

# Gastric and gastroesophageal junction cancer: Risk factors and prophylactic treatments for prevention of peritoneal recurrence after curative intent surgery

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## Abstract

**Aim:** Relapse after curative treatment for advanced gastric cancer, and especially peritoneal recurrence, is very common and has a dismal prognosis. The aim of this review is to summarize existing evidence regarding risk factors and prophylactic treatments intending to prevent peritoneal recurrence.

**Methods:** A structured search of relevant studies was conducted in MEDLINE, Embase, and the Cochrane Library.

**Results:** The main risk factors identified are advanced pathological T-stage ( $pT \geq 3$ ), regional lymph node involvement, diffuse/poorly cohesive type tumor, poorly differentiated cancer, and positive peritoneal wash cytology. Systemic chemotherapy in the perioperative or adjuvant setting improves survival for the patients but despite this peritoneal recurrence remains a common and yet an unsolved clinical problem. Different approaches of intraperitoneal chemotherapy such as hyperthermic intraperitoneal chemotherapy and early postoperative intraperitoneal chemotherapy have shown promising results as prophylactic treatments aiming to prevent peritoneal recurrence.

**Conclusion:** Future studies are warranted to find safe and effective treatments to prevent peritoneal recurrence.

## KEYWORDS

gastrectomy, peritoneal neoplasms, risk factors and chemoprevention, stomach neoplasms

## 1 | INTRODUCTION

Gastric cancer is the fifth most commonly diagnosed cancer and the fourth most common cause of cancer death worldwide.<sup>1</sup> A majority of patients are diagnosed at advanced stages and approximately 40% of the patients are diagnosed up-front with metastatic disease.<sup>2</sup> Overall survival after radical gastrectomy has improved over the years due to advances in oncological and surgical treatment. However, the relapse rate remains high at around 40% and

an increase in peritoneal recurrence has been described in recent years.<sup>3</sup> Several studies have shown that approximately 15%-17% of patients develop peritoneal carcinomatosis after curative gastrectomy.<sup>3-5</sup> Patients with peritoneal metastases have a very poor prognosis and their quality of life is also severely compromised as a result of refractory ascites, progressive bowel obstruction, and abdominal pain.<sup>2,6</sup>

Peritoneal carcinomatosis remains an essential oncological challenge since systemic chemotherapy has a limited efficacy.<sup>7</sup>

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This could be due to a weak penetration of chemotherapy agents into the peritoneum because of low intraperitoneal blood flow, subsequent hypoxic tumor cells with low apoptotic potential, and the plasma-peritoneal barrier.<sup>8</sup> Different methods of intraperitoneal administration of cytotoxic drugs such as hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy (EPIC) have been applied in order to prevent peritoneal carcinomatosis after curative intent surgery. Intraperitoneal chemotherapy has the theoretic advantages of delivering very high loco-regional drug concentration with very limited systemic cytotoxicity.<sup>9,10</sup> More recently, pressurized intraperitoneal aerosol chemotherapy (PIPAC) has demonstrated therapeutic potential with optimized drug distribution, very low procedure-related complications, improved patient tolerance, and quality of life.<sup>10,11</sup> PIPAC has until now only been used in the palliative setting for patients with confirmed peritoneal metastases. There is however an ongoing Scandinavian trial assessing the safety of PIPAC in conjunction with laparoscopic D2 gastrectomy (NCT-number NCT04047004) in patients with high risk of peritoneal recurrence. Results from this trial are expected during 2022.

The aim of this comprehensive review is to summarize current evidence regarding risk factors for development of peritoneal recurrence and therapeutic options for prevention of peritoneal recurrence after curative intent surgery for locally advanced gastric cancer.

## 2 | MATERIALS AND METHODS

For the assessment of risk factors for peritoneal carcinomatosis, we conducted a structured search in MEDLINE, Embase, and the Cochrane Library including the terms "peritoneal carcinomatosis" AND "gastric cancer" AND "gastrectomy" AND "risk factor." For the identification of potential preventive treatments, we performed a structured search in MEDLINE, Embase, and the Cochrane Library using the terms "survival OR relapse OR recurrence" AND "gastric cancer OR gastroesophageal junction cancer" AND "postoperative OR adjuvant" AND "chemotherapy OR chemoradiotherapy OR immunotherapy OR intraperitoneal chemotherapy." For systemic treatment options, only large randomized controlled trials (RCTs) published after 2000 were included. Furthermore, for intraperitoneal treatment options, we performed an additional search in MEDLINE using the terms "gastric cancer OR gastroesophageal junction cancer" AND "intraperitoneal" AND "chemotherapy" AND "adjuvant OR preventive OR prophylactic." The abovementioned search was limited to RCTs, meta-analyses, and high-quality cohort studies with control group. Only studies with full-text available in English were included. Additional studies were identified by screening of reference lists. Details of the included studies are presented in [Tables 1 and 2](#).

## 3 | RESULTS

### 3.1 | Risk factors for peritoneal recurrence after curative intent surgery

#### 3.1.1 | Histopathological factors

Serosal invasion has been found to be a risk factor for peritoneal recurrence in two prospective studies<sup>4,5</sup> and two retrospective studies.<sup>12,13</sup> In other studies, pT3-4 tumors were associated with increased risk for developing peritoneal recurrence.<sup>3,14-17</sup> The 6th edition of the American Joint Committee on Cancer (AJCC) staging system was mostly used where serosal invasion was classified as T3. Later studies using the 7th AJCC edition where serosal invasion was defined as T4a showed increased risk for developing peritoneal recurrence in pT4 tumors.<sup>18-21</sup> Macroscopic serosal invasion has been associated with peritoneal recurrence, regardless of pathological T-stage.<sup>20</sup> Furthermore, positive lymph node involvement has been identified as an independent risk factor of peritoneal recurrence,<sup>3,4,13,15,16,20,22,23</sup> unrelated to T-stage. As there is a clear risk of residual confounding from advanced T-stage and other factors in these studies, it may be questioned whether N-stage is an independent risk factor or if the association described above is mainly attributable to unadjusted confounding.

Diffuse/infiltrative tumors have been found to have increased risk of developing peritoneal recurrence.<sup>4,14,16,18,20,24,25</sup> Signet ring cell carcinoma, which is a subtype of diffuse/poorly cohesive type carcinoma, has been linked to peritoneal recurrence.<sup>3,26</sup> Moreover, undifferentiated/poorly differentiated gastric carcinoma is also associated with increased risk for developing peritoneal recurrence.<sup>3,13,15</sup> As diffuse/poorly cohesive carcinomas are poorly differentiated there is great overlap and it is therefore difficult to determine whether poor differentiation is an independent risk factor, or if the effect is mainly attributable to the diffuse and infiltrative growth pattern. Some other pathological features associated with peritoneal recurrence are venous invasion,<sup>16</sup> lymphovascular invasion,<sup>24</sup> and peritumoral desmoplasia.<sup>26</sup> Most of the histopathological findings are independent of T- and N-stage. Borrmann type 4 is macroscopically determined diffusely infiltrating tumor and has been identified as a risk factor for peritoneal recurrence.<sup>12,16</sup> Linitis plastica, a severe form of Borrmann type 4, has been found to increase the risk for peritoneal recurrence in signet ring cell carcinomas.<sup>22</sup> In addition, scirrhous stromal reaction has been correlated with increased risk of peritoneal recurrence.<sup>24</sup> Since Borrmann type 4 to a very large extent is the macroscopic manifestation of histologically diffuse/poorly cohesive carcinoma, it is likely to represent the same biological risk factor for peritoneal metastasis.

#### 3.1.2 | Other tumor-related factors

Tumor location has been studied in relation to peritoneal recurrence, but the reports are ambiguous. In two studies, distal tumors

TABLE 1 Summary of studies on risk factors for peritoneal recurrence after curative intent surgery

Title	Authors, year	Region	Study design	Cohort size	Risk factors of peritoneal recurrence
Incidence, time course, and independent risk factors for metachronous peritoneal carcinomatosis of gastric origin – a longitudinal experience from a prospectively collected database of 1108 patients	Seyfried et al, 2015 <sup>3</sup>	Germany	Retrospective	550 patients	Locally advanced tumor stage (pT3-4) <sup>a</sup> , pN-stage (pN $\geq$ 1) <sup>a</sup> , signet ring cells <sup>a</sup> and undifferentiated/poorly differentiated tumor <sup>a</sup>
Prospective study of peritoneal recurrence after curative surgery for gastric cancer	Roviello et al, 2003 <sup>4</sup>	Italy	Prospective	441 patients	Serosal invasion <sup>a</sup> , pN-stage (pN $\geq$ 1) <sup>a</sup> , diffuse type according to Lauren <sup>a</sup> and tumor size <sup>a</sup>
Pathological serosa and node-based classification accurately predicts gastric cancer recurrence risk and outcome, and determines potential and limitation of a Japanese-style extensive surgery for Western patients: A prospective with quality control 10-y follow-up study	Roukos et al, 2001 <sup>5</sup>	Greece	Prospective	151 patients	Serosal invasion
Risk factors which predict pattern of recurrence after curative surgery for patients with advanced gastric cancer	Moriguchi et al, 1992 <sup>12</sup>	Japan	Retrospective	405 patients	Serosal invasion <sup>a</sup> and Borrmann type 4 <sup>a</sup>
Recurrence following curative resection for gastric carcinoma	Yoo et al, 2000 <sup>13</sup>	Korea	Retrospective	2328 patients	Serosal invasion <sup>a</sup> , pN-stage (pN $\geq$ 1) <sup>a</sup> , undifferentiated/poorly differentiated tumor <sup>a</sup> , infiltrative or diffuse gross type <sup>a</sup> , total gastrectomy, <sup>a</sup> and young age (<50 y) <sup>a</sup>
Patterns of initial recurrence in completely resected gastric adenocarcinoma	D'Angelica et al, 2004 <sup>14</sup>	United States	Retrospective	1172 patients	Locally advanced tumor stage (pT3-4) <sup>a</sup> , diffuse type according to Lauren, <sup>a</sup> distal tumors, <sup>a</sup> and female gender <sup>a</sup>
Prediction of tumor recurrence after curative resection in gastric carcinoma based on bcl-2 expression	Wu et al, 2014 <sup>15</sup>	China	Retrospective	449 patients	Locally advanced tumor stage (pT3-4) <sup>a</sup> , pN-stage (pN $\geq$ 1) <sup>a</sup> , undifferentiated/poorly differentiated tumor <sup>a</sup> , and bcl-2 in tumor tissue <sup>a</sup>
Factors predicting peritoneal recurrence in advanced gastric cancer: implication for adjuvant intraperitoneal chemotherapy	Lee et al, 2014 <sup>16</sup>	Korea	Retrospective	805 patients	Locally advanced tumor stage (pT3-4) <sup>a</sup> , pN-stage (pN3) <sup>a</sup> , venous invasion <sup>a</sup> , infiltrative type according to Ming <sup>a</sup> and Borrmann type 4 <sup>a</sup>
Lauren histologic type is the most important factor associated with pattern of recurrence following resection of gastric adenocarcinoma	Lee et al, 2018 <sup>17</sup>	USA	Retrospective	957 patients	Locally advanced tumor stage (pT3-4) <sup>a</sup> , diffuse type according to Lauren <sup>a</sup> , distal tumor location <sup>a</sup> , and female gender <sup>a</sup>
Mesothelin expression is a predictive factor for peritoneal recurrence in curatively resected stage III gastric cancer	Shin et al, 2019 <sup>18</sup>	Korea	Retrospective	958 patients	Locally advanced tumor stage III <sup>a</sup> , diffuse type according to Lauren <sup>a</sup> and mesothelin in tumor tissue <sup>a</sup>
Increase in peritoneal recurrence induced by intraoperative hemorrhage in gastrectomy	Arita et al, 2015 <sup>19</sup>	Japan	Retrospective	540 patients	pT-stage (pT4 vs pT2-3) <sup>a</sup> , female gender <sup>a</sup> , and large intraoperative bleeding

TABLE 1 (Continued)

Title	Authors, year	Region	Study design	Cohort size	Risk factors of peritoneal recurrence
Development of a risk-scoring system to evaluate the serosal invasion for macroscopic serosal invasion positive gastric cancer patients	Wang et al, 2018 <sup>20</sup>	China	Retrospective	1301 patients	pT-stage (pT4a vs pT3) <sup>a</sup> , macroscopic serosal invasion <sup>a</sup> , pN-stage (pN $\geq$ 1) <sup>a</sup> , diffuse type according to Lauren <sup>a</sup> and Borrmann type <sup>a</sup>
Metabolomic profiling of gastric cancer tissues identified potential biomarkers for predicting peritoneal recurrence	Kaji et al, 2020 <sup>21</sup>	Japan	Prospective	140 patients	pT stage (pT4 vs pT1-3) <sup>a</sup> , $\beta$ -Ala in tumor tissue <sup>a</sup>
Risk factors of peritoneal recurrence in eso-gastric signet ring cell adenocarcinoma: Results of a multicentre retrospective study	Honoré et al, 2013 <sup>22</sup>	France	Retrospective	424 patients	pT-stage (pT $\geq$ 3) <sup>a</sup> , pN-stage (pN $\geq$ 1) <sup>a</sup> and linitis plastica <sup>a</sup> in signet ring cell cancer
Risk factors for peritoneal recurrence in stage II/III gastric cancer patients who received S-1 adjuvant chemotherapy after D2 gastrectomy	Aoyama et al, 2012 <sup>23</sup>	Japan	Retrospective	100 patients	pN-stage (pN3) <sup>a</sup> and tumor size $\geq$ 7 cm <sup>a</sup>
Factors affecting recurrence in node-negative advanced gastric cancer	Huang et al, 2009 <sup>24</sup>	Taiwan	Retrospective	372 patients	Serosal invasion <sup>a</sup> , diffuse type according to Lauren <sup>a</sup> , lymphovascular invasion <sup>a</sup> and schirrous stromal reaction <sup>a</sup> in node-negative tumors
Tumor infiltrative pattern predicts sites of recurrence after curative gastrectomy for stages 2 and 3 gastric cancer	Kanda et al, 2016 <sup>25</sup>	Japan	Retrospective	785 patients	Infiltration growth pattern c (INFc) <sup>a</sup> , tumor size $\geq$ 5 cm <sup>a</sup>
Predictive factors for survival and recurrence rate in patients with node-negative gastric cancer—a European single-centre experience	Dittmar et al, 2015 <sup>26</sup>	Germany	Retrospective	228 patients	pT-stage (pT $\geq$ 3) <sup>a</sup> , peritumoral desmoplasia <sup>a</sup> , and signet ring cells <sup>a</sup> in node-negative tumors
Role of serum tumor markers in monitoring for recurrence of gastric cancer following radical gastrectomy	Choi et al, 2006 <sup>27</sup>	Korea	Case-control study	104 patients	$\uparrow$ preoperative AFP and $\uparrow$ postoperative CA 19-9
Preoperative total cholesterol-lymphocyte score as a novel immunonutritional predictor of survival in gastric cancer	Matsubara et al, 2019 <sup>28</sup>	Japan	Retrospective	224 patients	$\downarrow$ prognostic nutritional index (PNI)
Reduced expression of exosomal miR-29s in peritoneal fluid is a useful predictor of peritoneal recurrence after curative resection of gastric cancer with serosal involvement	Ohzawa et al, 2020 <sup>29</sup>	Japan	Retrospective	85 patients	$\downarrow$ miR-29b in peritoneal lavage
Intraoperative blood loss is a critical risk factor for peritoneal recurrence after curative resection of advanced gastric cancer	Kamei et al, 2009 <sup>30</sup>	Japan	Retrospective	146 patients	Large intraoperative bleeding <sup>a</sup>
Clinicopathological analysis and prognostic significance of peritoneal cytology in Chinese patients with advanced gastric cancer	Jiang et al, 2011 <sup>31</sup>	China	Retrospective	139 patients	Positive peritoneal cytology
Prognostic significance of peritoneal lavage cytology in gastric cancer in Singapore	Chuwa et al, 2005 <sup>32</sup>	Singapore	Prospective	142 patients	Positive peritoneal cytology
Surgery-induced peritoneal cancer cells in patients who have undergone curative gastrectomy for gastric cancer	Takebayashi et al, 2014 <sup>33</sup>	Japan	Retrospective	102 patients	Positive peritoneal cytology

<sup>a</sup>Adjusted for confounding.

have shown increased risk for peritoneal recurrence,<sup>14,17</sup> while in another study, total gastrectomy was identified as a risk factor.<sup>13</sup> Furthermore, tumor size has been associated with peritoneal recurrence. This risk increased in the larger tumor groups, but the definition has varied.<sup>4,23,25</sup> Nonetheless, large tumor size is likely to be a proxy for generally more advanced disease.

### 3.1.3 | Biomarkers

The tumor marker alpha fetoprotein (AFP) may predict peritoneal recurrence after gastrectomy if elevated preoperatively, while elevated cancer-associated antigen 19-9 (CA 19-9) postoperatively was predictive for peritoneal recurrence.<sup>27</sup> Other less commonly used biomarkers associated with peritoneal recurrence include prognostic nutritional index (PNI, an immune-nutritional marker),<sup>28</sup>  $\beta$ -Ala (an anti-tumoral amino acid),<sup>21</sup> miR-29b (a microRNA tumor suppressor),<sup>29</sup> mesothelin (a tumor-associated antigen),<sup>18</sup> and bcl-2 (an oncogene indicating less aggressive tumor growth).<sup>15</sup>

### 3.1.4 | Other clinical factors

Patients below the age of 50<sup>13</sup> and female patients may have higher risk for developing peritoneal recurrence.<sup>14,17,19</sup> A higher proportion of diffuse carcinomas in younger and female patients may partly explain these findings. Additionally, plasma may enhance the ability of gastric cancer cells to adhere to mesothelial cells and promote peritoneal dissemination<sup>19</sup> and subsequently large intraoperative bleeding during gastrectomy has been linked to increased incidence of peritoneal recurrence.<sup>19,30</sup> Positive peritoneal cytology is a strong predictor of peritoneal recurrence, as up to 82% of patients with positive cytology develop peritoneal recurrence<sup>31</sup> and the risk may be 15 times higher compared to patients with negative cytology.<sup>32</sup> Cancer cells may also be spilled during resection and the spreading of viable cancer cells into the abdominal cavity is increased in advanced tumors.<sup>33</sup>

## 3.2 | Prophylactic treatment of peritoneal recurrence after curative intent surgery

### 3.2.1 | Systemic treatment

Various studies have tried to clarify the efficacy of perioperative chemotherapy in conjunction with curative intent surgery and to find the most effective treatment. Most of the large RCTs have focused on overall survival (OS) and relapse-free survival (RFS) and did not investigate specific recurrence patterns. Thus, the effects of systemic chemotherapy on prevention of peritoneal recurrence remains unclear in most studies. In the Macdonald study, of patients treated with adjuvant Fluorouracil and Leucovorin in combination with radiotherapy 72% had improved OS (36 vs 27 months,  $P = .005$ )

as well as RFS (30 vs 19 months,  $P < .001$ ), compared to patients treated with surgery only. Regional relapse, typically abdominal carcinomatosis, developed among 65% of the patients treated with adjuvant chemoradiotherapy, while the rate of regional relapse was 72% among the patients treated with surgery only.<sup>34</sup> Later, the MAGIC study reported positive effects of perioperative chemotherapy with Epirubicin, Cisplatin, and Fluorouracil (ECF) showing improved OS (HR 0.75, 95% CI 0.60-0.93) and progression-free survival (HR 0.66, 95% CI 0.52-0.81).<sup>35</sup> Subsequently, the ACTS-GC study reported improved OS (HR 0.669, 95% CI 0.540-0.828) and RFS (HR 0.653, 95% CI 0.537-0.793), as well as decreased incidence of peritoneal recurrence (HR 0.687, 95% CI 0.511-0.925) by adjuvant S-1 chemotherapy.<sup>36</sup> In the CLASSIC study, patients who received adjuvant Capecitabine and Oxaliplatin (CapOx) following D2 gastrectomy had improved OS (HR 0.66, 95% CI 0.51-0.85) and disease-free survival (DFS, HR 0.58, 95% CI 0.47-0.72) compared to patients treated with surgery only. Peritoneal recurrence occurred in 10.2% of patients in the adjuvant treatment group and in 11.7% of patients in the surgery only group.<sup>37</sup> Further on, Al-Batran et al<sup>38</sup> performed an RCT which showed that perioperative Docetaxel, Oxaliplatin, Leucovorin, and Fluorouracil (FLOT) was superior to perioperative Epirubicin, Cisplatin, and Fluorouracil/Capecitabine (ECF/ECX) in terms of OS (50 months vs 35 months,  $P = .012$ ) and DFS (30 months vs 18 months,  $P = .0036$ ). The CRITICS trial reported shortened OS (HR 1.62,  $P = .0004$ ) and a higher rate of peritoneal recurrence among patients who per protocol received postoperative chemoradiotherapy compared to patients who received postoperative chemotherapy (2-year cumulative incidence, 11% vs 4%,  $P = .005$ ).<sup>39</sup> In a recent RCT, Zhang et al showed superior 3-year DFS using perioperative Oxaliplatin and S-1 (SOX) compared to adjuvant Capecitabine and Oxaliplatin (CapOx; HR 0.77, 95% CI 0.61-0.97).<sup>40</sup>

Immunochemotherapy in the adjuvant setting for patients with locally advanced gastric cancer has also been studied. Jeung et al<sup>41</sup> used systemic polyadenylic-polyuridylic acid (poly A:U), which is believed to activate NK cells, in addition to Fluorouracil and Adriamycin, and found improved OS (68.4% vs 52.4%,  $P = .013$ ) and RFS (68.3% vs 52.1%,  $P = .005$ ), as well as a slightly lower rate of peritoneal recurrence (50.0% vs 53.2%) when comparing immunochemotherapy to chemotherapy alone.

### 3.2.2 | Intraperitoneal treatment

Different techniques of intraperitoneal treatment have been studied for prevention of peritoneal recurrence in patients undergoing curative intent surgery for locally advanced gastric cancer. Normothermic intraperitoneal chemotherapy (NIPEC) has been used in the adjuvant setting. While some studies failed to show positive effects of NIPEC on survival or recurrence,<sup>42,43</sup> other studies have reported survival benefit.<sup>44,45</sup> For example, the AMC0101 study showed that intraperitoneal Cisplatin and early initiation of adjuvant chemotherapy with Mitomycin C (MMC), Doxifluridine, and Cisplatin improved OS (HR 0.71, 95% CI 0.53-0.95) and decreased

TABLE 2 Summary of studies on prophylactic treatment of peritoneal recurrence after curative intent surgery

Intervention	Authors, year	Region	Study design	Study size	Effects of intervention
Surgery + adjuvant CRT (Fluorouracil + Leucovorin + 45 Gy) vs surgery alone	Macdonald et al, 2001 <sup>34</sup>	United States	RCT	CRT (n = 281) Surgery alone (n = 275)	↑ OS (36 vs 27 mo, P = .005) ↑ RFS (30 vs 19 mo, P < .001) ↓ Regional relapse (typically carcinomatosis, 65% vs 72%)
Perioperative CT (Epirubicin + Cisplatin + Fluorouracil) + surgery vs surgery only (MAGIC trial)	Cunningham et al, 2006 <sup>35</sup>	UK, Netherlands, Germany, Brazil, Singapore, and New Zealand	RCT	CT (n = 250) Surgery alone (n = 253)	↑ OS (HR 0.75, 95% CI 0.60-0.93, P = .009) ↑ PFS (HR 0.66, 95% CI 0.52-0.81, P < .001)
Surgery + adjuvant CT (S-1) vs surgery alone (ACTS-GC study)	Sasako et al, 2011 <sup>36</sup>	Japan	RCT	CT (n = 529) Surgery alone (n = 530)	↑ OS (HR 0.669, 95% CI 0.540-0.828) ↑ RFS (HR 0.653, 95% CI 0.537-0.793) ↓ Peritoneal recurrence rate (HR 0.687, 95% CI 0.511-0.925)
Surgery + adjuvant CT (Capecitabine + Oxaliplatin) vs surgery alone (CLASSIC study)	Noh et al, 2014 <sup>37</sup>	South Korea, China, and Taiwan	RCT	CT (n = 520) Surgery alone (n = 515)	↑ OS (HR 0.66, 95% CI 0.51-0.85, P = .0029) ↑ DFS (HR 0.58, 95% CI 0.47-0.72, P < .0001) 10.2% peritoneal recurrence in the CT group and 11.7% in the surgery alone group
Perioperative FLOT (Docetaxel + Oxaliplatin + Leucovorin + Fluorouracil) + surgery vs perioperative ECF/ECX (Epirubicin + Cisplatin + Fluorouracil/Capecitabine) + surgery	Al-Batran et al, 2019 <sup>38</sup>	Germany	RCT	FLOT (n = 352) ECF/ECX (n = 353)	↑ OS (50 mo vs 35 mo, HR 0.77, P = .012) ↑ DFS (30 mo vs 18 mo, HR 0.75, P = .0036)
Neoadjuvant CT (Epirubicin + Cisplatin/Oxaliplatin + Capecitabine) + surgery + adjuvant CRT (Cisplatin + Capecitabine + 45 Gy) vs perioperative CT (Epirubicin + Cisplatin/Oxaliplatin + Capecitabine) + surgery (CRITICS study)	de Steur et al, 2020 <sup>39</sup>	The Netherlands, Sweden, and Denmark	RCT	Neoadjuvant CT + adjuvant CRT (n = 245) Perioperative CT (n = 233)	↓ OS (HR 1.62, 95% CI 1.24-2.12, P = .0004) ↑ Peritoneal recurrence rate (11% vs 4%, P = .005)
Perioperative SOX (Oxaliplatin + S-1) + surgery vs surgery + adjuvant CapOx (Capecitabine + Oxaliplatin) vs surgery + adjuvant SOX	Zhang et al, 2021 <sup>40</sup>	China	RCT	Perioperative SOX (n = 337) Adjuvant CapOx (n = 345) Adjuvant SOX (n = 350)	↑ DFS perioperative SOX vs adjuvant CapOx (HR 0.77, 95% CI 0.67-0.91, P = .028) No difference in DFS adjuvant SOX vs adjuvant CapOx (HR 0.86, 95% CI 0.68-1.07, P = .17)
Surgery + adjuvant ICT (polyadenylic-polyuridylic acid + Fluorouracil and Adriamycin) vs surgery + adjuvant CT (Fluorouracil and Adriamycin)	Jeung et al, 2008 <sup>41</sup>	South Korea	RCT	ICT (n = 138) CT (n = 142)	↑ OS (68.4% vs 52.4%, P = .013) ↑ RFS (68.3% vs 52.1%, P = .005) ↓ Peritoneal recurrence rate (50.0% vs 53.2%)

(Continues)



TABLE 2 (Continued)

Intervention	Authors, year	Region	Study design	Study size	Effects of intervention
Surgery + NIPEC (carbon-adsorbed Mitomycin) vs surgery alone	Rosen et al, 1998 <sup>42</sup>	Austria	RCT	NIPEC (n = 46) Surgery alone (n = 45)	No difference in OS (738.9 vs 515.4 d, P = .44) or RFS (554.8 vs 380.3 d, P = .48) ↑ Postoperative complications (35% vs 12%, P < .02)
Surgery + NIPEC (Cisplatin) + adjuvant CT (Cisplatin + Fluorouracil + oral Fluorouracil) vs surgery alone	Miyashiro et al, 2011 <sup>43</sup>	Japan	RCT	NIPEC + CT (n = 135) Surgery alone (n = 133)	No difference in OS (62.0% vs 60.9%, P = .482) or RFS (57.5% vs 55.6%, P = .512)
Surgery + NIPEC (Mitomycin C) + high dose adjuvant CT (Cisplatin + Tegafur + Uracil) vs surgery + low dose adjuvant CT (Cisplatin + Tegafur + Uracil) vs surgery + low dose adjuvant CT (Cisplatin + Tegafur + Uracil)	Shimoyama et al, 1999 <sup>44</sup>	Japan	RCT	n = 87	↑ OS in the NIPEC + high dose adjuvant CT group vs the NIPEC + low dose adjuvant CT group (P < .05) vs the low dose adjuvant CT group (P = .049), respectively
Surgery + NIPEC (Cisplatin) + adjuvant CT (Mitomycin C, Doxifluridine and Cisplatin) vs surgery + adjuvant CT (Mitomycin C and Doxifluridine) (AMC0101 trial)	Kang et al, 2014 <sup>45</sup>	South Korea	RCT	NIPEC + CT (n = 263) CT (n = 258)	↑ OS (HR 0.71, 95% CI 0.53-0.95, P = .02) ↑ RFS (HR 0.70, 95% CI 0.54-0.90, P = .006) ↓ Peritoneal recurrence rate (17% vs 23%, P = .08)
Surgery + HIPEC (Mitomycin C or Fluorouracil) with/without adjuvant CT vs surgery with/without adjuvant CT	Sun et al, 2012 <sup>47</sup>	Japan and China	Meta-analysis	HIPEC (n = 518) Surgery (n = 544)	↑ OS (RR = 0.73, 95% CI 0.64-0.83, P < .00001) ↓ Peritoneal recurrence rate (RR = 0.45, 95% CI 0.28-0.72, P = .001)
Surgery + HIPEC (Mitomycin C, combinations of Mitomycin C and Cisplatin/Etoposide, Cisplatin or Cisplatin + Fluorouracil) vs surgery alone	Desiderio et al, 2017 <sup>48</sup>	Japan, China, and Taiwan	Meta-analysis Non-RCT (n = 9)	HIPEC (n = 731) Surgery alone (n = 1079)	↑ OS at 3-y (RR = 0.71, 95% CI 0.52-0.96, P = .03) and at 5-y (RR = 0.82, 95% CI 0.70-0.96, P = .01) ↓ Peritoneal recurrence rate (RR = 0.63, 95% CI 0.45-0.88, P < .01) ↑ Postoperative complications (RR 2.17, 95% CI 1.49-3.14, P < .01)
Surgery + HIPEC (Cisplatin) + adjuvant CT (Capecitabine + Oxaliplatin) vs surgery + adjuvant CT (Capecitabine + Oxaliplatin)	Beeharry et al, 2019 <sup>49</sup>	China	RCT	HIPEC + CT (n = 40) CT (n = 40)	↑ DFS (93% vs 65%, P = .0054) ↓ Peritoneal recurrence rate (3% vs 23%, P < .05)
Surgery + HIPEC (Cisplatin) + adjuvant CT (S-1 + Oxaliplatin) vs surgery + adjuvant CT (S-1 + Oxaliplatin)	Fan et al, 2021 <sup>50</sup>	China	RCT	HIPEC + CT (n = 33) CT (n = 17)	No difference in OS (87.9% vs 100%, P = .142) or DFS (84.8% vs 88.2%, P = .986)

TABLE 2 (Continued)

Intervention	Authors, year	Region	Study design	Study size	Effects of intervention
Surgery + HIPEC (Mitomycin C, Cisplatin or Oxaliplatin) + perioperative CT vs surgery + perioperative CT (various regimens)	Diniz et al, 2019 <sup>51</sup>	Brazil	Retrospective cohort study/ propensity-score matched analysis	HIPEC + CT (n = 28) CT (n = 56)	No difference in OS (HR 0.79, 95% CI 0.38-1.6), DFS (HR 0.99, 95% CI 0.52-1.9) or recurrence pattern (P = .676)
Surgery + EPIC (Mitomycin C and Fluorouracil) vs surgery alone	Yu et al, 2001 <sup>52</sup>	South Korea	RCT	EPIC (n = 125) Surgery alone (n = 123)	↑ OS (54% vs 38%, P = .0278) ↓ peritoneal recurrence rate (15% vs 30%) ↑ Postoperative intrabdominal bleeding (10% vs 1%, P = .002) and intraabdominal sepsis (14% vs 4%, P = .008)
Surgery + HIPEC (Oxaliplatin) + perioperative CT	Glehen et al, 2014 <sup>53</sup>	France and Spain	RCT	Planning for 306 patients	Ongoing study
Neoadjuvant laparoscopic HIPEC (Paclitaxel) + neoadjuvant CT (S-1 + Oxaliplatin) + surgery + HIPEC + adjuvant CT (S-1 + Oxaliplatin) vs surgery + adjuvant CT (S-1 + Oxaliplatin)	Beeharry et al, 2020 <sup>54</sup>	China	RCT	Planning for 326 patients	Ongoing study
Negative cytology → surgery + adjuvant CT (Paclitaxel + S-1) + adjuvant intraperitoneal Paclitaxel vs surgery + adjuvant CT (S-1 + Docetaxel)	Ishigami et al, 2021 <sup>55</sup>	Japan	RCT	Planning for 300 patients	Ongoing study
Positive cytology → neoadjuvant CT (S-1 + Oxaliplatin) + neoadjuvant intraperitoneal Paclitaxel + surgery + adjuvant CT (S-1 + Paclitaxel) + adjuvant intraperitoneal Paclitaxel vs neoadjuvant CT (S-1 + Oxaliplatin) + surgery + adjuvant CT (S-1 + Docetaxel)	Kuramoto et al, 2009 <sup>56</sup>	Japan	RCT	EIPL + NIPEC (n = 30) NIPEC (n = 29) Surgery + CT (n = 29)	↑ OS (43.8% vs 4.6%, P < .0001) EIPL + NIPEC vs NIPEC ↑ OS (43.8% vs 0%, P < .0001) EIPL + NIPEC vs surgery alone ↓ peritoneal recurrence rate (40.0% vs 79.3% vs 89.7%, P < .0001) EIPL + NIPEC vs NIPEC vs surgery alone
Surgery + EIPL + adjuvant CT (S-1) vs surgery + adjuvant CT (S-1) (CCOG 1102 trial)	Misawa et al, 2009 <sup>57</sup>	Japan	RCT	EIPL + adjuvant CT (n = 145) Adjuvant CT (n = 150)	No difference in OS (HR 0.91, 95% CI 0.60-1.37, P = .634) or peritoneal recurrence rate (HR 0.92, 95% CI 0.62-1.36, P = .676)

(Continues)



TABLE 2 (Continued)

Intervention	Authors, year	Region	Study design	Study size	Effects of intervention
Surgery + EIPL + adjuvant CT (various regimens) vs surgery + adjuvant CT (various regimens) (EXPEL trial)	Yang et al, 2021 <sup>58</sup>	South Korea, China, Japan, Malaysia, Hong Kong, and Singapore	RCT	EIPL + adjuvant CT (n = 398) Adjuvant CT (n = 402)	No difference in OS (HR 1.09, 95% CI 0.78-1.52, $P = .62$ ), DFS (HR 1.12, 95% CI 0.86-1.47, $P = .40$ ) or peritoneal recurrence rate (HR 1.33, 95% CI 0.73-2.42, $P = .35$ )

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; DFS, disease-free survival; EIPL, extensive intraoperative peritoneal lavage; EPIC, early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; ICT, immunochemotherapy; NIPEC, normothermic intraperitoneal chemotherapy; OS, overall survival; PFS, progression-free survival; RCT, Randomized clinical trial; RFS, relapse-free survival.

the peritoneal recurrence rate even though the difference was not statistically significant (17% vs 23%,  $P = .08$ ), compared to adjuvant chemotherapy with MMC and Doxifluridine, in resectable gastric cancer with macroscopic serosal invasion.<sup>45</sup>

A more widely used technique is hyperthermic intraperitoneal chemotherapy (HIPEC), using hyperthermia to achieve better penetration of cytotoxic drugs into the tumor tissue and synergistic effects of some cytotoxic drugs.<sup>46</sup> While the role of HIPEC in combination with cytoreductive surgery in gastric cancer with peritoneal metastases is controversial, the results are more promising for patients without manifest peritoneal carcinomatosis undergoing curative intent resection and prophylactic HIPEC.<sup>47</sup> A meta-analysis including 10 RCTs and a total of 1062 patients with macroscopic serosal invasive gastric cancer demonstrated improved OS (RR = 0.73, 95% CI 0.64-0.83) by performing HIPEC. MMC was used in seven trials, while Fluorouracil was used in three trials. The authors found no statistically significant difference regarding postoperative complications such as bone marrow suppression, anastomotic leak, ileus, or liver dysfunction. In the two RCTs that reported peritoneal recurrence, HIPEC reduced the risk (RR = 0.45, 95% CI 0.28-0.72).<sup>47</sup> Similar effects were shown in a later meta-analysis based on nine RCTs and nine high-quality non-RCTs including a total of 1810 patients. Most of the included studies performed HIPEC using MMC but also Cisplatin, Etoposide, and Fluorouracil were used in some studies. The HIPEC group had improved OS at 3 years (RR = 0.71, 95% CI 0.52-0.96) and at 5 years (RR = 0.82, 95% CI 0.70-0.96). Also, the authors found a lower peritoneal recurrence rate in the HIPEC group (RR = 0.63, 95% CI 0.45-0.88), while risk reduction was not observed for other recurrence patterns. However, the HIPEC patients suffered from higher postoperative morbidity (RR 2.17, 95% CI 1.49-3.14), in particular renal dysfunction.<sup>48</sup> In a more recent small RCT, BeeHarry et al reported patients who underwent HIPEC with Cisplatin having a lower peritoneal recurrence rate (3% vs 23%,  $P < .05$ ) as well as a better 3-year DFS (93% vs 65%,  $P = .0054$ ), but similar postoperative morbidity burden, compared to surgery only.<sup>49</sup> However, in another recent RCT conducted by Fan et al, no survival benefit was seen for patients treated with HIPEC using Cisplatin.<sup>50</sup> This discrepancy may be attributed to a higher percentage of patients with T4 tumors in BeeHarry's study and the different regimens of adjuvant chemotherapy given in the two studies (CapOx in BeeHarry's study and SOX in Fan's study). The use of perioperative chemotherapy in combination with HIPEC has also been studied in a retrospective cohort by propensity-score matched analysis, and no differences were found regarding survival or relapse, which further questions the role of HIPEC when perioperative chemotherapy is used.<sup>51</sup>

Early postoperative intraperitoneal chemotherapy (EPIC) has been studied in an RCT using intraperitoneal MMC on postoperative day 1 followed by Fluorouracil on postoperative day 2-5 for patients with stage I-IV gastric cancer. Compared to patients who underwent surgery only, patients who underwent EPIC had improved overall survival (54% vs 38%,  $P = .0278$ ) and lower peritoneal recurrence rate (15% vs 30%), however, at the expense of increased complication

rates with intrabdominal bleeding (10% vs 1%,  $P = .002$ ) and intraabdominal sepsis (14% vs 4%,  $P = .008$ ).<sup>52</sup> There are two ongoing HIPEC trials, the European GASTROCHIP trial investigating the efficacy of intraoperative HIPEC with Oxaliplatin in addition to D1-D2 gastrectomy and perioperative chemotherapy<sup>53</sup> and the Chinese Dragon II trial studying the efficacy of neoadjuvant laparoscopic HIPEC and intraoperative HIPEC using Paclitaxel combined with perioperative chemotherapy and D2 gastrectomy.<sup>54</sup> Moreover, the ongoing PHOENIX-GC2 trial in Japan will evaluate the effects of adjuvant or perioperative administration of intraperitoneal Paclitaxel in addition to systemic chemotherapy for patients with resectable type 4 carcinomas with/without positive cytology.<sup>55</sup>

Extensive intraoperative peritoneal lavage (EIPL) is an alternative method using at least 10 liters of saline as prophylactic therapy of peritoneal metastases. In an RCT including 88 patients with resectable gastric cancer and positive cytology, patients treated with EIPL, intraperitoneal Cisplatin, and adjuvant chemotherapy (Fluorouracil) had improved OS compared to patients treated with only intraperitoneal Cisplatin and adjuvant Fluorouracil (43.8% vs 4.6%,  $P < .0001$ ), and patients treated with only adjuvant Fluorouracil (43.8% vs 0%,  $P < .0001$ ). The EIPL group also had lower incidence of peritoneal recurrence compared to the other groups (40.0% vs 79.3% vs 89.7%,  $P < .0001$ ).<sup>56</sup> However, EIPL was later evaluated in two RCTs, the CCOG 1102 trial and the EXPEL trial, including 295 and 800 patients, respectively.<sup>57,58</sup> EIPL had no survival benefit or impact on peritoneal recurrence in these two trials, and could therefore not be recommended. The later trials had larger sample sizes, mostly patients with negative peritoneal lavage and used presumably more potent adjuvant chemotherapy, which may explain the contradictory findings.

## 4 | CONCLUSION

In summary, peritoneal recurrence after curative treatment for gastric cancer is associated with histopathological, biochemical, clinical, and surgical risk factors. The main risk factors identified are advanced T-stage (T4a/T3), regional lymph node involvement, diffuse/poorly cohesive type tumor, poorly differentiated cancer, and positive peritoneal wash cytology. Systemic chemotherapy may help reduce the risk of peritoneal recurrence to some extent, but the evidence is scarce. Intraperitoneal administration of chemotherapy such as HIPEC in the adjuvant setting has been effective to prevent peritoneal recurrence, and there are ongoing studies trying to find safer and more effective intraperitoneal treatments to prevent peritoneal recurrence.

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## REFERENCES

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021;71(3):209-249. <http://dx.doi.org/10.3322/caac.21660>
- Thomassen I, van Gestel YR, van Ramshorst B, Luyer MD, Bosscha K, Nienhuijs S, et al. Peritoneal carcinomatosis of gastric origin: A population-based study on incidence, survival and risk factors. *Int J Cancer.* 2014;134(3):622-628. <http://dx.doi.org/10.1002/ijc.28373>
- Seyfried F, von Rahden BH, Miras AD, Gasser M, Maeder U, Kunzmann V, et al. Incidence, time course and independent risk factors for metachronous peritoneal carcinomatosis of gastric origin – a longitudinal experience from a prospectively collected database of 1108 patients. *BMC Cancer.* 2015;15(1). <http://dx.doi.org/10.1186/s12885-015-1081-8>
- Roviello F, Marrelli D, de Manzoni G, Morgagni P, Di Leo A, Saragoni L, et al. Prospective study of peritoneal recurrence after curative surgery for gastric cancer. *Br J Surg.* 2003;90(9):1113-1119. <http://dx.doi.org/10.1002/bjs.4164>
- Roukos DH, Lorenz M, Karakostas K, Paraschou P, Batsis C, Kappas AM. Pathological serosa and node-based classification accurately predicts gastric cancer recurrence risk and outcome, and determines potential and limitation of a Japanese-style extensive surgery for Western patients: a prospective with quality control 10-year follow-up study. *Br J Cancer.* 2001;84(12):1602-9.
- Lambert LA, Hendrix RJ. Palliative management of advanced peritoneal carcinomatosis. *Surg Oncol Clin N Am.* 2018;27(3):585-602.
- Klaver YLB, Simkens LHJ, Lemmens VEPP, Koopman M, Teerenstra S, Bleichrodt RP, et al. Outcomes of colorectal cancer patients with peritoneal carcinomatosis treated with chemotherapy with and without targeted therapy. *Eur J Surg Oncol.* 2012;38(7):617-23.
- Coccolini F, Gheza F, Lotti M, Virzì S, Iusco D, Ghermandi C, et al. Peritoneal carcinomatosis. *World J Gastroenterol.* 2013;19(41):6979-94.
- Markman M. Intraperitoneal antineoplastic drug delivery: rationale and results. *Lancet Oncol.* 2003;4(5):277-83.
- Chia DKA, So JBY. Recent advances in intra-peritoneal chemotherapy for gastric cancer. *J Gastric Cancer.* 2020;20(2):115-26.
- Alyami M, Hübner M, Grass F, Bakrin N, Villeneuve L, Laplace N, et al. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. *Lancet Oncol.* 2019;20(7):e368-77.
- Moriguchi S, Maehara Y, Korenaga D, Sugimachi K, Nose Y. Risk factors which predict pattern of recurrence after curative surgery for patients with advanced gastric cancer. *Surg Oncol.* 1992;1(5):341-6.
- Yoo CH, Noh SH, Shin DW, Choi SH, Min JS. Recurrence following curative resection for gastric carcinoma: recurrence of gastric cancer after resection. *Br J Surg.* 2000;87(2):236-42.
- D'Angelica M, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. *Ann Surg.* 2004;240(5):808-16.

15. Wu J, Liu X, Cai H, Wang Y. Prediction of tumor recurrence after curative resection in gastric carcinoma based on bcl-2 expression. *World J Surg Oncol*. 2014;21(12):40.
16. Lee J-H, Son S-Y, Lee CM, Ahn SH, Park DJ, Kim H-H. Factors predicting peritoneal recurrence in advanced gastric cancer: implication for adjuvant intraperitoneal chemotherapy. *Gastric Cancer*. 2014;17(3):529–36.
17. Lee JH, Chang KK, Yoon C, Tang LH, Strong VE, Yoon SS. Lauren histologic type is the most important factor associated with pattern of recurrence following resection of gastric adenocarcinoma. *Ann Surg*. 2018;267(1):105–13.
18. Shin S-J, Park S, Kim MH, Nam CM, Kim H, Choi YY, et al. Mesothelin expression is a predictive factor for peritoneal recurrence in curatively resected stage III gastric cancer. *Oncologist*. 2019;24(11):e1108–14.
19. Arita T, Ichikawa D, Konishi H, Komatsu S, Shiozaki A, Hiramoto H, et al. Increase in peritoneal recurrence induced by intraoperative hemorrhage in gastrectomy. *Ann Surg Oncol*. 2015;22(3):758–64.
20. Wang P, Huang J, Zhu Z, Gong B, Huang H, Duan S, et al. Development of a risk-scoring system to evaluate the serosal invasion for macroscopic serosal invasion positive gastric cancer patients. *Eur J Surg Oncol J*. 2018;44(5):600–606. <http://dx.doi.org/10.1016/j.ejso.2018.01.240>
21. Kaji S, Irino T, Kusahara M, Makuuchi R, Yamakawa Y, Tokunaga M, et al. Metabolomic profiling of gastric cancer tissues identified potential biomarkers for predicting peritoneal recurrence. *Gastric Cancer*. 2020;23(5):874–883. <http://dx.doi.org/10.1007/s10120-020-01065-5>
22. Honoré C, Goéré D, Messager M, Souadka A, Dumont F, Piessen G, et al. Risk factors of peritoneal recurrence in eso-gastric signet ring cell adenocarcinoma: Results of a multicentre retrospective study. *Eur J Surg Oncol*. 2013;39(3):235–241. <http://dx.doi.org/10.1016/j.ejso.2012.12.013>
23. Aoyama T, Yoshikawa T, Hayashi T, Kuwabara H, Mikayama Y, Ogata T, et al. Risk Factors for Peritoneal Recurrence in Stage II/III Gastric Cancer Patients Who Received S-1 Adjuvant Chemotherapy After D2 Gastrectomy. *Ann Surg Oncol*. 2012;19(5):1568–1574. <http://dx.doi.org/10.1245/s10434-011-2158-5>
24. Huang K-H, Chen J-H, Wu C-W, Lo S-S, Hsieh M-C, Li A F-Y, et al. Factors affecting recurrence in node-negative advanced gastric cancer. *J Gastroenterol Hepatol*. 2009;24(9):1522–1526. <http://dx.doi.org/10.1111/j.1440-1746.2009.05844.x>
25. Kanda M, Mizuno A, Fujii T, Shimoyama Y, Yamada S, Tanaka C, et al. Tumor Infiltrative Pattern Predicts Sites of Recurrence After Curative Gastrectomy for Stages 2 and 3 Gastric Cancer. *Ann Surg Oncol*. 2016;23(6):1934–1940. <http://dx.doi.org/10.1245/s10434-016-5102-x>
26. Dittmar Y, Schüle S, Koch A, Rauchfuss F, Scheuerlein H, Settmacher U. Predictive factors for survival and recurrence rate in patients with node-negative gastric cancer—a European single-centre experience. *Langenbecks Arch Surg*. 2015;400(1):27–35.
27. Choi SR, Jang JS, Lee JH, Roh MH, Kim MC, Lee WS, et al. Role of Serum Tumor Markers in Monitoring for Recurrence of Gastric Cancer Following Radical Gastrectomy. *Dig Dis Sci*. 2006;51(11):2081–2086. <http://dx.doi.org/10.1007/s10620-006-9166-5>
28. Matsubara D, Shoda K, Kubota T, Kosuga T, Konishi H, Shiozaki A, et al. Preoperative total cholesterol-lymphocyte score as a novel immunonutritional predictor of survival in gastric cancer. *Langenbecks Arch Surg*. 2019;404(6):743–752. <http://dx.doi.org/10.1007/s00423-019-01824-8>
29. Ohzawa H, Saito A, Kumagai Y, Kimura Y, Yamaguchi H, Hosoya Y, et al. Reduced expression of exosomal miR-29s in peritoneal fluid is a useful predictor of peritoneal recurrence after curative resection of gastric cancer with serosal involvement. *Oncol Rep*. 2020;43(4):1081–8.
30. Kamei T, Kitayama J, Yamashita H, Nagawa H. Intraoperative blood loss is a critical risk factor for peritoneal recurrence after curative resection of advanced gastric cancer. *World J Surg*. 2009;33(6):1240–6.
31. Jiang C-G, Xu Y, Wang Z-N, Sun Z, Liu F-N, Yu M, et al. Clinicopathological analysis and prognostic significance of peritoneal cytology in Chinese patients with advanced gastric cancer. *ANZ J Surg*. 2011;81(9):608–613. <http://dx.doi.org/10.1111/j.1445-2197.2010.05536.x>
32. Chuwa EWL, Khin L-W, Chan W-H, Ong H-S, Wong W-K. Prognostic significance of peritoneal lavage cytology in gastric cancer in Singapore. *Gastric Cancer*. 2005;8(4):228–37.
33. Takebayashi K, Murata S, Yamamoto H, Ishida M, Yamaguchi T, Kojima M, et al. Surgery-Induced Peritoneal Cancer Cells in Patients Who Have Undergone Curative Gastrectomy for Gastric Cancer. *Ann Surg Oncol*. 2014;21(6):1991–1997. <http://dx.doi.org/10.1245/s10434-014-3525-9>
34. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after Surgery Compared with Surgery Alone for Adenocarcinoma of the Stomach or Gastroesophageal Junction. *N Engl J Med*. 2001;345(10):725–730. <http://dx.doi.org/10.1056/nejmoa010187>
35. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. *N Engl J Med*. 2006;355(1):11–20. <http://dx.doi.org/10.1056/nejmoa055531>
36. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, et al. Five-Year Outcomes of a Randomized Phase III Trial Comparing Adjuvant Chemotherapy With S-1 Versus Surgery Alone in Stage II or III Gastric Cancer. *J Clin Oncol*. 2011;29(33):4387–4393. <http://dx.doi.org/10.1200/jco.2011.36.5908>
37. Noh SH, Park SR, Yang H-K, Chung HC, Chung I-J, Kim S-W, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15(12):1389–1396. [http://dx.doi.org/10.1016/s1470-2045\(14\)70473-5](http://dx.doi.org/10.1016/s1470-2045(14)70473-5)
38. Al-Batran S-E, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet Lond Engl*. 2019;393(10184):1948–1957. [http://dx.doi.org/10.1016/s0140-6736\(18\)32557-1](http://dx.doi.org/10.1016/s0140-6736(18)32557-1)
39. de Steur WO, van Amelsfoort RM, Hartgrink HH, Putter H, Meershoek-Klein Kranenbarg E, van Grieken NCT, et al. Adjuvant chemotherapy is superior to chemoradiation after D2 surgery for gastric cancer in the per-protocol analysis of the randomized CRITICS trial. *Ann Oncol*. 2021;32(3):360–367. <http://dx.doi.org/10.1016/j.annonc.2020.11.004>
40. Zhang X, Liang H, Li Z, Xue Y, Wang Y, Zhou Z, et al. Perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy (RESOLVE): an open-label, superiority and non-inferiority, phase 3 randomised controlled trial. *Lancet Oncol*. 2021;22(8):1081–1092. [http://dx.doi.org/10.1016/s1470-2045\(21\)00297-7](http://dx.doi.org/10.1016/s1470-2045(21)00297-7)
41. Jeung HC, Moon YW, Rha SY, Yoo NC, Roh JK, Noh SH, et al. Phase III trial of adjuvant 5-fluorouracil and adriamycin versus 5-fluorouracil, adriamycin, and polyadenylic-polyuridylic acid (poly A:U) for locally advanced gastric cancer after curative surgery: final results of 15-year follow-up. *Ann Oncol*. 2008;19(3):520–526. <http://dx.doi.org/10.1093/annonc/mdm536>

42. Rosen HR, Jatzko G, Repse S, Potrc S, Neudorfer H, Sandbichler P, et al. Adjuvant intraperitoneal chemotherapy with carbon-adsorbed mitomycin in patients with gastric cancer: results of a randomized multicenter trial of the Austrian Working Group for Surgical Oncology. *J Clin Oncol.* 1998;16(8):2733–2738. <http://dx.doi.org/10.1200/jco.1998.16.8.2733>
43. Miyashiro I, Furukawa H, Sasako M, Yamamoto S, Nashimoto A, Nakajima T, et al. Randomized clinical trial of adjuvant chemotherapy with intraperitoneal and intravenous cisplatin followed by oral fluorouracil (UFT) in serosa-positive gastric cancer versus curative resection alone: final results of the Japan Clinical Oncology Group trial JCOG9206-2. *Gastric Cancer.* 2011;14(3):212–218. <http://dx.doi.org/10.1007/s10120-011-0027-3>
44. Shimoyama S, Shimizu N, Kaminishi M. Type-oriented intraoperative and adjuvant chemotherapy and survival after curative resection of advanced gastric cancer. *World J Surg.* 1999;23(3):284–91. discussion 291–292.
45. Kang Y-K, Yook J-H, Chang H-M, Ryu M-H, Yoo C, Zang D-Y, et al. Enhanced efficacy of postoperative adjuvant chemotherapy in advanced gastric cancer: results from a phase 3 randomized trial (AMC0101). *Cancer Chemother Pharmacol.* 2014;73(1):139–149. <http://dx.doi.org/10.1007/s00280-013-2332-5>
46. Witkamp AJ, de Bree E, Van Goethem R, Zoetmulder FA. Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy. *Cancer Treat Rev.* 2001;27(6):365–74.
47. Sun J, Song Y, Wang Z, Gao P, Chen X, Xu Y, et al. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. *BMC Cancer.* 2012;12(1). <http://dx.doi.org/10.1186/1471-2407-12-526>
48. Desiderio J, Chao J, Melstrom L, Warner S, Tozzi F, Fong Y, et al. The 30-year experience—A meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. *Eur J Cancer Oxf Engl.* 2017;79:1–14. <http://dx.doi.org/10.1016/j.ejca.2017.03.030>
49. Beeharry MK, Zhu Z-L, Liu W-T, Yao X-X, Yan M, Zhu Z-G. Prophylactic HIPEC with radical D2 gastrectomy improves survival and peritoneal recurrence rates for locally advanced gastric cancer: personal experience from a randomized case control study. *BMC Cancer.* 2019;19(1):932.
50. Fan B, Bu Z, Zhang J, Zong X, Ji X, Fu T, et al. Phase II trial of prophylactic hyperthermic intraperitoneal chemotherapy in patients with locally advanced gastric cancer after curative surgery. *BMC Cancer.* 2021;21(1). <http://dx.doi.org/10.1186/s12885-021-07925-2>
51. Diniz TP, Costa WL, Fonseca de Jesus VH, Ribeiro HSC, Diniz AL, Godoy AL, et al. Does hipec improve outcomes in gastric cancer patients treated with perioperative chemotherapy and radical surgery? A propensity-score matched analysis. *J Surg Oncol.* 2020. <http://dx.doi.org/10.1002/jso.25823>
52. Yu W, Whang I, Chung HY, Averbach A, Sugarbaker PH. Indications for early postoperative intraperitoneal chemotherapy of advanced gastric cancer: results of a prospective randomized trial. *World J Surg.* 2001;25(8):985–90.
53. Glehen O, Passot G, Villeneuve L, Vaudoyer D, Bin-Dorel S, Boschetti G, 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(1). <http://dx.doi.org/10.1186/1471-2407-14-183>
54. Beeharry MK, Ni Z-T, Yang ZY, Zheng YN, Feng RH, Liu W-T, et al. Study protocol of a multicenter phase III randomized controlled trial investigating the efficiency of the combination of neoadjuvant chemotherapy (NAC) and neoadjuvant laparoscopic intraperitoneal hyperthermic chemotherapy (NLHIPEC) followed by R0 gastrectomy with intraoperative HIPEC for advanced gastric cancer (AGC): dragon II trial. *BMC Cancer.* 2020;20(1). <http://dx.doi.org/10.1186/s12885-020-6701-2>
55. Ishigami H, Tsuji Y, Shinohara H, Kodera Y, Kanda M, Yabusaki H, et al. Intraperitoneal Chemotherapy as Adjuvant or Perioperative Chemotherapy for Patients with Type 4 Scirrhou Gastric Cancer: PHOENIX-GC2 Trial. *J Clin Med.* 2021;10(23):5666. <http://dx.doi.org/10.3390/jcm10235666>
56. Kuramoto M, Shimada S, Ikeshima S, Matsuo A, Yagi Y, Matsuda M, et al. Extensive Intraoperative Peritoneal Lavage as a Standard Prophylactic Strategy for Peritoneal Recurrence in Patients with Gastric Carcinoma. *Ann Surg.* 2009;250(2):242–246. <http://dx.doi.org/10.1097/sla.0b013e3181b0c80e>
57. Misawa K, Mochizuki Y, Sakai M, Teramoto H, Morimoto D, Nakayama H, 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(12):1602–1610. <http://dx.doi.org/10.1002/bjs.11303>
58. Yang HK, Ji J, Han SU, Terashima M, Li G, Kim HH, et al. Extensive peritoneal lavage with saline after curative gastrectomy for gastric cancer (EXPEL): a multicentre randomised controlled trial. *Lancet Gastroenterol Hepatol.* 2021;6(2):120–127. [http://dx.doi.org/10.1016/s2468-1253\(20\)30315-0](http://dx.doi.org/10.1016/s2468-1253(20)30315-0)

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