INTRODUCTION

Gastric cancer is the fifth most commonly diagnosed cancer and the fourth most common cause of cancer death worldwide. A majority of patients are diagnosed at advanced stages and approximately 40% of the patients are diagnosed up-front with metastatic disease. 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. Several studies have shown that approximately 15%-17% of patients develop peritoneal carcinomatosis after curative gastrectomy. 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.

Peritoneal carcinomatosis remains an essential oncological challenge since systemic chemotherapy has a limited efficacy.
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. 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. 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. 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 and two retrospective studies. In other studies, pT3-4 tumors were associated with increased risk for developing peritoneal recurrence. 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. Macroscopic serosal invasion has been associated with peritoneal recurrence, regardless of pathological T-stage. Furthermore, positive lymph node involvement has been identified as an independent risk factor of peritoneal recurrence, 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. Signet ring cell carcinoma, which is a subtype of diffuse/poorly cohesive type carcinoma, has been linked to peritoneal recurrence. Moreover, undifferentiated/poorly differentiated gastric carcinoma is also associated with increased risk for developing peritoneal recurrence. 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, lymphovascular invasion, and peritumoral desmoplasia. 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. Linitis plastica, a severe form of Borrmann type 4, has been found to increase the risk for peritoneal recurrence in signet ring cell carcinomas. In addition, scirrhous stromal reaction has been correlated with increased risk of peritoneal recurrence. 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 ≥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 ≥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<sup>a</sup> |
| 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 ≥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 ≥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 |
| 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 ≥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>, β-Ala in tumor tissue | |
| Risk factors of peritoneal recurrence in esophagogastric signet ring cell adenocarcinoma: Results of a multicentre retrospective study | Honoré et al, 2013<sup>22</sup> | France | Retrospective | 424 patients | pT-stage (pT ≥3)<sup>a</sup>, pN-stage (pN ≥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 ≥7 cm | |
| 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 ≥5 cm | |
| 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 ≥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 | ↑ preoperative AFP and ↑ 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 | ↓ prognostic nutritional index (PNI) |
| Reduced expression of exosomal miR-29b 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 | ↓ 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, while in another study, total gastrectomy was identified as a risk factor. Furthermore, tumor size has been associated with peritoneal recurrence. This risk increased in the larger tumor groups, but the definition has varied. 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. Other less commonly used biomarkers associated with peritoneal recurrence include prognostic nutritional index (PNI, an immune-nutritional marker), β-Ala (an anti-tumoral amino acid), miR-29b (a microRNA tumor suppressor), mesothelin (a tumor-associated antigen), and bcl-2 (an oncogene indicating less aggressive tumor growth).

### 3.1.4 Other clinical factors

Patients below the age of 50 and female patients may have higher risk for developing peritoneal recurrence. 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 and subsequently large intraoperative bleeding during gastrectomy has been linked to increased incidence of peritoneal recurrence. Positive peritoneal cytology is a strong predictor of peritoneal recurrence, as up to 82% of patients with positive cytology develop peritoneal recurrence and the risk may be 15 times higher compared to patients with negative cytology. Cancer cells may also be spilled during resection and the spreading of viable cancer cells into the abdominal cavity is increased in advanced tumors.

### 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. 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). 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. 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. Further on, Al-Batran et al performed an RCT which showed that perioperative Docetaxel, Oxaliplatin, Leucovorin, and Fluorouracil (FLOT) was superior to perioperative Epirubicin, Cisplatin, and Fluorouracil/Capcitabine (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%, \( P = .005 \)). 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).

Immunotherapy in the adjuvant setting for patients with locally advanced gastric cancer has also been studied. Jeung et al used systemic polyadenyl-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 immunotherapy 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, other studies have reported survival benefits. 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>24</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 0.66, 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 |
| 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) |
| 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) | ↑ 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) ↑ DFS (68.3% vs 52.1%, P = .005) ↑ Peritoneal recurrence rate (50.0% vs 53.2%) |

(Continues)
| 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)       | No difference in OS (738.9 vs 515.4 d, P = .44) or RFS (554.8 vs 3803 d, P = .48)   |
|                                                                               |               |              |              | Surgery alone (n = 45) | ↑ 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) | No difference in OS (62.0% vs 60.9%, P = .482) or RFS (57.5% vs 55.6%, P = .512) |
|                                                                               |               |              |              | Surgery alone (n = 133) | ↑ OS in the NIPEC + high dose adjuvant CT group vs the NIPEC + low dose adjuvant CT group (P = .049), respectively |
| Surgery + NIPEC (Mitomycin C) + high dose adjuvant CT (Cisplatin + Tegafur + Uracil) vs surgery + NIPEC + 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 at 3-y (RR = 0.71, 95% CI 0.53-0.95, P = .02) 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 + NIPEC (Cisplatin) + adjuvant CT (Mitomycin C, Doxorubicin and Cisplatin) vs surgery + adjuvant CT (Mitomycin C and Doxorubicin) (AMC0101 trial) | Kang et al, 2014<sup>45</sup> | South Korea  | RCT          | NIPEC + CT (n = 263) | ↑ OS (RR = 0.73, 95% CI 0.64-0.83, P < .0001)                                           |
|                                                                               |               |              |              | CT (n = 258)       | ↓ Peritoneal recurrence rate (RR = 0.45, 95% CI 0.28-0.72, P = .003)                  |
| 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) | ↑ OS (RR = 0.73, 95% CI 0.64-0.83, P < .0001)                                         |
|                                                                               |               |              |              | Surgery (n = 544)  | ↓ Peritoneal recurrence rate (RR = 0.45, 95% CI 0.28-0.72, P = .003)                 |
| Surgery + HIPEC (Mitomycin C, combinations of Mitomycin C and 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) | ↑ 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) | ↑ DFS (93% vs 65%, P = .0054)                                                        |
|                                                                               |               |              |              | CT (n = 40)       | ↓ 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) | No difference in OS (87.9% vs 100%, P = .142) or DFS (84.8% vs 88.2%, P = .986) |
|                                                                               |               |              |              | CT (n = 17)       | ↑ OS in the NIPEC + high dose adjuvant CT group vs the NIPEC + low dose adjuvant CT group (P = .049), respectively |
| 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 | 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 | 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 | 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 | 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 | 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) | | | | | |
| Surgery + EIPL + NIPEC (Cisplatin) + adjuvant CT (Fluorouracil) vs Surgery + NIPEC (Cisplatin) + adjuvant CT (Fluorouracil) vs surgery + adjuvant CT (Fluorouracil) | Kuramoto et al, 2009 | 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 surgery alone |
| Surgery + EIPL + adjuvant CT (S-1) vs surgery + adjuvant CT (S-1) (CCOG 1102 trial) | Misawa et al, 2009 | 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) |
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.\(^{45}\)

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.\(^{46}\) 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.\(^{47}\) 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).\(^{47}\)

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.\(^{48}\) 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.\(^{49}\)

However, in another recent RCT conducted by Fan et al, no survival benefit was seen for patients treated with HIPEC using Cisplatin.\(^{50}\) 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.\(^{51}\)

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%, \(P = .008\)). 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 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. 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.

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%, \(P < .0001\)). However, EIPL was later evaluated in two RCTs, the CCGO 1102 trial and the EXPHEL trial, including 295 and 800 patients, respectively. 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. Intraoperative 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 intraoperative treatments to prevent perioperative recurrence.

ACKNOWLEDGEMENTS
None.

DISCLOSURES
Funding: This research received no specific funding.
Conflict of Interest: The authors declare no conflict of interests for this article.

Author Contributions: All authors planned and designed the article. Dr Huang performed the literature review. All authors scrutinized and confirmed the literature review. Dr Huang drafted the manuscript with revisions from all authors. All authors revised and finally accepted the final version of the manuscript.

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How to cite this article: Huang B, Rouvelas I, Nilsson M. Gastric and gastroesophageal junction cancer: Risk factors and prophylactic treatments for prevention of peritoneal recurrence after curative intent surgery. Ann Gastroenterol Surg. 2022;6:474-485. doi:10.1002/ags.3.12565