DOI: 10.4274/terh.galenos.2022.82997
J Tepecik Educ Res Hosp 2023;33(1):85-93

CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

Extensive Peritoneal Lavage (EIPL) with Saline After Curative D2 Gastric Resection For Treatment of Locally Advanced Gastric Cancer Patients

Lokal İleri Mide Kanseri Hastalarının Tedavisinde Küratif D2 Rezeksiyonu Sonrası İzotonik Sıvı ile Extensive Peritoneal Lavage (EIPL)

Ali Alemdar[1], Mehmet Güray Duman[1], Selma Şengiz Erhan[2], Ali Güner[3], İsmayil Yılmaz[1]

[1]University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of General Surgery, İstanbul, Turkey
[2]University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Pathology, İstanbul, Turkey
[3]Karadeniz Technical University Faculty of Medicine, Department of General Surgery, Division of Upper GI Surgery and Institute of Medical Science, Trabzon, Turkey

Cite as: Alemdar A, Duman MG, Şengiz Erhan S, Güner A, Yılmaz İ. Extensive Peritoneal Lavage (EIPL) with Saline After Curative D2 Gastric Resection For Treatment of Locally Advanced Gastric Cancer Patients. J Tepecik Educ Res Hosp 2023;33(1):85-93

Abstract

Objective: This study evaluated extensive intraoperative peritoneal lavage (EIPL) on overall survival (OS), adverse events, and recurrence type in gastric cancer patients who underwent curative D2 lymph node dissection.

Methods: Medical records of 235 patients undergoing D2 curative gastrectomy for clinically locally advanced gastric cancer without peritoneal carcinomatosis between January 2011 and October 2021 were reviewed retrospectively. Patients were grouped according to surgery plus EIPL and non-EIPL. Clinicopathological features and recurrence type, prognostic factors on OS, and incidence of adverse events were evaluated.

Results: The mean age of patients included in this study was 63 years in the EIPL group and 61 in the non-EIPL group. The OS rate of patients with EIPL was 63%, and the non-EIPL group was 61.6%. All postoperative complications were less in the EIPL group (p=0.008). Peritoneal metastases were less in the EIPL group (p=0.003).

Conclusion: Free cancer cells in the abdominal cavity may be detected due of tumor manipulation and lymphovascular dissection during surgery. Using EIPL can reduce peritoneal recurrence. Postoperative complications due to exudate, debris, and possible intestinal content caused by perioperative dissection can be prevented with EIPL.

Keywords: EIPL, gastric cancer, surgery, peritoneal recurrence, adverse events, overall survival

Öz

Amaç: Bu çalışmanın amacı, küratif D2 lenf nodu diseksiyonu uygulanan mide kanseri hastalarında ekstensiv intraoperative peritoneal lavaj (EIPL) yapılmasının sağkalım, nüks tipi ve postoperatif komplikasyonlar üzerindeki etkisini araştırmaktır.

Yöntem: Ocak 2011 ile Ekim 2021 arasında klinik olarak lokal ileri mide kanseri nedeniyle küratif gastrektomi ve D2 lenf nodu diseksiyonu uygulanan periton metastazı olmayan 235 hastanın kayıtları geriye dönük olarak incelendi. Cerrahi sonrası EIPL yapılan ve yapılmayan hastalar değerlendirildi. Genel sağkalım

Address for Correspondence/Yazışma Adresi: Ali Alemdar MD, University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of General Surgery, İstanbul, Turkey
Phone: +90 212 221 77 77 **E-mail:** alemdarali@gmail.com
ORCID ID: orcid.org/0000-0002-1354-7887

Received/Geliş tarihi: 05.10.2022
Accepted/Kabul tarihi: 18.11.2022

Öz

(OS), nüks tipi, klinikopatolojik özellikler ve postoperative komplikasyonlar değerlendirildi. EIPL yapılan ve EIPL yapılmayan (non-EIPL) hasta grupları karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen hastaların ortalama yaşı non-EIPL grubunda 61, EIPL grubunda 63 idi. OS oranı EIPL grubunda %63, non-EIPL grubunda ise %61,6 idi. Tüm postoperatif komplikasyonlar EIPL grubunda daha azdı (p=0,008). Peritoneal metastaz EIPL grubunda daha azdı (p=0,003).

Sonuç: Cerrahi rezeksiyon sırasında tümör manipülasyonu ve lenfovasküler diseksiyona bağlı intraabdominal kavitede serbest kanser hücreleri görülebilir. EIPL uygulanması ile iatrojenik serbest kanser hücreleri peritoneal implantasyonu gelişmesi azaltılabilir. Peroperatif diseksiyona bağlı periton içerisine dökülen debrislerin, eksudanın ve muhtemel barsak içeriğinin EIPL ile yok edilmesiyle postoperatif komplikasyonlar azaltılabilir.

Anahtar Kelimeler: EIPL, mide kanseri, cerrahi, periton nüksü, postoperatif komplikasyonlar, genel sağkalım

Introduction

Gastric cancer is the fifth most commonly diagnosed malignancy and the third leading cause of cancer-related deaths worldwide[1]. In Asian countries, D2 lymphadenectomy is a standard surgical procedure for clinically node-positive (cN+) or locally advanced (≥cT2) gastric cancers[2]. In Western countries, D2 lymphadenectomy is conducted in specialized, high-volume centers with appropriate surgical expertise and postoperative care[3].

Peritoneal metastasis is the most common recurrence pattern after gastric cancer surgery and is associated with a poor prognosis. After peritoneal metastasis, the average survival is 3-6 months[4]. Standard treatment has not yet been developed against peritoneal metastasis[5]. According to the American Joint Committee on Cancer (AJCC) staging, the detection of free peritoneal cancer cells in the cytological examination is defined as metastatic (M1) disease[6]. Free cancer cells reach the peritoneal cavity exfoliated from the serosal surface of the stomach, shedding from the intraluminal space, manipulation of the primary tumor, intraperitoneal hemorrhage during surgery, or when lymphadenectomy was performed via blood vessels and lymphatic channels[7,8]. Peritoneal metastasis occurs through very complex mechanisms, and the details of these steps are not clearly known. Several factors have been accepted to play a role in metastasis formation[8,9]. In the peritoneal cavity, free cancer cells first adhere to the peritoneal mesothelial cells, then the invasion of the peritoneal membrane and formation of the peritoneal metastasis occurs[10]. Peritoneal metastasis can be reduced if free cancer cells reaching the peritoneal cavity can be eliminated before they are implanted in the peritoneal membrane. The extensive intraoperative peritoneal lavage (EIPL) procedure is washing the peritoneal cavity ten times with one liter of normal saline and complete aspiration of the fluid after the surgical resection and anastomosis. This procedure is repeated ten times using one liter of fluid. A total of ten liters or more saline was used. This procedure is based on the limiting dilution theory[11,12]. Reducing free cancer cells in the peritoneal cavity to almost zero decreases the risk of tumor implantation. Studies have shown that additional EIPL treatment contributes to survival[12-14]. Kuramoto and colleagues conducted a statistically significant decrease in peritoneal recurrence in patients who underwent curative resection with EIPL having positive peritoneal cytology (CY +) without overt peritoneal metastasis in their randomized controlled study[13]. They recommended the EIPL procedure as a routine prophylactic strategy to prevent peritoneal recurrence in patients with advanced gastric cancer patients[15]. In the previous randomized controlled studies, it has been shown that performing EIPL does not contribute to survival but reduces postoperative complications[16-19]. The reverse transcriptase-polymerase chain reaction (RT-PCR) molecular biologic method is one of the cytologic investigation methods[11].

The present study evaluated EIPL on overall survival (OS), adverse events, and recurrence pattern in locally advanced gastric cancer patients who underwent curative gastric resection and D2 lymphadenectomy.

Materials and Methods

Our study is retrospective. Patients with a diagnosis of locally advanced gastric cancers who had curative R0 resection and D2 lymph node dissection between January 2011-October 2021 in University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital are included in the study. Inclusion criteria were: age above 18, histologically proven locally advanced gastric adenocarcinoma, and patients who had curative gastrectomy. Exclusion criteria were: having preoperative peritoneal implants and CY+, metastatic disease, non-curative surgery, and having another malignancy. All patients were discussed in a multidisciplinary tumor council, and a treatment algorithm was determined. Patients

planned for neoadjuvant treatment had staging laparoscopy to rule out peritoneal carcinomatosis, and patients with CY+ or peritoneal implants were excluded from the study. The primary aim of the study is to evaluate OS; a secondary aim is to detect recurrence patterns and postoperative complication rates. Medical records of 235 patients who were operated on for gastric cancer at the University of Health Sciences Turkey, Prof. Dr. Cemil Tascıoglu City Hospital Department of General Surgery between January 2011 and October 2021 were reviewed retrospectively, and 200 were enrolled in the study based on the inclusion and exclusion criteria. Patients' age, sex, operation date, diagnosis date, neoadjuvant treatment, comorbidities, BMI, type of gastrectomy, additional organ resection, pathological stage, T stage, N stage, the number of harvested lymph nodes, metastatic lymph nodes, postoperative complications (30 days postoperatively), length of hospital stay, and readmission were evaluated. Data were obtained from prospectively recorded patients' medical records. Patients having neoadjuvant treatment, adjuvant treatment, survival, and recurrence (local/anatomic, systemic peritoneal) were recorded. Stages were determined according to the 8th edition of the AJCC Cancer Staging Manual[6]. Complications were evaluated according to the Clavien-Dindo classification system[20]. The highest grade, according to Dindo, was considered in the case of more than one complication. Dindo grade 3 and above were accepted as a severe complications. As EIPL has been routinely performed since July 2016, patients operated on between July 2016 and October 2021 are accepted as the EIPL group. Patients between January 2011 and July 2016 were taken as a non-EIPL group. Standard washing with one liter of saline was performed in the non-EIPL group after resection and anastomosis. In the EIPL group, washing and aspirating all fluids with one liter of saline was repeated ten times after resection and anastomosis. The peritoneal cytology was examined on all patients before and after dissection, after EIPL or non EIPL washing. Firstly 100-mL saline was given into the abdomen before dissection and aspirated. The sample was sent for cytologic examination. Second, after the completion of dissection and anastomosis, irrigation and aspiration with 100 mL saline is performed and sent for cytology. A third sample was taken for cytology in the EIPL and non-EIPL groups after lavage with ten liters or 1 liter. A conventional smear was prepared after centrifuging at 2000 rpm for 5 min. Smears prepared with Papanicolaou and May-Grunwald Giemsa (MGG) dye were examined under light microscopy. The surgical technique was according to the current Japanese guidelines[2]. Patients were divided into two groups in terms of having EIPL or not. Patients having neoadjuvant chemotherapy also had postoperative adjuvant chemotherapy, namely, perioperative chemotherapy. Patients with pathologic stage ≥T2 or lymph node positivity detected after the operation had adjuvant chemotherapy treatment. Postoperative controls were performed every three months in the first two years and every six months in the following three years. Complete blood count, biochemical tests, abdominal CT, and, if necessary, PET-CT was performed. Abdominal CT was taken every six months in the first three years and annually in the following two years. Annual endoscopy was made for patients with subtotal resection and on-demand if the patient had a complaint. Peritoneal recurrence was detected clinically, radiologically, and, if necessary, with laparoscopy or laparotomy. This retrospective study was approved by the Ethics Committee of the University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital (2021/322, date: 13.09.2021).

Statistical Analysis

Statistical analysis was performed using R software (R Foundation for Statistical Computing, Vienna, Austria) with the required R packages, including tidy verse and final fit. Data were presented as median (first-third quartiles) for continuous variables and as frequencies (percentages) for categorical variables. The normality distribution of continuous variables was assessed with the Shapiro-Wilk test. Differences between groups were analyzed using Student's t-test, the Mann-Whitney test for continuous variables, and the chi-square test/Fisher exact test for categorical variables. Cox proportional hazards regression models were used to evaluate the prognostic effects of variables on survival. Survival outcomes were analyzed using Kaplan–Meier curve analysis, and comparisons between groups were performed using the log-rank test. Since the follow-up periods of the two patient groups were different, the maximum censoring time was determined as five years. The results were described as hazard ratios (HRs) with 95% confidence intervals (CIs). P-values were two-sided, and statistical significance was defined as a p-value <0.05.

Results

Of the patients, 138 were male, and 62 were female. The mean age was 61(54-69.5) in the non-EIPL and 63(53-70) years in the EIPL group. Subtotal gastrectomy was performed in 73 patients. There were more patients with proximally located tumors regarding tumor location. Both groups had an average tumor size of 4 (2-6) cm. The number

of patients receiving neoadjuvant chemotherapy was 109 (54.5%). The clinicopathological parameters of the patients are summarized in Table 1. No complication was observed due to intervention in the EIPL group. Pulmonary embolism in one patient, myocardial infarction (MI) in 1 patient, pneumonia in 4 patients, and atelectasis in 1 patient was diagnosed as medical complications. Pulmonary embolism, MI, and two patients with pneumonia were in the non-EIPL group. Atelectasis and two patients with pneumonia were in the EIPL group. A comparison of the postoperative complications between the two groups is shown in Table 2. All postoperative complications were less in the EIPL group (p=0.008). Mortality was seen in four patients, all in the non-EIPL group. Anastomotic leakage in two patients, pulmonary embolism in 1 patient, and MI in one patient, were the causes of postoperative mortality. No difference was observed in terms of length of hospital stay between groups (p=0.247). Major surgical complications (≥ grade-III) were higher in the non-EIPL group, which was statistically significant (16.4% vs. 4.8%, p=0.016). The report median follow-up for patients without the event was 34 months (95% CI 29.8-38.1). The OS curve of the patient according to treatment is shown in Figure 1. Five-year survival was 63 % in the EIPL group and 61.6% non-EIPL group (HR (CIs,

Table 1. The demographic and clinical characteristics of patients

Variables		Non-EIPL	EIPL	P-value
		n=55 (27.5)	n=145 (72.5)	-
Age (years)		61 (54-69.5)	63 (53-70)	0.852
Sex	Female	25 (45.5)	37 (25.5)	**0.011**
	Male	30 (54.5)	108 (74.5)	-
BMI (kg/m^2)		25 (24-27)	26 (24-28)	0.877
Preoperative chemotherapy		18 (32.7)	91 (62.8)	**<0.001**
Differentiation	Well	12 (21.8)	26 (17.9)	**0.042**
	Moderate	13 (23.6)	62 (42.8)	-
	Poor	30 (54.5)	57 (39.3)	-
Localization	Antrum	28 (50.9)	46 (31.7)	0.043
	Corpus	15 (27.3)	55 (37.9)	-
	Cardia	12 (21.8)	44 (30.3)	-
Type of gastrectomy	Subtotal	29 (52.7)	44 (30.3)	**0.006**
	Total	26 (47.3)	101 (69.7)	-
LVI		35 (63.6)	80 (55.2)	0.357
PNI		24 (43.6)	75 (51.7)	0.388
T stage	T1	15 (27.3)	29 (20)	0.513
	T2	7 (12.7)	21 (14.5)	-
	T3	20 (36.4)	67 (46.2)	-
	T4	13 (23.6)	28 (19.3)	-
N stage	N0	17 (30.9)	58 (40)	0.676
	N1	10 (18.2)	21 (14.5)	-
	N2	13 (23.6)	29 (20)	-
	N3	15 (27.3)	37 (25.5)	-
Stage	Stage I	16 (29.1)	39 (26.9)	0.903
	Stage II	15 (27.3)	44 (30.3)	-
	Stage III	24 (43.6)	62 (42.8)	-
Tumor size (cm)	-	4 (2-5.8)	4 (2-6)	0.843

BMI: Body mass index, LVI: Lymphovascular invasion, and PNI: Perineural invasion, EIPL: Extensive intraoperative peritoneal lavage
Data were presented as n (%) or median (Q1-Q3)

log-rank): 0.90 (0.51-1.58, p=0.718) (Figure 1). Univariate and multivariate analyzes were performed to determine the predictors of OS (Table 3). In a multivariate analysis of five-year survival, no difference was observed between the EIPL and non-EIPL groups [HR (CIs 95%) 0.84 (0.46-1.54, p=0.567)]. Multivariate analysis of factors affecting OS and Cox regression analysis was performed to determine the independent predictors of OS (Table 3). Survival rates of advanced tumors were lower in both groups and statistically significant (p=0.032). A comparison of recurrence patterns

Table 2. Postoperative complications

Variables	Non-EIPL	EIPL	P-value
	n=55 (27.5)	n=145 (72.5)	
Any postoperative complication	25 (45.5)	36 (24.8)	**0.008**
Any surgical complication	22 (40.0)	34 (23.4)	**0.031**
Bleeding	3 (5.5)	7 (4.8)	1.000
Chylous leakge	5 (9.1)	10 (6.9)	0.562
Wound complication	8 (14.5)	15 (10.3)	0.458
Pancreatic fistula	3 (5.5)	2 (1.4)	0.129
Anastomotic leakage	3 (5.5)	-	**0.020**
Major surgical complication	9 (16.4)	7 (4.8)	**0.016**
Postoperative mortality	4 (7.3)	0 (0.0)	**0.005**
Hospital stay	7.0 (7.0 to 10.5)	7.0 (7.0 to 10.0)	0.247

Data were presented as n (%) or median (Q1-Q3), EIPL: Extensive intraoperative peritoneal lavage

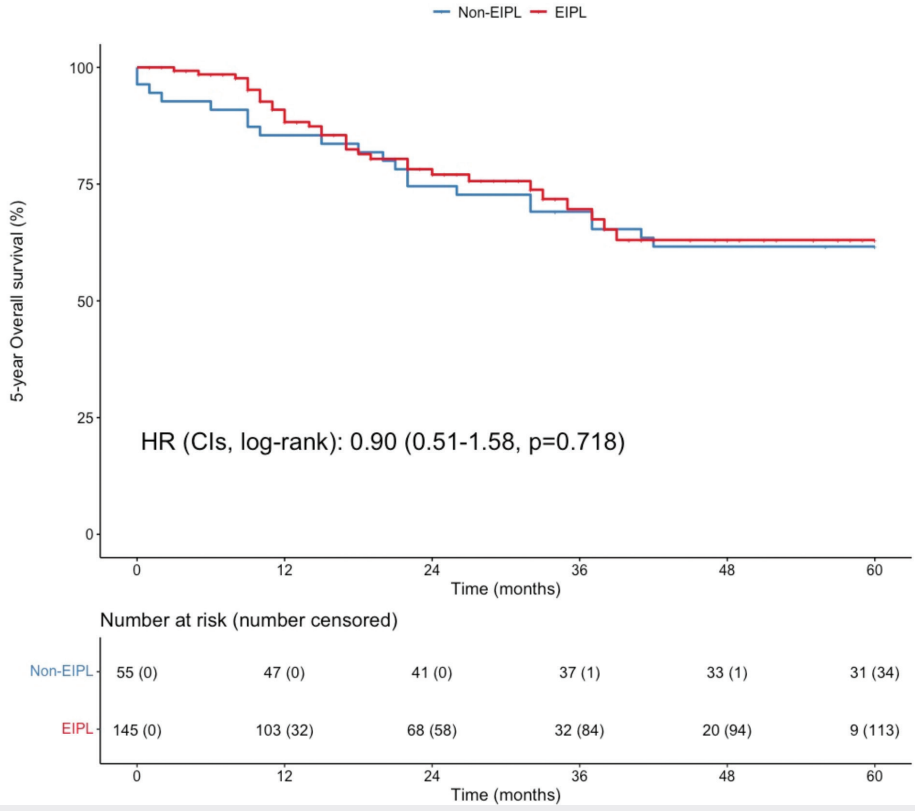

Figure 1. Overall survival [HR (CIs, log-rank): 0.90 (0.51-1.58, p=0.718)].

HR: Hazard ratio, EIPL: Extensive intraoperative peritoneal lavage

is given in Table 4. Peritoneal recurrence was the most common pattern in the non-EIPL group compared with the EIPL group (16.4% vs 3.4%, p=0.003).

Discussion

The peritoneum is the most common site of metastasis after gastric cancer surgery[4]. No effective, standardized treatment for peritoneal metastases has been developed[5]. For this reason, EIPL is important to prevent possible metastases. EIPL is a short and simple procedure that can be performed in every institution without requiring extra equipment. Kuramoto et al.[13] performed EIPL in locally advanced CY (+) gastric cancer patients. After curative surgery, they performed EIPL and intraperitoneal chemotherapy (IPC) with a survival rate of 43.8% (p<0.0001). In the non-EIPL group, they get a 2-year survival rate of 0%. The exact treatment scheme with IPC in gastric cancer patients is not well established

Table 3. Uni- and multivariable Cox regression analysis of variables for 5-year survival

Variables		HR (Crude)	HR (Adjusted)
Age	≤60 years	-	-
	>60 years	1.17 (0.68-2.03, p=0.567)	1.40 (0.80-2.45, p=0.243)
Sex	Female	-	-
	Male	1.44 (0.79-2.62, p=0.234)	-
BMI (kg/m^2)	-	0.95 (0.88-1.04, p=0.288)	-
Preoperative chemotherapy	No	-	-
	Yes	1.85 (1.06-3.24, p=0.030)	1.59 (0.87-2.87, p=0.129)
Differentiation	Well	-	-
	Moderate	2.60 (0.87-7.75, p=0.086)	1.72 (0.56-5.26, p=0.344)
	Poor	3.64 (1.29-10.30, p=0.015)	1.53 (0.49-4.76, p=0.460)
Type of gastrectomy	Subtotal	-	-
	Total	1.78 (1.00-3.18, p=0.051)	-
LVI	No	-	-
	Yes	3.32 (1.71-6.45, p<0.001)	1.80 (0.83-3.91, p=0.136)
PNI	No	-	-
	Yes	2.99 (1.66-5.39, p<0.001)	-
Stage	Stage I	-	-
	Stage II	1.85 (0.67-5.09, p=0.233)	1.44 (0.50-4.10, p=0.497)
	Stage III	5.18 (2.18-12.31, p<0.001)	3.10 (1.11-8.68, p=0.032)
Lavage group	Non-EIPL	-	-
	EIPL	0.90 (0.51-1.58, p=0.718)	0.84 (0.46-1.54, p=0.567)

HR: Hazard ratio, BMI: Body mass index, LVI: Lymphovascular invasion, PNI: Perineural invasion, EIPL:Extensive intraperitoneal lavage
Data were presented as HR (CIs 95%, p-value)

Table 4. Recurrence pattern

Variables	Non-EIPL	EIPL	P-value
	n=55 (27.5)	n=145 (72.5)	
Any recurrence	15 (27.3)	20 (13.8)	**0.042**
Locoregional	3 (5.5)	2 (1.4)	0.129
Liver	2 (3.6)	7 (4.8)	1.000
Peritoneal	9 (16.4)	5 (3.4)	**0.003**
Others	1 (1.8)	6 (4.1)	0.676

EIPL: Extensive intraoperative peritoneal lavage
Data are presented as n (%)

yet[15,21,22]. Besides difficulty, the potential side effects and effectiveness of treatment are questioned in the application of IPC[23]. In our study, we performed EIPL in CY-negative patients without giving IPC. Peritoneal metastasis was less compared with the non-EIPL group (p=0.003). In patients without overt peritoneal implants, the abdomen is irrigated with 100 mL saline, and samples are obtained from the right and left subphrenic areas and rectovesical recess for cytologic examination. RT-PCR molecular biologic system can be used for evaluation[11,12]. Detection of free cancer cells in the peritoneal cavity and decreased survival rate are usually observed together. The sensitivity of detecting free cancer cells in the peritoneal cavity by cytologic investigation may differ according to the pathologist's experience and the equipment of institutions[19]. According to pathologists and institutions, the cytologic demonstration of cancer cells can be variable[10,19,24,25]. Molecular investigations may not be available in every clinic. In our study for cytologic examination, conventional smears with Papanicolaou and MGG histochemical stains were performed, and primary cytologic exam-positive patients were excluded. Masuda et al.[26] demonstrated that if EIPL is performed in CY + patients, intraperitoneal free cancer cells can be decreased nearly to zero, and the prognosis can be better. Preoperative positive cytology was detected in 3.4% and 8% of patients with EIPL and non-EIPL, respectively; in the study of Misawa et al.[16], recurrence rates were 33.1% and 40% in the EIPL and non-EIPL groups. Our study excluded CY+ patients, and we detected a recurrence rate of 13.8% in EIPL and 27.3% in the non-EIPL group. In a randomized controlled trial by Guo et al.[17], the postoperative complication rate (11% vs 17%) and mortality (0% vs 1.9%) of the EIPL group were less. A study conducted in Brazil announced an increased anastomotic leakage risk in EIPL patients[27]. If this RCT is examined in detail, low number of patients and early termination of the study before the targeted patient number due to the slow recording of patients is observed. Studies reported lower intraabdominal infections and abscesses with EIPL by removing tissue debris, exudate, and inflammatory cells[18,28]. In our research, we also evaluated two groups regarding postoperative complications. No procedure-related complications were observed in the EIPL group. Intraabdominal abscesses, adhesions, and ileus were not observed in both groups. Postoperative complications were less in the EIPL group (p=0.008). Major surgical complications (≥ grade-III) were less in the EIPL group (16.4% vs 4.8%, p=0.016). EIPL of inflammatory cells, bacteria, and intraperitoneal debris of dissection, also known as a method of limiting dilution, resulted in fewer complications by a decreased inflammatory reaction and accelerated wound healing[29]. Postoperative mortality was not observed in the EIPL group. We applied EIPL to locally advanced gastric cancer patients. If there is lymph node positivity or lymphatic invasion, free peritoneal cancer cells are found in high numbers in patients with D2 lymph dissection. This was 14.3% in submucosal lesions and 53.8% in subserosal invasion[11]. Studies have revealed that intraabdominal hemorrhage is a reason for free cancer cell spillage to the peritoneal cavity. These cells may be shedding from the resected border of the specimen or during lymphoid dissection. Lymphoid dissection itself may be responsible for peritoneal spread by spillage of tumor cells from lymphatic vessels[30]. In patients locally advanced gastric cancer who are thought to have a lymphatic invasion, after curative resection and lymph node dissection without considering whether CY+ or not, it is shown that EIPL can prevent iatrogenic peritoneal spread[11,14,26]. In our study, we foresee that cleaning cancer cells with EIPL may be the reason for less metastasis in this group. Intraoperative coagulation and other factors in plasma participate in the adhesion of gastric cancer and mesothelial cells and, consequently, may play a role to some extent in the initial steps of peritoneal metastasis of gastric cancer[8,9]. Inflammation in the peritoneal cavity may lead to the proliferation of free cancer cells and adhesion to the mesothelium. As a result, impaired adaptive immune response facilitates metastasis[9]. Increased peritoneal metastasis and decreased survival rates due to intraabdominal hemorrhage is a known entity[8]. It is stated that with EIPL, cleaning cells in the peritoneal cavity before implantation may prevent peritoneal metastasis[26]. A study showed that peritoneal metastases were less in patients with 350 ccs perioperative bleeding and having EIPL[16]. This is explained by removing cancer cells with EIPL before implantation in the peritoneal cavity. Studies offer IPC and EIPL to clean free cancer cells prophylactically from the peritoneal cavity before the invasion occurs[21]. The peritoneal spread was also less in the EIPL group in patients with pancreatic cancer[31]. In terms of patient prognosis, lymphovascular invasion, TNM stage, type of gastrectomy, performing lavage, and tumor differentiation were analyzed with multivariate Cox regression analysis. We preferred OS instead of disease-free survival. Sometimes, it may be difficult to detect early metastasis of the peritoneum radiologically and clinically. No difference was present between the two groups in terms of survival. Five-year survival was 63% and 61.6% in the EIPL and non-EIPL groups, respectively.

Performing EIPL in patients with clinically advanced stages, large tumor diameter, poorly differentiated, high lymph node involvement, and high perioperative bleeding will reduce tumor seeding.

Study Limitations

This study had some limitations. The first relapse site was determined as the recurrence pattern. The first limitation is that metastases developed after the first relapse were not explained in detail. The second limitation is accepting the most severe complication, according to Dindo, as a postoperative complication. In case of more than one complication, especially medical complications, it could be specified in detail for patients. The third limitation is that grading of peritoneal inflammation and pain scoring in the postoperative period could be screened, and its' effect on medical complications could be detected. Another limitation is the unequal number of groups and having surgery in different periods.

Conclusion

Free intraabdominal cancer cells can be seen in the case of tumor manipulation and lymphovascular dissection during surgical resection. These cells can be removed before implantation with EIPL. EIPL can be performed at every institution without the need for special equipment and can be completed in a short time. It can be used as an adjuvant surgical technique benefiting from its' cytoreductive effect to prevent peritoneal spread. EIPL can reduce postoperative complications due to the removal of proinflammatory cells and debris. EIPL has no impact on OS.

Ethics

Ethics Committee Approval: Ethics Committee approval was received for this study University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital (2021/322, date: 13.09.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., İ.Y., Concept: A.A., A.G., İ.Y., Design: S.Ş.E., A.G., İ.Y., Data Collection or Processing: Analysis or Interpretation: A.A., M.G.D., S.Ş.E., İ.Y., Literature Search: M.G.D., A.G., İ.Y., Writing: A.A., M.G.D., A.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study received no financial support.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021;24:1-21.
3. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D; ESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:38-9.
4. Wei J, Wu ND, Liu BR. Regional but fatal: Intraperitoneal metastasis in gastric cancer. World J Gastroenterol 2016;22:7478-85.
5. Dahdaleh FS, Turaga KK. Evolving Treatment Strategies and Outcomes in Advanced Gastric Cancer with Peritoneal Metastasis. Surg Oncol Clin N Am 2018;27:519-37.
6. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67:93-9.
7. Ji ZH, Zhang Y, Li Y. Intra-operative hyperthermic intraperitoneal chemotherapy for prevention and treatment of peritoneal metastases from gastric cancer: a narrative review. J Gastrointest Oncol 2021;12:70-8.
8. Arita T, Ichikawa D, Konishi H, et al. Increase in peritoneal recurrence induced by intraoperative hemorrhage in gastrectomy. Ann Surg Oncol 2015;22:758-64.
9. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008 24;454:436-44.
10. Kanda M, Kodera Y. Molecular mechanisms of peritoneal dissemination in gastric cancer. World J Gastroenterol 2016;22:6829-40.
11. Marutsuka T, Shimada S, Shiomori K, et al. Mechanisms of peritoneal metastasis after operation for non-serosa-invasive gastric carcinoma: an ultrarapid detection system for intraperitoneal free cancer cells and a prophylactic strategy for peritoneal metastasis. Clin Cancer Res 2003;9:678-85.
12. Shimada S, Tanaka E, Marutsuka T, et al. Extensive intraoperative peritoneal lavage and chemotherapy for gastric cancer patients with peritoneal free cancer cells. Gastric Cancer 2002;5:168-72.
13. Kuramoto M, Shimada S, Ikeshima S, et al. Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma. Ann Surg 2009;250:242-6.
14. Shimada S, Kuramoto M, Marutsuka T, Yagi Y, Baba H. Adopting extensive intra-operative peritoneal lavage (EIPL) as the standard prophylactic strategy for peritoneal recurrence. Rev Recent Clin Trials 2011;6:266-70.
15. Kuramoto M, Shimada S, Ikeshima S, et al. A proposal of a practical and optimal prophylactic strategy for peritoneal recurrence. J Oncol 2012;2012:340380.
16. Misawa K, Mochizuki Y, Sakai M, et al. Randomized clinical trial of extensive intraoperative peritoneal lavage versus standard treatment for resectable advanced gastric cancer (CCOG 1102 trial). Br J Surg 2019;106:1602-10.
17. Guo J, Xu A, Sun X, et al. Combined Surgery and Extensive Intraoperative Peritoneal Lavage vs Surgery Alone for Treatment of Locally Advanced

Gastric Cancer: The SEIPLUS Randomized Clinical Trial. JAMA Surg 2019;154:610-16.

18. Yang HK, Ji J, Han SU, et al. EXPEL study group. Extensive peritoneal lavage with saline after curative gastrectomy for gastric cancer (EXPEL): a multicentre randomised controlled trial. Lancet Gastroenterol Hepatol 2021;6:120-7.
19. Virgilio E, Giarnieri E, Giovagnoli MR, et al. Gastric Cancer Cells in Peritoneal Lavage Fluid: A Systematic Review Comparing Cytological with Molecular Detection for Diagnosis of Peritoneal Metastases and Prediction of Peritoneal Recurrences. Anticancer Res 2018;38:1255-62.
20. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
21. Glehen O, Passot G, Villeneuve L, et al. GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study. BMC Cancer 2014;14:183.
22. Coccolini F, Fugazzola P, Ansaloni L, et al. Advanced gastric cancer: the value of systemic and intraperitoneal chemotherapy. Acta Biomed 2018;89:104-9.
23. Ceelen W, Braet H, van Ramshorst G, Willaert W, Remaut K. Intraperitoneal chemotherapy for peritoneal metastases: an expert opinion. Expert Opin Drug Deliv 2020;17:511-22.
24. Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. Gastric Cancer 2012;15:S27-7.
25. Ronellenfitsch U, Ernst K, Mertens C, et al. Extensive intraperitoneal lavage to eliminate intraperitoneal tumor cells in gastrectomy with D2 lymphadenectomy for gastric cancer. Tumori 2018;104:361-8.
26. Masuda T, Kuramoto M, Shimada S, et al. The effect of extensive intraoperative peritoneal lavage therapy (EIPL) on stage III B + C and cytology-positive gastric cancer patients. Int J Clin Oncol 2016;21:289-4.
27. Batista TP, Martins MR, Martins-Filho ED, Santos RL. A PHASE II TRIAL EXPLORING THE EXTENSIVE INTRA-OPERATIVE PERITONEAL LAVAGE (EIPL) AS A PROPHYLACTIC STRATEGY FOR PERITONEAL RECURRENCE IN LOCALLY ADVANCED GASTRIC CANCER: reporting postoperative morbidity and mortality after early closure. Arq Gastroenterol 2015;52:161-4.
28. Rodríguez-Santiago J, Luna A, Garsot E, Aldeano A, Balagué C, Rada A. Extended intraoperative peritoneal lavage as prophylactic peritoneal recurrence for locally advanced gastric cancer: a prospective randomized trial. Clin Transl Oncol 2021;23:1857-65.
29. Ruiz-Tovar J, Llavero C, Muñoz JL, Zubiaga L, Diez M. Effect of Peritoneal Lavage with Clindamycin-Gentamicin Solution on Post-Operative Pain and Analytic Acute-Phase Reactants after Laparoscopic Sleeve Gastrectomy. Surg Infect (Larchmt) 2016;17:357-62.
30. Han TS, Kong SH, Lee HJ, et al. Dissemination of free cancer cells from the gastric lumen and from perigastric lymphovascular pedicles during radical gastric cancer surgery. Ann Surg Oncol 2011;18:2818-25.
31. Yamamoto K, Shimada S, Hirota M, Yagi Y, Matsuda M, Baba H. EIPL (extensive intraoperative peritoneal lavage) therapy significantly reduces peritoneal recurrence after pancreatectomy in patients with pancreatic cancer. Int J Oncol 2005;27:1321-8.