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The yield of diagnostic laparoscopy with peritoneal lavage in gastric adenocarcinoma: A retrospective cohort study

S.J.M. van Hootegem [a,*], J. Chmelo [b], P.C. van der Sluis [a], S.M. Lagarde [a], A.W. Phillips [b,c], B.P. L. Wijnhoven [a]

[a] Department of Surgery, Erasmus MC University, Rotterdam, the Netherlands
[b] Northern Oesophagogastric Unit, Royal Victoria Infirmary, Newcastle-Upon-Tyne, UK
[c] School of Medical Education, Newcastle University, UK

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ABSTRACT

Introduction: Diagnostic laparoscopy (DL) with peritoneal lavage has been adopted as a standard staging procedure for patients with gastric cancer (GC). Evaluation of the value of DL is important given ongoing improvements in diagnostic imaging and treatment. As contemporary data from European centres are sparse, this retrospective cohort study aimed to assess the yield of DL in patients with potentially curable gastric cancer, and to identify predictive factors for peritoneal metastases.

Methods: Patients with adenocarcinoma of the stomach, treated between January 2016 and December 2018, were identified from institutional databases of two high volume European Upper-GI centres. Patients who underwent a DL with peritoneal lavage for potentially curable disease after clinical staging with imaging (cT1-4N0-3M0) were included. The primary outcome was the proportion of patients with a positive DL, defined as macroscopic metastatic disease, positive peritoneal cytology washings (PC+) or locally irresectable disease.

Results: Some 80 of 327 included patients (24.5%) had a positive DL, excluding these patients from neoadjuvant treatment (66 of 327; 20.2%) and/or surgical resection (76 of 327; 23.2%). In 34 of 327 patients (10.3%), macroscopic metastatic disease was seen, with peritoneal deposits in 30 of these patients. Only 16 of 30 patients with peritoneal disease had positive cytology. Some 41 of 327 patients (12.5%) that underwent DL had PC+ in the absence of macroscopic metastases and five patients (1.5%) had an irresectable primary tumour. Diffuse type carcinoma had the highest risk of peritoneal dissemination, irrespective of cT and cN categories.

Conclusion: The diagnostic yield of staging laparoscopy is high, changing the management in approximately one quarter of patients. DL should be considered in patients with diffuse type carcinoma irrespective of cT and cN categories.

1. Introduction

Gastric cancer (GC) is one of the most frequently diagnosed cancers globally and the third leading cause of cancer-related deaths [1]. Distant metastases are seen in more than 40% of newly diagnosed GC patients [2,3]. As resection of the primary tumour is often not of benefit in patients with distant metastases, it is key to identify patients with metastatic disease before commencing neoadjuvant therapy. Timely detection can prevent patients from undergoing futile surgery, allows for appropriate counselling, may reduce complications and costs, and could improve quality of life [4].

The diagnosis of peritoneal metastases portends a poor prognosis with a median overall survival of only three to four months [3]. Conventional imaging methods (CT and FDG-PET) are imperfect in diagnosing disseminated disease in the peritoneal cavity. Hence, diagnostic laparoscopy (DL) with peritoneal lavage is performed to exclude (microscopic) metastases and to assess local resectability.

Multiple guidelines recommend a DL in patients with potentially curable gastric cancer on the basis of clinical tumour and nodal stage [5–7]. Previous studies have underlined the accuracy, safety, and superiority of DL compared with imaging in the detection of peritoneal metastases [8]. As DL is performed under general anaesthesia in the operating theatre, and has a small but not insignificant risk of perioperative complications, periodically evaluating the yield of DL is

* Corresponding author. Department of Surgery, Erasmus MC, University Medical Center, P.O. Box 2040, 3000CA, Rotterdam, the Netherlands
E-mail address: s.vanhootegem@erasmusmc.nl (S.J.M. van Hootegem).

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warranted given the ongoing improvement of diagnostic imaging.

From 2016 onwards, several guidelines recommend the use of FDG-PET in locally advanced tumours [7,9,10]. More recent data suggest that new tracers including fibroblast activating protein inhibitor (FAPI) have a high sensitivity for detecting peritoneal metastases [11]. This may impact on the diagnostic yield of DL that is often performed after imaging studies. However, recent reports from European centres assessing the value of DL are sparse and included patients treated within a long time span (≥8 years) while having a small sample size which limits the assessment of predictive factors for peritoneal dissemination. Therefore, the aim of this study was to assess the current diagnostic yield of DL in two high-volume European centres who routinely perform DL on potentially curable patients with GC and to identify predictive factors of peritoneal dissemination.

2. Methods

2.1. Patients

Before start of the study, ethical approval was obtained (MEC-2019-0284). Patients treated between January 2016 and December 2018 for an upper gastrointestinal malignancy were retrospectively reviewed using two institutional databases (Erasmus Medical Centre, Rotterdam, the Netherlands and the Northern Oesophagogastric Unit, Newcastle-upon-Tyne, UK). All patients with biopsy-proven gastric or oesophagogastric junction (OGJ) adenocarcinoma who underwent a DL were included. Patients with radiological evidence of metastatic disease (M1), Siewert type I and II tumours and patients who were directly planned for resectional surgery, without separate DL, were excluded [12].

2.2. Staging procedures

Clinical staging of the tumours was done according to the 8th edition of AJCC-IUCC TNM-classification [13]. Clinical work-up included upper gastrointestinal endoscopy with biopsy for histological diagnosis, computed tomography (CT) of the thorax and abdomen and FDG-PET in case of advanced tumours (cT3-4 and/or cN1-3) or a tumour located at the OGJ (Siewert II and III). Endoscopic ultrasonography for was done when indicated (junctional cancers to assess infiltration of the oesophagus and distal gastric cancers to assess infiltration of the duodenum).

In both centres, DL was routinely performed on patients with potentially curable (cT1-4N0-3M0) gastric cancer (tumour bulk located below Z-line), *i.e.* no evidence of metastatic (M1) or irresectable disease (T4b) after diagnostic imaging and fit for chemotherapy and/or surgery at time of diagnosis. Exceptions were patients eligible for endoscopic resection [5] and patients with no primary tumour visible on CT at the Erasmus MC (typically cT1 cancer).

DL was performed according to local preferences and performed under general anaesthesia. Typically, the primary tumour, and adjacent structures including the peritoneum, liver, greater and lesser omentum, pouch of Douglas, pelvis, and Treitz' ligament were inspected. In case the tumour was located on the posterior side of the stomach the omental bursa was opened. Lesions suspicious for malignancy were biopsied for histological evaluation. Peritoneal lavage samples were routinely taken and obtained by instilling and aspirating saline in the upper and lower abdomen. The volume of the saline used for washings and analysis by the pathologist was not standardised.

2.3. Outcomes

The primary outcome was the proportion of patients with a positive DL, defined as findings that precluded patients from undergoing treatment with curative intent (*i.e.,* macroscopic metastatic disease, peritoneal washings with free cancer cells on cytology (PC+) or locally irresectable disease). Secondary outcomes were the proportion of patients with metastases or locally irresectable disease during planned resection, risk factors associated with peritoneal disease and the number needed to test (for one positive DL), stratified according to tumour characteristics.

2.4. Statistical analysis

Categorical variables were reported as numbers and percentages. The distribution of continuous variables was reported as median with interquartile range (IQR). Differences between groups were tested using Pearson's χ^2 test, unless otherwise specified. A p-value ≤0.05 (two-sided) was considered to be statistically significant. Missing data were handled using multiple imputation under the missing at random assumption. Fifty datasets were imputed to comply with the recommendation of one imputation per percent of missing observation [14]. Logistic regression analysis was used to identify factors associated with peritoneal disease. Factors with a p-value <0.1 in univariable analysis were entered in the multivariable model. Pooled estimates were computed using Rubin's rules. The number needed to test was calculated as follows: 1/(number of patients with a positive diagnosis/total number of patients tested). All analyses were performed using SPSS version 28.0 (IBM Corp, Armonk, NY, USA).

3. Results

3.1. Patient characteristics

In total, 327 consecutive patients underwent a DL. Baseline characteristics are presented in Table 1 and Supplementary Table 1. The

Table 1
Baseline characteristics of study patients.

Variables	*Total*
	n = 327
Age, years (median [IQR])	68 [59–75]
Sex	
Male	224 (69)
Female	103 (32)
Tumour origin	
OGJ	63 (19)
Proximal	75 (23)
Middle	60 (18)
Distal	71 (22)
Body (linitis)	58 (18)
Clinical T-stage	
Tx	36 (11)
T1-2	25 (8)
T3-4	266 (81)
Clinical N-stage	
Nx	32 (10)
N0	110 (34)
N1-3	185 (57)
Tumour histology (biopsy)	
Intestinal	95 (29)
Diffuse	68 (20)
Mixed	12 (4)
Not recorded	166 (51)
Differentiation grade (biopsy)	
G1	3 (1)
G2	34 (10)
G3	77 (24)
Not recorded	169 (65)
WHO PS	
0	129 (40)
1	98 (30)
2	15 (5)
3	2 (1)
Not recorded	87 (27)

IQR interquartile range; OGJ oesophagogastric junction; WHO PS World Health Organization performance status.
Data are presented as counts and percentages, unless otherwise indicated. Percentages may not total to 100% because of rounding.

median age was 68 years [interquartile range (IQR) 59–75] and 69.5% was male. The majority of patients had a cT3-4 tumours (81.0%) and more than half had suspicion of locoregional nodal disease (59.6%). The median number of days between date of (histological) diagnosis and DL was 27 days [IQR 19–35].

3.2. Diagnostic laparoscopy

In three patients (0.9%), adhesions from previous abdominal surgery prevented complete examination of the peritoneal cavity. There was no surgery-related mortality or complications requiring a re-intervention.

The proportion of patients with a positive DL was 24.5% ($n = 80$). Macroscopic metastases were seen in 34 (10.4%) patients with 16 of these patients also had PC+ and one patient had a locoregional irresectable tumour. Some 41 patients (12.5%) had PC + without macroscopic metastases and five patients (1.5%) had locally irresectable disease only. All six patients with cT1N0 stage had a negative laparoscopy and one of 12 patients (8.3%) with cT2N0 stage had PC + without macroscopic metastases. Three of seven patients (42.9%) with stage cT1-2N + disease had macroscopic metastases. Laparoscopy findings, including locations of distant metastases, are shown in Table 2.

3.3. Treatment

Overall, a positive DL excluded 66 (20.2%) patients from neoadjuvant chemotherapy and 76 patients (23.2%) from surgical resection. Twelve of 34 patients (35.2%) with macroscopic disease during DL received palliative chemotherapy, of which one patient also received palliative radiotherapy. The remaining patients received best supportive care. All five patients with locally irresectable disease during DL received palliative care with chemotherapy and/or radiotherapy. One patient had signs of obstruction due to local tumour ingrowth and a gastro-jejunostomy was created during DL.

Of 41 patients with PC + only, 25 patients received palliative care and two were lost to follow-up. Induction chemotherapy was given to 14 patients, and these underwent a re-laparoscopy ($n = 12$) or restaging with CT ($n = 2$). Four patients proceeded to surgical resection after conversion or no signs of progressive disease. Fig. 2 shows treatment details of PC + patients.

Of 247 patients with a negative DL, five patients were lost to follow-up or were treated in the referring hospital. Some 169 of 247 patients (68%) patients received neoadjuvant chemotherapy. 197 (80%) patients underwent surgery with curative intent and in 17 of them (8.6%) incurable disease was detected. A further 45 (20%) patients did not proceed to surgical resection after a negative DL for several reasons (Fig. 1). Amongst those patients, seven were diagnosed with metastatic disease before surgery, including four patients with peritoneal lesions. The median time between DL and surgery was 18 weeks [IQR 16–21] for patients who received neoadjuvant chemotherapy and 3 weeks [IQR 2–5] for patients who were directly planned for resection.

Table 2
Results of diagnostic laparoscopy.

Outcomes	Total
	n = 327
Macroscopic metastatic disease	
Yes	34 (10)
Peritoneal	27[a]
Liver	2
Liver & peritoneal	3
Distant nodes	2
No	293 (90)
Positive cytology	
Yes	57 (17)[a]
No	265 (81)
Suspect	5 (2)
Positive cytology without macroscopic metastatic disease	41 (13)
Locally irresectable disease only	5 (1)
Total yield	
Positive[b]	80 (24)
Negative	247 (76)

Data are presented as *n* (%).
[a] Including one patient with locally irresectable disease.
[b] Excluding patients with suspect positive cytology only.

3.4. Risk factors associated with peritoneal disease and numbers needed to test

Nodal status (Nx), serosal involvement (T4), diffuse type carcinoma, WHO performance status and age were associated with a peritoneal disease in univariable analysis (Supplementary Table 2). In multivariable analysis, nodal status (Nx), serosal involvement (T4), diffuse type carcinoma, WHO performance status and age remained significantly associated with peritoneal disease (Table 3). The corresponding number needed to test was three for patients with diffuse type carcinoma, lower than all other groups (Table 4).

4. Discussion

This study confirms that the yield of DL in patients with GC from Europe is high. In 24.5% of the patients, metastases including PC + or locally irresectable disease was diagnosed leading to a change in oncological treatment. Given the almost negligible harm, this study supports the recommendation that DL should be performed routinely in all Western patients with advanced GC.

Macroscopic metastatic disease or locally irresectable disease was seen in 11.9% of patients, of which a third received palliative chemotherapy. This percentage is comparable to the recently published prospective PLASTIC study [15]. Historically, these patients are given palliative chemotherapy, but treatment of patients with limited peritoneal disease is shifting towards more aggressive therapies. In addition to systemic chemotherapy, pressurized intraperitoneal aerosol chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC) plus cytoreductive surgery have been reported to be feasible [16–18]. Whether these treatments improve survival compared to palliative chemotherapy alone remains to be determined in randomized studies like the PERISCOPE-II trial, that includes patients with PC+ and limited peritoneal disease [19].

To date, there is no evidence-based treatment for patients with PC + only. Although PC+ is staged as M1, Dutch, British and ESMO guidelines have no clear recommendations on how to treat this subgroup of patients [5,7,20]. However, it seems clear that performing a gastrectomy in patients with PC + offers no survival benefit [21,22]. The proportion of patients with PC+ in the absence of macroscopic metastases in this study was 12.5%, comparable to previously reported rates of 9–13% [15,23]. During the inclusion period of this study, both centres advocated induction chemotherapy followed by a re-laparoscopy. Several cohort studies report conversion surgery after induction chemotherapy may be associated with a survival benefit [24,25]. Conversion from positive to negative cytology was, however, not common in our study (4 of 14 patients). The majority of patients received a MAGIC-based chemotherapy regimen (ECX/ECF), but the implementation of FLOT may improve this conversion rate as suggested by Valletti et al. who assessed the impact of converting PC + on survival [24,26,27]. In their study conversion was achieved in 9 out of 14 patients using a FLOT regimen.

In this cohort, the proportion of patients with incurable disease at the time of planned resection was 8.6% after a negative DL. Comparable percentages of 8.6% and 10% were reported by studies evaluating the yield of DL in a similar setting, including FDG-PET for clinical staging

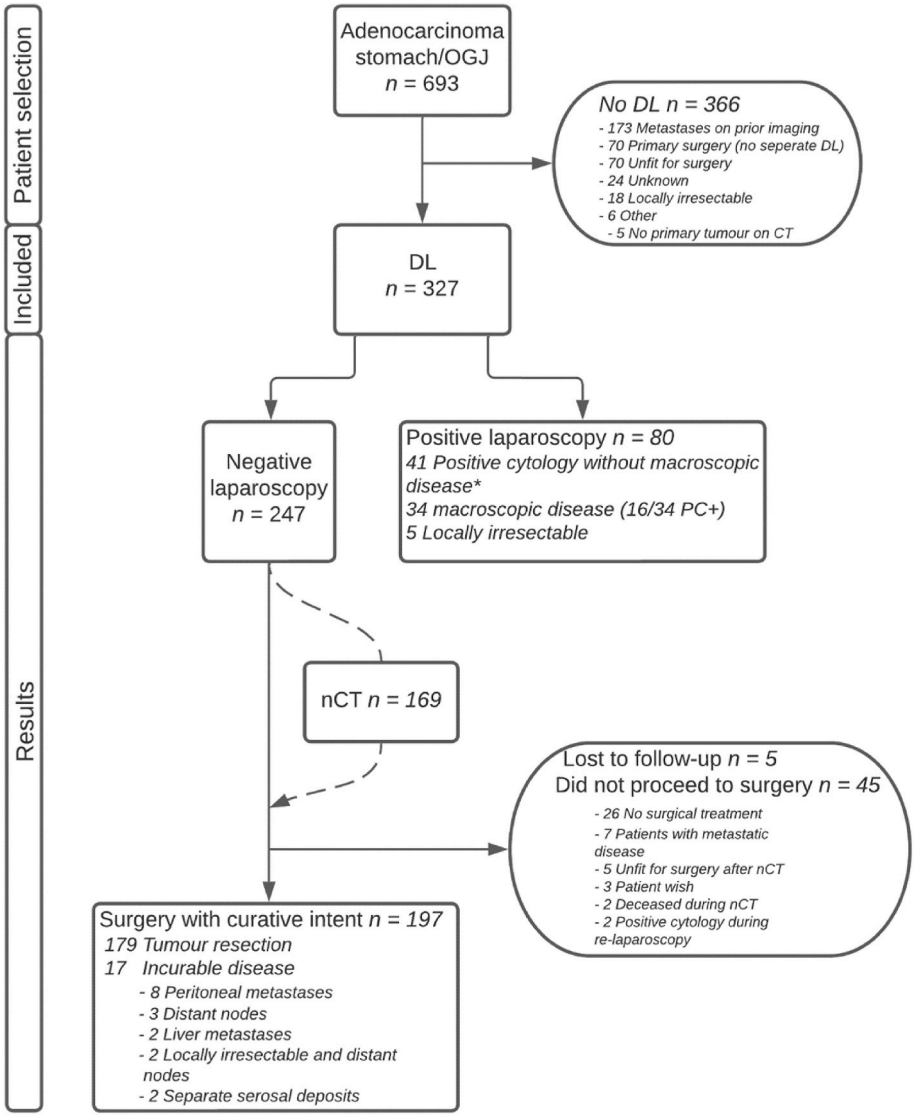

Fig. 1. Study flowchart
OGJ oesophagogastric junction *DL* diagnostic laparoscopy *CT* computed tomography *PC* + positive peritoneal cytology *nCT* neoadjuvant chemotherapy
* See Fig. 2 for treatment of patients with positive cytology without macroscopic disease.

[28,29]. False negatives are inherent to a diagnostic test, but these rates of incurable disease raise the question if current restaging with CT is sufficient to assess the response after chemotherapy as interval metastases may develop. A re-laparoscopy has been proposed to exclude occult (peritoneal) metastases and irresectable tumour growth after neoadjuvant therapy, while also allowing to assess cytology [30]. However, which patients should be selected for this is unknown and planning this in all patients may be not cost-effective.

An important finding of our study is that diffuse type carcinoma is associated with presence of peritoneal metastases. This is also reflected by a low number needed to test (three). This is in line with two European studies that reported that diffuse type tumours were associated with the presence of peritoneal disease during DL in Western patients [31,32]. However, current guidelines do not include diffuse type histology as an indication for performing a DL. Our data suggest that diffuse type carcinoma are associated with peritoneal disease, irrespective of cT or cN stage. This underlines the importance of reporting the histological subtype as performing a DL should be considered in patients with diffuse type gastric cancer. Besides serosal involvement and tumour histology, factors such as lymphovascular invasion, perineural growth, presence of signet ring cells and HER-2 neu status are known to be of prognostic factors [33–36]. These may also aid in selecting patients with a high risk of peritoneal metastases, particularly in patients with early-stage cT1-2 disease where the benefit of DL seems less. Both centres routinely performed DL in all patients, including early stage GC, unless endoscopic (sub)mucosal resection was performed. As this is not recommended by most guidelines, this may undermine the external validity of this study [7,37,38]. However, the yield of DL in GC patients with limited cT1-2 disease was 16% (4 of 25; three patients with macroscopic metastases, one patient with PC+). As current clinical staging modalities understage up to a quarter of all patients, in particular those with poor histology and cT2 disease, further investigation may be required to determine the role of the DL in cT1-2 GC patients [39].

In addition, we found that WHO performance score and unknown nodal status (Nx) were associated with peritoneal disease. The latter has not been previously reported as a predictor, but perhaps could be explained by a higher disease burden, complicating radiological assessment and accurate documentation [40]. A possible explanation for the predictive value of WHO performance status could be that patients with more advanced disease present in poorer physical condition due to weight loss and fatigue, both symptoms of peritoneal dissemination that are well known [41,42].

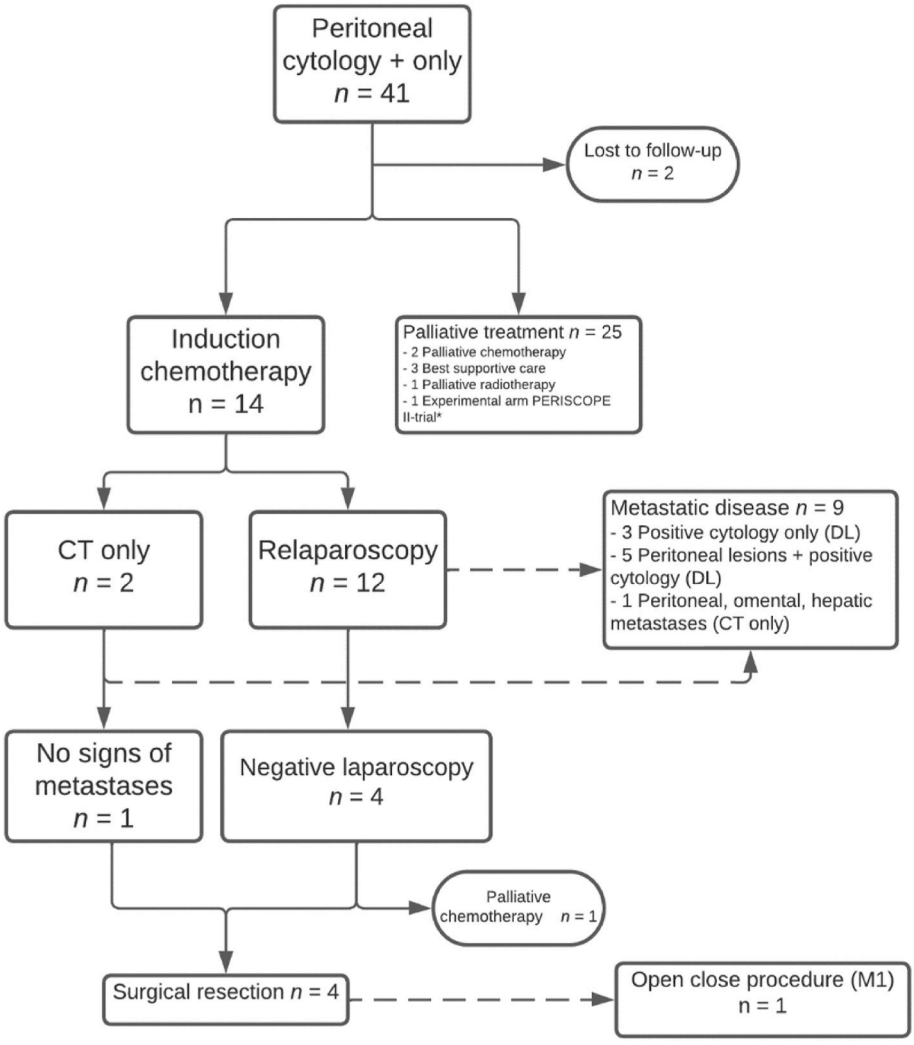

Fig. 2. Flowchart – treatment of patients with peritoneal cytology without macroscopic metastatic disease *CT* computed tomography *DL* diagnostic laparoscopy *PERISCOPE-II trial [19].

Table 3
Multivariable logistic regression analysis – peritoneal disease[a].

Variables	aOR	Multivariable analysis[b]	p-value
		CI (95%)	
Age, per year	0.97	0.94–0.99	**0.010**
WHO PS			
WHO 0-1	Ref.		
WHO 2-3	2.65	1.21–5.80	**0.015**
Tumour histology (Lauren)			
Intestinal	Ref.		
Diffuse	2.49	1.08–5.70	**0.032**
Mixed	2.59	0.50–13.49	0.256
cN stage			
N0	Ref.		
Nx	4.38	1.64–11.67	**0.003**
N1-3	1.00	0.51–1.97	0.996
cT stage			
T1-3	Ref.		
Tx	0.83	0.27–2.53	0.744
T4	2.16	1.12–4.17	**0.022**

aOR Adjusted odds ratio *CI* Confidence interval *WHO PS* World Health Organization performance status.
Bold values indicate a *p*-value of <0.05.
[a] Defined as macroscopic peritoneal metastases or peritoneal washings with free cancer cells on cytology.
[b] Results were pooled according to Rubin's rules after multiple imputation.

Table 4
Number needed to test stratified according to tumour characteristics[a].

Tumour characteristics	NNT[a]
cT1-2	6.25
cT3-4	4.15
cN1-3	4.56
cN0	4.95
cT1-2N0	18
Diffuse type	3
Intestinal type	5.53

NNT number needed to test.
[a] NNT = 1/(number of patients with a positive diagnosis/total number of patients tested).

This is one of the largest studies evaluating the yield of DL in GC patients in a European cohort. Our study included patients from recent years and a short three-year time span, minimizing the influence of evolving treatment practices on outcomes. However, the retrospective nature of this study introduces the risk of bias, such as variation in the execution of DL. This may have affected the reported yield, but currently no guidelines or consensus exists, especially on how to perform lavage for cytological assessment [43]. A European Delphi consensus study is currently underway aiming to standardize DL and determine its quality

indicators. This cohort sets a reference as standardizing the DL may improve the detection rate of peritoneal disease. Additionally, a substantial number of patients (20%; $n = 45$) did not proceed to gastrectomy after a negative laparoscopy due to various reasons, which may have allowed some attrition bias. Only in seven patients this was due to metastatic disease, which was proportionate to a recent study by Borgstein et al. [28] Moreover, cT-categories, serosal involvement being associated with peritoneal metastases, were similar. Finally, it must be noted that for half of the included patients, some histological data were missing. We used multiple imputation to handle missing data and limit bias in the logistic regression analysis.

Despite advanced imaging, the yield of the DL remains high (24.5%) and often leads to a change in oncological treatment. Although further investigation may be required to selectively perform DL in patients with cT1-2 disease, performing a DL in patients with diffuse type carcinoma should be considered, irrespective of cT and cN categories.

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None.

Availability of data

The datasets used and analysed will be available upon reasonable request.

CRediT authorship contribution statement

S.J.M. van Hootegem: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **J. Chmelo:** Formal analysis, Writing – review & editing. **P.C. van der Sluis:** Conceptualization, Resources, Writing – review & editing. **S.M. Lagarde:** Resources, Writing – review & editing. **A.W. Phillips:** Resources, Writing – review & editing. **B.P.L. Wijnhoven:** Conceptualization, Resources, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2024.108233.

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