RESEARCH ARTICLE

Extended intraoperative peritoneal lavage as prophylactic peritoneal recurrence for locally advanced gastric cancer: a prospective randomized trial

J. Rodríguez-Santiago[1] · A. Luna[2] · E. Garsot[3] · A. Aldeano[4] · C. Balagué[5] · A. Rada[4]

Abstract

Background To demonstrate whether extensive intraoperative peritoneal lavage (EIPL) could yield better results in overall survival and less recurrence, regardless of peritoneal cytology, compared to standard peritoneal lavage (SPL).

Methods A prospective randomised multicenter study including 94 patients (47 per arm) to detect a 20% difference in 3-year overall survival in patients with locally advanced tumours without peritoneal carcinomatosis. Three samples of peritoneal fluid were obtained (at the beginning, the end of procedure and after the assigned peritoneal lavage). Clinicopathological and surgical data were analysed by group. Postoperative complications, location of recurrence and surgical approach were evaluated. Overall survival was calculated by the Kaplan–Meier method and the uni/multivariate analysis for prognostic factors was carried out using Cox regression analysis.

Results A total of 86 patients were analysed (4 excluded per group). No statistical differences were observed in clinicopathological or surgical data between groups, considering both groups well-balanced for analysis. Overall survival at 3 years was 64.3% for SPL vs. 62.3% for EIPL (p 0.421). Only three patients had at least one positive peritoneal cytology (1:2). There were no differences regarding postoperative complications (SPL: 37.2% vs. EIPL: 32.5%, p 0.65) or between location of recurrence and number of recurrences. The number of recurrences did not differ between surgical approaches, but locoregional and peritoneal recurrences were fewer with the laparoscopic approach (p 0.048).

Conclusions The regular use of extensive peritoneal lavage in patients with locally advanced gastric cancer, regardless of peritoneal cytology, has not been effective as prophylaxis of peritoneal recurrence or better survival.

Keywords Extended intraperitoneal lavage · Gastric cancer · Prophylaxis of recurrence · Randomized trial

✉ J. Rodríguez-Santiago
25533jrs@gmail.com

1 Department of Surgery, Gastro-Oesophageal Surgery Unit, Hospital Universitari Mútua de Terrassa, University of Barcelona, Plaza Dr. Robert, n. 5, 08221 Terrassa, Barcelona, Spain

2 Gastro-Oesophageal Surgery Unit, Consorci Sanitari Parc Taulí, Sabadell, Spain

3 Gastro-Oesophageal Surgery Unit, Hospital Germans Trias i Pujol, Badalona, Spain

4 Gastro-Oesophageal Surgery Unit, Hospital General de Granollers, Granollers, Spain

5 Gastro-Oesophageal Surgery Unit, Hospital Sant Pau, Barcelona, Spain

Introduction

Advanced gastric cancer (AGC) is the most common form of presentation at the moment of diagnosis in Western countries and Europe. T3–T4 gastric wall invasion cancer has a poor prognosis with a 5-year survival of less than 35%, even after curative resection [1]. The most frequent cause of treatment failure after surgery for gastric cancer is peritoneal metastasis that is reported as the most frequent pattern of recurrence in advanced gastric cancer (32–54%) and the most frequent cause of death (> 60%) during the first 2 years after surgery [1–3]. Both the Japanese Gastric Cancer Association (since 1998) and the American Joint Committee on Cancer (since 2010, 7th TNM) established positive peritoneal cytology as a metastatic disease [4].

Free cancer cells in the peritoneal cavity may be the result of the exfoliation of cells from the serosa surface of

the primary tumour or after manipulation during surgery (gastrectomy plus lymphadenectomy) through blood vessels and perigastric lymphatic channels and posterior growth and dissemination in peritoneal surface.

A relevant study published by Kuramoto et al. demonstrated that patients with AGC and positive peritoneal lavage cytology (CY1) without carcinomatosis (P0) had important benefits in 5-year overall survival with intraperitoneal chemotherapy (IPC) plus extended intraperitoneal lavage (EIPL) with 10 L of physiologic serum by the "limiting dilution method" (1 L diluted by tenfold) (43.8%) compared to intraperitoneal chemotherapy alone (4.6%) [5]. This observation suggests that EIP, but not IPC, was key to the significant results obtained, proposing this method as a possible standard prophylactic strategy for peritoneal recurrence in patients with gastric cancer [6]. Some trials have tried to demonstrate the effect of extensive intraoperative lavage (EIPL) in cases of positive peritoneal cytology and P0 after potentially curative surgery for gastric cancer [7, 8].

Makino et al. in a prospective series of 113 patients with invaded serosa gastric tumour without peritoneal metastasis, reported 31% of positive cytologies in a preoperative peritoneal lavage [9]. However, the sensitivity of peritoneal cytology and molecular methods for the detection of free cancer cells in the peritoneal cavity may vary among centres and pathologists [1, 10–12]. For this reason, the aim of the present study was to investigate the role of EIPL as a standard prophylactic strategy for peritoneal recurrence and its impact on survival in cases with clinically local advanced gastric cancer and potentially curative surgery regardless of the peritoneal cytology.

This procedure has several advantages due to its simplicity, easy reproducibility, low cost and minimal complications. For this reason, the authors believe that EIPL may be used as a standard prophylactic strategy for peritoneal recurrence and survival in cases with suspected macroscopic serosa invasion or lymph node infiltration observed during surgery, cT3–4 or cN+ (by preoperative staging CT, EUS) independently from a perioperative positive peritoneal cytology. The aim of this trial is to demonstrate this hypothesis.

Materials and methods

This is a prospective randomised multi-institutional phase III trial. Patients were enrolled from five institutions that form part of the Spanish EURECCA Esophagogastric Cancer Project. The study was approved by the Clinical Trial Committee of the reference hospital (Hospital Mútua de Terrassa) and the ethic committees of each participating hospital. All candidates who accepted to participate provided written informed consent.

Outcomes

The primary outcome was overall survival and the secondary outcomes were incidence of adverse events and type of recurrence.

Inclusion criteria

Two types of inclusion criteria were applied (preoperative or intraoperative).

(a) Preoperative: cT3–4 and/or cN+, M0, P0 (by previous staging CT, EUS), histologically–confirmed gastric adenocarcinoma (biopsy), planned total or distal gastrectomy plus D2 lymphadenectomy (or D1 in total spleen-preserving gastrectomy) according to the Japanese Classification of Gastric carcinoma, Fourth English edition.

(b) Intraoperative (depending on surgeon criteria): Macroscopic infiltration of gastric serosa previously unsuspected, suspicion of macroscopic lymph nodes involvement without macroscopic serosa infiltration, no evidence of carcinomatosis (P0) and curative surgery (R0).

All patients with neoadjuvant chemotherapy ± radiotherapy were excluded if staging laparoscopy was not performed before the treatment to rule out peritoneal carcinomatosis.

Study variables

Age, sex, tumour location, Lauren classification, surgical approach (open or laparoscopy), type of gastrectomy (total or subtotal), lymphadenectomy type, surgical resection (R0,R1,R2), reconstruction (Roux-en-Y, Billroth I or II), combined resection of other organs, clinical and pathological stage (according according to the TNM 7th edition), standard lavage vs. EIPL, number of resected nodes, number of invaded nodes, peritoneal cytology (before and after surgery and after lavage), postoperative morbidity (Clavien-Dindo classification), reintervention, hospital stay (days), neoadjuvant therapy, adjuvant therapy, recurrence and site of recurrence.

Sample size

The number of patients was determined comparing the difference of expected survival with the log-rank test with a two-sided alpha level of 0.05 and a power of 90%. A previous study showed that overall 3-year survival for patients of a cohort of 115 patients T3–T4, M0 (TNM 6th edition)

with R0 and surgical D2 lymphadenectomy in the University Hospital Mútua de Terrassa was 50.3%. A total of 94 patients (47 patients in each group) were needed to detect a 20% difference in 3-year OS of 50% for the surgery alone group and 70% for the surgery plus EIPL group.

Patients were randomised to surgery alone or surgery plus EIPL group in a 1:1 ratio stratified by every participating hospital (with a block size of four) using a computer program. This decision was taken because one of the important biases could be the results of the peritoneal cytology due to the different sensitivity between participating centres or pathologists. Allocation was communicated to the surgeon after the end of the surgery to ensure the same procedure for every group. Patients were blinded to the procedure assignment.

Procedure

All patients were proposed to be treated with open or laparoscopic curative D2 gastrectomy (R0) depending of the hospital and according the Guidelines of the Japanese Research Society for the study of gastric cancer (4th English version) [13]. A total or subtotal gastrectomy was performed depending of the location of the tumour. In cases of total gastrectomy, the preservation of splenic nodes (group 10) was considered D1 but these patients were also included in the essay.

Three peritoneal cytology samples were collected from every patient. The first at the beginning of surgery with a wash in all abdominal cavity of 100 cc physiological serum, or a direct sample was taken in cases with ascites. The second at the end of the surgery with a wash of 100 cc physiological serum. And the third after a standard lavage (< 2 L) or EIPL (10 L). All the samples were identified separately and collected in different tubes. All the samples were analysed in each respective hospital by centrifugation 1000×10 min with Papanicolau and Giemsa staining.

Adjuvant chemotherapy was recommended for patients with locally advanced tumours and curative resection by the multidisciplinary tumour board of each centre.

Follow-up

Physical examination and analysis with tumours markers were done postoperatively at 3 months and every 6 months up to 3 years. Abdominal and chest CT was performed every 6 months for the first 3 years after surgery and once a year thereafter. Upper endoscopy was carried out every year. However, in cases of suspected recurrence by clinical symptoms during this period, additional imaging examination (CT or PET) was performed for confirmation.
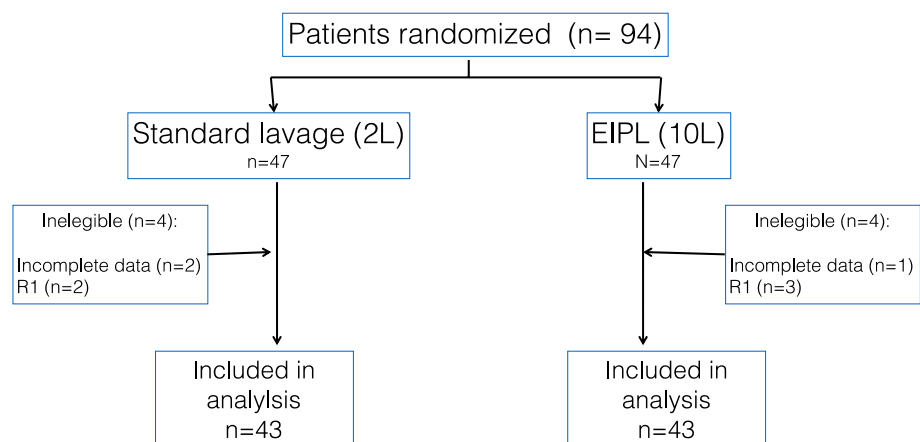
Statistical analysis

The data were analysed on an intention-to-treat basis for all patients that fulfilled the inclusion criteria. The difference of overall survival was compared using the Kaplan–Meier method (Log-rank). Uni/multivariate analysis of survival was done using the Cox regression method. Exploratory subgroup analysis was also conducted to evaluate the effects of perioperative factors on between-group differences in OS using the Cox regression model including interaction term of treatment group and each perioperative factor. Qualitative or quantitative variables were compared using a χ^2 test or t test. All $p < 0.05$ values were considered statistically significant. The analysis was performed using the SPSS software, version 25 (IBM Corporation).

Results

From January 2015 to December 2017, 94 patients were randomised to surgery plus EIPL or surgery plus standard lavage (47 patients in each group). Eight patients were excluded from the analysis after randomisation: Two due to

Fig. 1 Flow chart

postoperative Clavien V complications (1:1), three for R1 resection (1:2) and three for incomplete data (2:1). A total of 86 patients were included in the statistical analysis (43 per group) (Fig. 1).

Clinical and surgical outcomes characteristics

The clinical characteristics of patients are shown in Table 1. A good statistical balance between both groups was observed. There were no statistical differences between age, sex, ASA, tumour localisation, histologic type, pTNM classification or stage. The surgical outcomes are shown in Table 2. There were no differences in types of gastrectomy and lymphadenectomy, number of resected lymph nodes, surgical approach (open vs. laparoscopy), postoperative complications, reoperations, hospital stay and adjuvant chemotherapy, between groups. Distal tumours, intestinal type, subtotal gastrectomy and open approach were the most frequent in global series.

Prognostic factors

The characteristics of clinical and pathological data showed that tumour localisation ($p < 0.001$), type of gastrectomy (p 0.013) and lymph nodes status (pN) (p 0.010) were independent factors by univariate Cox regression for survival in this series. Multivariate Cox regression analysis (by steps) demonstrated that lymph nodes status (pN) was the most important prognostic factor in this series (p 0.006).

In the subgroup analyses, there were no significant interactions between treatment effect and any patient's characteristics (Table 3).

Overall survival

The median follow-up of survival was 45 months (95% CI 34.6–55.4). The 3-year OS for the standard lavage group was 64.6% and 62.3% for the EIPL group (HR 1.36 (95%CI 0.64–2.91; p 0.421) (Fig. 2).

Peritoneal cytology

Three peritoneal cytology samples were collected from every patient. In the first peritoneal cytology (at the beginning of the surgery), only 1 case was positive in the EIPL group and none in the standard lavage group. In the second peritoneal cytology (at the end of the surgery) only 1 case was positive in each group. In the third peritoneal cytology (after lavage) there were no positive cases in EIPL and only 1 positive in standard lavage.

In summary, four cytologies were positive in three patients. In the SL group, one patient had (first−/second + /third +) and died 15 months after

Table 1 Clinic and pathological data

	Surgery + SL ($n = 43$)	Surgery + EIPL ($n = 43$)	p
Age mean ± SD	67.9 ± 11.2	66.4 ± 12.6	0.58
Sex			0.37
Male	25	29	
Female	18	14	
ASA			0.41
1	1	3	
2	17	21	
3	23	16	
4	2	3	
Tumour location			0.67
Upper	5	4	
Middle	15	12	
Distal	22	24	
Linnitis	1	3	
Histological type			0.77
Intestinal	22	23	
Diffuse	14	13	
Mixed	6	7	
Undifferentiated	1	0	
pT category			0.44
pT0	2	0	
pT1	6	3	
pT2	5	8	
pT3	14	15	
pT4	16	17	
pN category			0.43
pN0	17	20	
pN1	6	6	
pN2	12	6	
pN3	8	11	
Number lymph nodes			
Mean ± SD	31.1 ± 12	27.7 ± 12.7	0.22
Number pathologic lymph nodes			
Mean ± SD	4.6 ± 6.7	5.5 ± 8.1	0.57
pTNM stage			0.17
IA	6	2	
IB	2	7	
IIA	4	9	
IIB	9	4	
IIIA	11	9	
IIIB	6	7	
IIIC	3	5	
IV	0	0	
Neoadjuvant treatment			
Yes	14	19	0.27
No	29	24	
Adjuvant treatment			

Table 1 (continued)

	Surgery + SL (n = 43)	Surgery + EIPL (n = 43)	p
Yes	26	26	0.88
No	16	15	
Hospital days			
Mean ± SD	12.3 ± 10.1	14.0 ± 11.7	0.47

surgery for locoregional recurrence. In EIPL, one patient had (first + /second−/third−) and another patient had (first−/second + /third−).

Complications

No intraoperative complications related to EIPL were observed. There was no difference in postoperative complications between groups (37.2% standard lavage vs. 32.5% EIPL p 0.65). Intraabdominal collection and pancreatic fistula were seen more often in standard than extended lavage. Clavien–Dindo classification of surgical complications did not demonstrate differences between groups (p 0.47). Open vs. laparoscopic approach showed differences in overall complications 39 vs. 29% but not significant (p 0.30).

There were two postoperative in-hospital deaths, one in each group, for anastomotic leakage and another for pneumonia with respiratory failure (Table 2).

Neoadjuvant or postoperative adjuvant chemotherapy

A total of 38.4% of patients received neoadjuvant chemotherapy, 60.5% adjuvant chemotherapy and 30% both, according to the oncological protocols of each institution. There were no differences between groups in neoadjuvant chemotherapy (32.6% standard lavage vs. 44.1% EIPL, p 0.27) or in adjuvant chemotherapy (62% standard lavage vs. 63.4% EIPL, p 0.88).

Site of recurrence/lavage

There were no differences between groups in recurrence (p 0.37) or between site of recurrence (peritoneal, locoregional, hepatic, others) (p 0.79) (Table 4).

Recurrence/surgical approach

No differences in recurrence between open or laparoscopic approach were observed (41.6% open vs. 42.2% laparoscopic approach, p 0.34). Locoregional and peritoneal recurrence were more frequent in open than laparoscopic approach. However, this does not allow to conclude that the

Table 2 Surgical outcomes

	Surgery + SL (n = 43)	Surgery + EIPL (n = 43)	p
Gastrectomy			
Total	12	13	0.36
Distal	29	30	
Total + spleen	2	0	
Approach			
Open	27	21	0.19
Laparoscopy	16	22	
Reconstruction			
Roux Y	38	39	0.92
Billroth I	1	1	
Billroth II	4	3	
Lymph node dissection			
D2	28	28	0.93
D1+	6	7	
D1	9	8	
Number lymph nodes			
Mean ± SD	31.1 ± 12	27.7 ± 12.7	0.22
Additional organ resection			
Yes	1	4	0.17
No	42	39	
Postoperative complications			
Yes	16 (37%)	14 (35%)	0.65
No	27	29	
Type of complications			
Anastomotic leak	4	3	
Duodenal leak	2	3	
Abdominal abscess	3	0	
Pancreatic fistula	2	0	
Others	5	8	
Clavien–Dindo classification			
Grade 0	27	29	0.50
I–II	9	6	
III–IV	6	7	
V	1	1	
Reoperation			
Yes	5	5	1
No	38	38	
Hospital stay (days)			
Mean ± SD	12.3 ± 10.1	14.0 ± 11.7	0.47

laparoscopic approach produces less locoregional recurrence as the present study was not designed to respond this question (Table 4).

Table 3 Prognostic factors by Cox regression analysis (overall survival) and interaction by type of lavage

	HR (CI 95)	p	Adjusted by type of lavage p adjusted
Type of lavage			
Standard (×2L)	1	0.421	0.421
EIPL (×10L)	1.36 (0.64–2.91)		
Histological type			
Intestinal	1	0.931	0.404
Diffuse	1.17 (0.49–2.81)		
Mixed	1.40 (0.50–3.94)		
Localisation			
Distal	1	< 0.001	0.665
Medium	0.38 (0.11–1.32)		
Upper	1.67 (0.61–4.64)		
Linnitis	9.94 (3.04–32.5		
Gastrectomy type			
Distal	1	0.013	0.284
Total	2.69 (1.29–5.91)		
Lymphadectomy			
D1	1	0.150	0.482
D1+	2.15 (0.88–5.28)		
D2	2.21 (0.73–6.76)		
Approach			
Open	1	0.189	0.313
Laparoscopy	0.56 (0.23–1.33)		
pT			
T1	1	0.240	0.424
T2	0.36 (0.03–3.98)		
T3	1.08 (0.22–5.18)		
T4	1.95 (0.48–8.48)		
pN			
N0	1	0.010	0.193
N1	4.46 (1.27–15.61)		
N2	3.55 (1.08–11.69)		
N3	6.31 (2.12–18.74)		
Postoperative complications			
No	1	0.908	0.417
Yes	0.95 (0.42–2.16)		
Reoperation			
No	1	0.349	0.424
Yes	1.67 (0.57–4.87)		
Neoadjuvant treatment			
No	1	0.234	0.545
Yes	1.61 (0.73–3.52)		
Adjuvant treatment			
No	1	0.131	0.426
Yes	0.54 (0.24–1.20)		

Discussion

This study was designed to demonstrate whether EIPL can be effective as a prophylactic approach to prevent recurrence in locally advanced gastric cancer, independently from the presence of a positive peritoneal cytology. The results obtained show that there is no benefit in overall survival, recurrence or type of recurrence. However, some relevant

Fig. 2 Kaplan–Meier analysis of overall survival by type of lavage
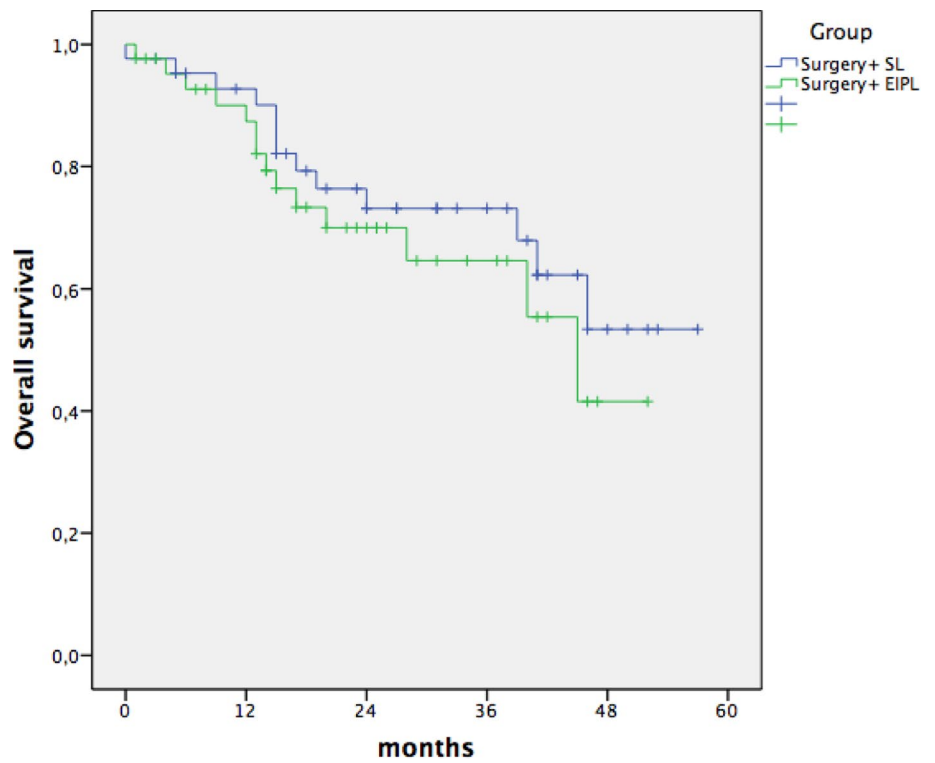
SL   43   35   23   15   4
EIPL 43   33   17   9   1

p: 0.42

Table 4 Recurrence and site of recurrence by group and by surgical approach

	Surgery + SL ($n = 43$)	Surgery + EIPL ($n = 43$)	p
Overall	18 (42%)	14 (33%)	0.37
Site first recurrence			
Peritoneum	4	4	0.80
Local–regional	7	6	
Liver	4	3	
Other site	3	1	
Surgical approach			
	Open ($n = 48$)	Laparoscopic ($n = 38$)	p
Recurrence			
No	28	26	0.34
Yes	20	12	
Site first recurrence			
Peritoneum	5	3	0.05
Local–regional	11	2	
Liver	4	3	
Other site	0	4	

aspects should be highlighted. Intraabdominal collections and pancreatic fistula were not observed in EIPL group comparing to standard lavage and the recurrence site differs between surgical approaches. There were no statistical differences between the number of cases with recurrence but locoregional and peritoneal site was most frequent in the open than in the laparoscopic approach (*p* 0.048) and the only patient with three positive cytologies was in the SL group. OS was chosen as the primary outcome rather than disease-free survival because of the difficulty to detect early recurrence or peritoneal dissemination by imaging studies or clinical symptoms.

Since Kuramoto and colleges demonstrated that EIPL plus peritoneal chemotherapy could play a special role in CY1/P0 cases, some authors have tried to demonstrate the contribution of EIPL alone in the good results obtained in their study [7]. Moreover, in Western countries, free peritoneal tumour cells are detected only sporadically in the staging cytology and sensitivity could differ between pathologists and institutions [11–13]. For these reasons, we designed this trial to evaluate the EIPL in patients with clinical suspicion of locally advanced cancer but independently from the results of peritoneal cytology. The results obtained could be very promising due to the simplicity, easy reproducibility, low cost and time-saving aspect of the technique. One of the most interesting aspects was the concept of "limiting dilution theory" that consists in a peritoneal wash of one litre of physiological saline followed total aspiration repeated 10 times expecting to lead to a logarithmic reduction of cancer cells to zero [14, 15].

To date, there are three prospective trials, from different eastern countries, that try to analyse whether EIPL could be a standard procedure in locally advanced gastric cancer to prevent recurrence and improve survival. The CCOG 1102 included 314 patients (Japan), EXPEL with a total of 800 subjects (Singapore, Malaysia, Korea, China and Japan) and SEIPLUS with 662 patients (China) [7, 16, 17]. Of these trials, CCOG 1102 trial results has not shown an improvement in survival or peritoneal recurrence in the EIPL group [18]. SEIPLUS trial recently published the results of short-term postoperative complications and mortality, showing a significant difference in postoperative complications (17 vs. 11.1%), reduced mortality (1.9 vs. 0%) and less postoperative pain (17.7 vs. 10.8%) favouring EIPL. The results of survival and recurrence are pending [17]. During the editorial revision of this manuscript, the EXPEL trial concluded that EIPL did not have a survival benefit and cannot be recommended for standardised use [19].

To our knowledge, this is the first randomised trial performed in a Western country and the results could be different from the East experience. The percentage of postoperative complications is significantly higher than in Eastern countries. However, the difference between both groups were similar (37.2 vs. 32.5%, *p* 0.65) and all types of complications were included (even Clavien–Dindo I–II grade). Another possible justification may be the influence of different surgical approaches (open vs. laparoscopic) but we could not demonstrate statistical differences between postoperative complication and the approach (*p* 0.30).

In the univariate analysis for prognostic factors, tumour localisation, gastrectomy type and pN have been shown as independent factors related to survival. In this study, pT and type of lymphadenectomy were not so relevant because the majority of patients were pT3–4 (locally advanced) and D2 lymphadenectomies. In the multivariate analysis, pN was the only independent prognostic factor. These results are in line with those previously published. We have observed that pT3–4 in SL was 70 vs. 74.4% in EIPL and it could seem strange because one of the inclusion criteria was cT3–4. However, the majority of these understaged patients received neoadjuvant chemotherapy (according to the oncologic protocol of the institution) or have enlarged or pathological lymph nodes by CT in the preoperative staging. The CGOG 1102 trial, with similar ethodology, also showed pT3–4 in 77.9% in EIPL and 86% in SL [17].

Peritoneal washing cytology has a high specificity but a questionable sensitivity (11.1 vs. 80%) [9]. The sensitivity (12.3–67%) and specificity (94–100%) of immunochemistry does not show a clear benefit compared to conventional Papanicolau staining. Molecular methods for the detection of intraperitoneal free cancer cells such as mature messenger ribonucleic acid of carcinoembryonic antigen (CEA mRNA) and cytokeratin 20 (CK-20 mRNA) have expressed a sensitivity and specificity of 38–100% and 7.3–100% and 25–64% and 80.3–94%, respectively. Due to the limitations of each method, the use of both cytology and molecular examination could be mandatory [20]. However, lack of immediate intraoperative results, relatively high false-positive results, higher cost and lack of this technology in each centre are some of the limitations for the standard use [20, 21].

An analysis of the number of cases with positive cytology and the number of cases with peritoneal or locoregional recurrence in both groups may account for the scepticism of their use in the habitual practice. The sensitivity of peritoneal cytology in this study was very low: only 1 case in EIPL and 0 in standard lavage at the beginning of the surgery. After resection there was 1 positive cytology in each group (both patients were previously negative and it may be explained by exfoliation during surgery). No patient remained positive after EIPL and 1 patient after SL. This patient died of loco-regional recurrence 15 months after surgery. The authors consider that the cytology may have been negative if EIPL had been performed. Another aspect that requires a special mention is that the number of patients with positive peritoneal cytologies (3.5%) does not match with the number of recurrences observed in this study (41.6% SL

and 42.2% EIPL). The Misawa K. study showed a similar number of positive cytologies in 3.4% with EIPL group and 8% with SL with recurrence in 33.1 vs. 40%, respectively without statistical significance, in contrast with the study of Kuramoto et al. [5].

The results of the present study are in concordance with those of the CCOG 1102. However, our sample size is significantly minor and may be underpowered. Although a longer follow-up may produce more solid results, we believe that outcomes are very unlikely to change after 3 years. Large studies with a greater number of patients, EXPEL and SEI-PLUS could demonstrate if a subgroup of patients could benefit of EIPL as prophylactic strategy for recurrence [15–18].

In conclusion, our findings suggest that EIPL, regardless of the peritoneal cytology, cannot be supported as a prophylactic standard method to reduce peritoneal recurrence or to increase OS in locally advanced gastric cancer.

Declarations

Conflict of interest None of the authors have any conflict of interest.

Ethical approval The study was approved by the Clinical Trial Commitee of the the reference hospital (Hospital Universitary Mutua de Terrassa) and the ethics committees of each participating hospital.

Informed consent All candidates accepted to participate provided written informed consent.

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