non-curative ESD (5/11, 45.5%) compared to curative ESD (3/29, 10.3%). Moreover, one patient receiving follow-up after non-curative ESD was diagnosed with distant metastasis and carcinomatosis. Therefore, we think that surgery should be highly recommended after non-curative ESD whenever surgery-related risk is acceptable.

Although DFS was significantly better in the surgery group, OS did not differ between the two groups in this study. Unexpectedly, even the non-curative ESD group did not show considerably worse OS. Several factors might be responsible for these results. First, the non-curative ESD group was rather small, and a significant number of patients (5/12, 41.6%) from this group underwent additional surgery during the first 6 months after initial ESD. Second, 8 of 9

patients who were diagnosed with the recurrent disease after primary ESD were radically treated either with repeated ESD or surgery. Radical treatment or recurrence resulted in complete cure of cancer, and probably later EGC did not have an impact on OS. Third, according to the latest World Health Organization report published in 2015, life expectancy in Lithuania is 73.6 years, and the mean age of patients in both groups exceeded 72 years. Therefore, we can assume that OS is mainly affected by general health status and natural mortality rates of the cohort. This feature of our cohort also explains the differences between OS rates found in our study and those reported in Asia, where 5-year OS after ER and surgery for EGC is 97.5% and 97.0%, respectively [16].

The present study has several limitations. First, it is retrospective design study in which patients were not randomly assigned to ESD or surgery groups. To reduce the selection bias, we performed propensity score matching analysis. Even with the use of this statistical method, a significant difference remained between the two groups regarding tumor size. Wider tumors were more frequent in the surgery group, and this difference may have negatively biased outcomes against the surgery group. Nevertheless, the surgery group showed significantly higher 5-year DFS rate and comparable OS rate. Second, the number of patients who underwent non-curative ESD was low. Therefore, we could not compare the outcomes of additional surgery or only follow-up in these patients. Third, the total number of patients in our study was relatively low, especially compared to similar studies performed in Asia. However, due to the low prevalence of EGC in Western countries, only large international multicenter studies can overcome this limitation. Despite all flaws, we managed to show differences between the two treatment groups in the first study comparing ESD and surgery for EGC in a Western setting.

In conclusion, curative ESD might be an excellent alternative to surgery for EGC, because of shorter operation and hospitalization time and comparable long-term outcomes. However, the rate of recurrence after ESD is significant. Therefore, careful surveillance after endoscopic treatment is needed. As non-curative ESD leads to a poor DFS rate, additional surgery should be recommended for these patients whenever treatment-associated risk is acceptable.

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Compliance with ethical standards

Disclosures All authors—R.Bausys, A.Bausys, J.Stanaitis, I.Vysniauskaite, K.Maneikis, B.Bausys, E.Stratilatovas, and K.Strupas—have no conflicts of interest or financial ties to disclose.

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