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Systematic review of treatment options for gastric cancer and future therapeutic perspectives

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ABSTRACT

Background: Gastric cancer is the fourth most prevalent type of cancer and the second leading cause of cancer-related mortality worldwide, with an annual global incidence of 1 million cases and 700,000 deaths. Treatment modalities include surgery, chemotherapy, radiation therapy, and novel biological agents such as immune checkpoint inhibitors. The aim of the study is to summarise the existing literature on current treatment modalities and explore novel and emerging approaches to provide a detailed understanding of future advances in gastric cancer management.
Methods: A systematic review was conducted from September 2022 to May 2024 using the online databases PubMed, Scopus, and Google Scholar. The risk of bias assessment was carried out using the Newcastle-Ottawa Scale.
Results: The final review comprised 68 records. The analysis revealed that laparoscopic gastrectomy and other minimally invasive surgical approaches have yielded promising outcomes, either as standalone procedures or in combination with neoadjuvant and adjuvant chemotherapy regimens. The management of gastric cancer has been transformed by Human Epidermal Growth Factor Receptor 2-targeting agents, checkpoint inhibitors and other immunotherapies, with trastuzumab providing significant benefits when combined with chemotherapy.
Conclusion: Larger prospective or randomized controlled trials should be conducted, incorporating neoadjuvant chemotherapy regimens, targeted agents, or other innovative approaches, to confirm current research findings and enhance the efficacy and safety of various therapeutic strategies. A thorough evaluation of existing treatments and novel therapeutic interventions is imperative to guide future research initiatives, formulate effective patient care strategies, and inform policy makers.

Keywords: gastric cancer; Helicobacter pylori; monoclonal antibodies; immunotherapy; systematic review.

INTRODUCTION

Gastric cancer (GC) is an aggressive disease and a major global health problem. Overall incidence and mortality from GC have decreased significantly in recent years. The global incidence of late-onset GC fell from 59.53 per 100,000 in 1990 to 41.26 in 2019, with an average annual percentage change (AAPC) of –1.23 (95% confidence interval (CI) -1.39 to-1.06; p<0.001), while the incidence of young-onset GC (diagnosed in individuals under the age of 40) decreased from 2.20 per 100,000 in 1990

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to 1.65 in 2019, with an AAPC of –0.95 (95% CI –1.25 to-0.65; p<0.001). The mortality rates for both young- and late-onset GC decreased during this timeframe with an AAPCs of –1.82 for young-onset (95% CI-2.15 to-1.56; p<0.001) and –1.69 for late-onset GC (95% CI –1.79 to-1.59; p<0.001) [1]. Despite these improvements, GC is still the fourth most common cancer and the second leading cause of cancer-related deaths worldwide. It is still diagnosed yearly in about 1 million people and is responsible for more than 700,000 deaths, accounting for 8% of all cancer cases and 9.7% of all cancer deaths [2].

Men are two to three times more likely to develop GC than women. The number of cases varies greatly by geographical area. The regions most likely to develop GC are Central and South America, Eastern Europe, and East Asia, while Australia and New Zealand, South Asia, North and East Africa, and North America are the low-risk regions. The incidence of GC increases steadily with age, with the average age of diagnosis being 70 years. However, about 10% of GC is found in people aged 45 years or younger [3]. Although the incidence is decreasing due to improved diet, food preservation methods, better prevention strategies, and earlier detection and treatment, the disease is associated with a poor prognosis [4].

Despite the marked decrease in distal intestinal-type GC, there has been an increase in proximal diffuse gastric cardia-type adenocarcinoma in Western countries. *Helicobacter pylori* (*H. pylori*) infection and dietary habits are the major risk factors associated with distal GC. *H. pylori* is the most important etiologic factor for GC and accounts for approximately 89% of cases worldwide. The prevalence of *H. pylori* infection is higher in Central and South America, as well as in parts of Asia and Eastern Europe, compared to North America, Australia, and Western Europe [5]. Its eradication has been linked to a decrease in the incidence of GC, but the rise in antibiotic resistance to commonly used treatments like metronidazole and clarithromycin is driving the failure of eradication efforts. Prophylactic vaccination against *H. pylori* shows promise as a potential option, but a commercial vaccine is not yet available on the market [6]. In contrast, gastro-esophageal reflux disease and obesity are key factors contributing to proximal GC [7].

The biological differences in the tumours between Eastern and Western countries make it difficult to determine the standard of care based on international trials [8]. The introduction of early detection programs and new surgical techniques has led to improved survival rates for patients with localized disease, but the average 5-year survival rate for patients with advanced GC is still only 3.1% [9]. This extremely poor outcome highlights the need for better comprehensive surgical treatment of advanced GC and to promote the potential development of new therapeutic approaches. Surgery, chemotherapy, and radiation therapy have been the top treatment modalities for upper gastrointestinal malignancies for the last three decades, with the only potential cure being surgical resection. However, this has changed with the development of immune checkpoint inhibitors (ICIs), which move the protein model to a new level by providing patients with unique and long-lasting periods of improvement without surgery [10]. Nevertheless, challenges include the identification of suitable patient populations, the overcoming of resistance mechanisms, and the addressing of inter-patient variability. Meanwhile, molecular profiling and biomarker discoveries are the driving force behind the new era of precision medicine, offering the chance to increase the efficacy of therapy while minimizing side effects.

This systematic review aims to synthesize the existing literature on current treatment modalities and explore novel and emerging approaches to provide a detailed understanding of future advances in GC management.

METHODS

The present systematic review follows the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [11]. The protocol of the study is available on Zenodo [12].

Search strategy

An extensive search was conducted in September 2022 and updated in May 2024 using three electronic databases: PubMed, Scopus, and Google Scholar. The following search string was created with the most appropriate MeSH terms and Boolean operators and adapted for each of the databases: *(Gastric OR Stomach) AND (Cancer OR Neoplasm OR Tumour* OR Adenocarcinoma) AND (treatment OR therapy OR antineoplastic OR neoadjuvant OR immunotherapy OR chemotherapy OR molecular targeted therapy)*. In addition, the references from identified systematic reviews were screened for eligible articles. Studies were eligible for inclusion in the systematic review if they met the following criteria: a) original research; b) published in English and French languages in the last decade, i.e., between 2013 and 2023 (updated to May 2024); c) studies reporting treatment options for any type of GC; d) studies including future therapeutic perspectives or directions; and e) retrospective and prospective observational studies, such as cohort, case-control, and cross-sectional studies with more than 30 GC cases. Records were excluded if GC data were merged with those from different types of cancers of the digestive tract or with cancers originating from other systems (i.e., gastroesophageal, gastrointestinal, neuroendocrine cancers).

Study selection

The title and abstracts of the retrieved records were downloaded and imported into Rayyan, enabling the removal of duplicate records [13]. The remaining

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records were then screened by four reviewers working in pairs, with any disagreements resolved through consensus-based discussions.

The full-text screening followed the same inclusion criteria as the title and abstract phase.

Data extraction

An extraction form was created, based on the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis [14], to collect data on:

- study characteristics (first author, publication year, country of the research);
- study methods (study design, patients' inclusion criteria, duration of the study);
- sample characteristics (size, age, gender, ethnicity/race, clinical stage of the GC according to the tumour, node, and metastasis classification, presence of metastasis, treatment modality and lines, adverse effects);
- primary and secondary outcomes, future directions or recommendations provided by the authors.

Each reviewer conducted an independent extraction that was checked by a second reviewer for accuracy.

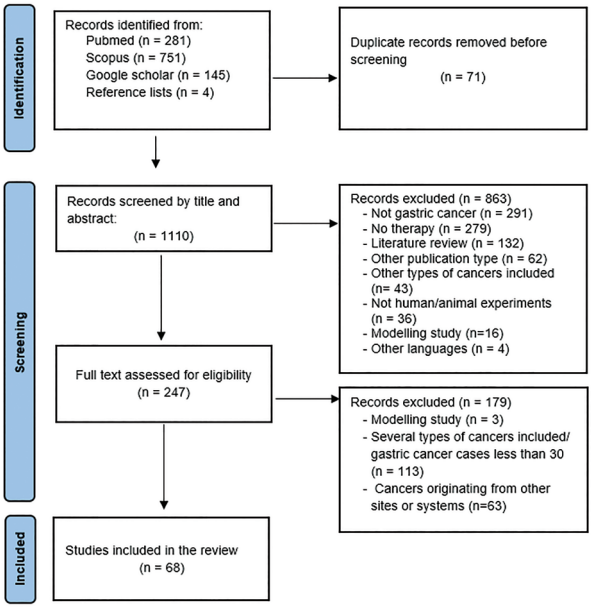
Quality assessment

The risk of bias assessment was carried out after the data extraction phase using the Newcastle-Ottawa Scale (NOS) for cohort, case-control [15] and cross-sectional studies [16]. The tool for cohort and case-control studies consisted of three domains: selection (four points), comparability (two points), and outcome (three points). The adapted version for cross-sectional studies differed from the original tool in the maximum achievable score in the selection domain (five points). The results of the assessment are also presented according to the Agency for Healthcare Research and Quality (AHRQ) standards. The thresholds for converting the NOS to AHRQ standards (good, fair, and poor quality studies) [17] are reported in Table 1.

RESULTS

Sixty-eight studies, published between 2013 and 2024, were included in the systematic review (Figure 1).

Figure 1. Flow chart of the selection process indicating the number of selected articles for each step of the systematic review on gastric cancer and future perspectives



The main characteristics of the studies are depicted in Table 2.

Table 1. Threshold values for converting the NOS to AHRQ standards of the included studies

Cohort and case-control studies	Points in Selection Domain	Points in Comparability Domain	Points in Outcome Domain
Good	≥3	≥1	≥2
Fair	2	≥1	≥2
Poor	0-1	0	0–1
Cross-sectional studies*			
Good	≥4	≥1	≥2
Fair	≥2	≥1	≥2
Poor	0–1	0	0–1

NOS, Newcastle-Ottawa Scale; AHRQ, Healthcare Research and Quality Standards; *Based on AHRQ Methodology Checklist for cross-sectional studies [18].

Table 2. Characteristics of the studies on gastric cancer and future therapeutic perspectives

First Author, year	Country	Study design	Inclusion Criteria	Study duration (years)	Number of patients (N)	Age (mean ± SD or range)	Ethnicity/ Race
Ahn, 2014 [53]	ROK	Clinical trial	Untreated, pathologically proven advanced GC with measurable lymph node metastases, ECOG 0–1, age 18–75, ASA I–II, adequate organ function, no prior chemotherapy/radiotherapy	3.5	140 (neoadjuvant chemotherapy = 48; surgery alone = 92)	Neoadjuvant: 53.8 ± 8.9; Surgery alone: 58.9 ± 11.2	NR
Ali, 2023 [56]	Pakistan	Retrospective cohort	Operable GC with lymphadenectomy; received perioperative or adjuvant chemotherapy	6	108	27–80 (range)	NR
Bao, 2017 [32]	China	Observational study	GC meeting surgical indications, R0 resection, ≥1 cycle adjuvant chemotherapy after radical gastrectomy	7	286 (Laparoscopic = 157; Open = 129)	Laparoscopic: 61 (42–70); Open: 59 (40–69)	NR
Beeharry, 2019 [24]	China	Case-control	Age 18–76, T ≥ 3 by staging, KPS > 50, adequate laboratory values, no major comorbidities; randomized to D2 resection ±HIPEC	0.5	80 (HIPEC = 40, Control = 40)	HIPEC: 59 ± 10; Control: 58 ± 10	NR
Chen, 2019 [22]	China	Case-control	Poor performance status (2 or 3), advanced GC, ≥2 prior lines of chemotherapy, declined additional chemotherapy, consenting to Apatinib + BSC vs. BSC alone	2.2	61 (apatinib group = 20; control = 41)	41–79 (range)	NR
Chen, 2021 [29]	Japan	Prospective cohort	Unresectable advanced/recurrent GC, receiving ramucirumab for the first time in routine clinical practice	3.6	609	21–94 (range)	NR
Cho, 2020 [51]	ROK	Cohort	Pathologically proven advanced GC with acute bleeding requiring transarterial embolization	10	58	62.5 ± 12.8	NR
Choi, 2018 [59]	ROK	Cohort	Histologically confirmed recurrent/metastatic GC, received ≥1 line of palliative chemotherapy	11	682	81.8% < 70 years (exact mean NR)	NR
Choi, 2019 [45]	ROK	Cohort	Underwent EMR or ESD for premalignant lesions or early GC; length of stay ≤2 days	11.3	914	63.4 (mean)	NR
Cordova-Delgado, 2021 [30]	Chile	Case-control	Histologically confirmed GC; ≥2 cycles of fluoropyrimidine ± platinum chemotherapy; adequate organ function; age >18; available biological sample	12.9	93 (cases=32; controls=61)	>18 (range not specified)	Latin
Deftereos, 2021 [31]	Australia	Prospective observational	Age ≥18, inpatient, curative gastrointestinal surgery (gastrectomy/esophagectomy/pancreatectomy), SGA by dietitian within 7 days, adequate communication	0.8	50 (GC subset only)	67 ± 10	NR
Dong, 2016 [35]	China	Case-control	Age 30–70, Borrmann type II/III, no distant metastases, T2–T3; Groups: FOLFOX6, SOX, XELOX vs. Surgery alone	3	603 (control = 141, FOLFOX6 = 157, SOX = 160, XELOX = 145)	Median 54	NR

(*continued*)

Table 2. Characteristics of the studies on gastric cancer and future therapeutic perspectives (continued)

First Author, year	Country	Study design	Inclusion Criteria	Study duration (years)	Number of patients (N)	Age (mean ± SD or range)	Ethnicity/ Race
Dong, 2018 [60]	China	Case-control	Advanced or metastatic GC or locally advanced GC not suited for surgery, no history of other malignancies	9.8	177	20–76 (range)	NR
Gamboa-Hoil, 2020 [50]	Mexico	Cohort	GC patients (T2/T3) undergoing surgery	4	70	43–86 (range)	NR
Garbarino, 2020 [33]	Italy	Retrospective observational	Excluding cT1, cT4b, metastatic, or neoadjuvant chemotherapy; laparoscopic distal gastrectomy vs. open in a Western center	5	123 (laparoscopic = 60, Open = 63)	Lap: 72.2 ± 9.9; Open: 72.1 ± 10.1	NR
Guo, 2023 [25]	China and USA	Cohort	Primary GC stage II/III, underwent gastrectomy	13	1,636	19–98 (range)	NR
Han, 2024 [68]	China	Cohort	Diagnosed GC, received immune checkpoint inhibitors (± chemotherapy)	3	584	IQR 46–69	NR
Hao, 2024 [70]	China	Observational study	Advanced GC on immunotherapy (Dec 2017–Apr 2022)	4.3	402 (immune-related AEs = 191; non-immune AEs = 211	Mean ~63 (both groups)	NR
He, 2024 [37]	China	Observational study	HER2+ advanced GC treated with trastuzumab (2011–2019)	8	207	Training: 60.8 ± 10.7; Internal: 60.0 ± 12.8; External: 63.8 ± 10.5; Prospective: 67.0 ± 19.5	NR
Hernanz, 2019 [23]	Spain	Retrospective cohort	Underwent esophagogastroduodenoscopy, histologically proven GC, diagnosed in participating centers	8	1,289	74.1 ± 11.2	NR
Higuchi, 2013 [46]	Japan	Observational study	Early gastric tubular/papillary adenocarcinoma with ulcer scar ≤3 cm intramucosal, no distant LN, double-endoscope ESD performed	3.7	57 (double-endoscope = 30; control = 27)	Double: 67 (51–87); Control: 69 (43–82)	NR
Hsieh, 2016 [74]	Taiwan	Retrospective cohort	Age ≥18, metastatic GC, data on NLR/mGPS/PG-SGA within 1 week pre-chemotherapy, ≥1 cycle of chemotherapy for metastatic GC	7	256	26–85 (range)	NR
Huang (W), 2023 [69]	China	Cohort	Histologically confirmed GC, standard CT within 4 weeks before immunotherapy	5.3	294	IQR 48–66	NR
Huang (K), 2023 [85]	China	Retrospective cohort	High-grade dysplasia or early GC resected by ESD	7	286	62.5 ± 9.3	NR
Jeong, 2015 [75]	ROK	Retrospective cohort	Patients undergoing gastrectomy for GC	3	2,107	61.2 ± 12.0	NR
Kaito, 2017 [40]	Japan	Cohort	GC (II–III) undergoing distal or total gastrectomy + D2 lymph node dissection	4.7	148	Laparoscopic: 35–85; Open: 41–81	NR
Kalinka-Warzocha, 2015 [87]	7 European countries	Prospective observational	Adults with GC (any stage), receiving ≥3 consecutive cycles of myelosuppressive chemotherapy; febrile neutropenia risk ≥20% or <20%	2.2	163	60 ± 14	NR

(*continued*)

Table 2. Characteristics of the studies on gastric cancer and future therapeutic perspectives (continued)

First Author, year	Country	Study design	Inclusion Criteria	Study duration (years)	Number of patients (N)	Age (mean ± SD or range)	Ethnicity/ Race
Kang, 2017 [48]	ROK	Observational study	Early GC with signet ring cell histology, underwent surgery	5	789	Mean 61.98	NR
Kim, 2021 [65]	ROK	Experimental study	Excluding distant metastases, no preoperative chemotherapy/radiotherapy, analyzing MET pathway and outcomes	1.9	272	135 <60 yrs, remainder ≥60 yrs	NR
Kim, 2020 [52]	ROK	Cohort	Unresectable GC with obstruction at EGJ or pylorus (e.g., nausea, vomiting, dysphagia)	10	118	EGJ group: 67.7 ± 9.97; Pylorus: 64.6 ± 11.81	NR
Kim, 2019 [80]	ROK	Cohort	Age >20, unresectable/metastatic/recurrent GC, ECOG 0–2, no prior palliative chemotherapy, estimated survival >3 months	2.3	527	25–86 (range)	NR
Kim, 2018 [36]	ROK	Observational study	Stage II–III GC, post-D2 gastrectomy with R0 resection, no preoperative chemotherapy/radiotherapy, age 20–75, ≥25 LN examined, no synchronous/metachronous cancers, received either S-1 or XELOX adjuvant within 8 weeks	1.8	1,774 (pre-PSM = 1,088; post-PSM = 686)	Pre-PSM: S-1 ~61.4±11.7 vs. XELOX ~56.4±10.6; Post-PSM: S-1 ~59.1±12.0 vs. XELOX ~57.5±10.8	NR
Kim, 2016 [77]	ROK	Observational study	Advanced or early GC with Helicobacter pylori (+), suitable for subtotal gastrectomy, no preoperative chemotherapy, provided informed consent	2.8	169 (treatment = 87; placebo = 82)	Treatment: 58 (48–65); Placebo: 56 (48–64)	NR
Li (J), 2018 [43]	China	Retrospective observational	GC with synchronous liver metastases, comparing minimally invasive surgery vs. open approach	10.5	53 (minimally invasive surgery=11, Open=42)	MIS: 58.9 ± 3.4; Open: 56.8 ± 1.6	NR
Li (Q), 2018 [66]	China	Prospective observational	Inoperable, HER2+ advanced GC, receiving first-line palliative chemotherapy + trastuzumab, measurable lesions, ECOG PS 0–2, LVEF >50%, adequate organ function	5	107	<65 yrs = 56; ≥65 yrs = 51	NR
Li, 2020 [67]	China	Prospective cohort	HER2+ advanced/metastatic GC or EGJ cancer, 6 cycles of trastuzumab-based first-line therapy, then maintenance strategies	5.5	78	Mean 64	NR
Liu, 2015 [81]	China	Observational study	GC patients operated on Jan 2008–Dec 2013, comparing those who received IIC vs. no IIC	6	845 (IIC = 356; Control = 489)	IIC group: 56 ± 11; Control: 56 ± 12	NR
Martinez-Lago, 2015 [63]	Spain	Retrospective cohort	Histologically proven advanced GC/GEJ, curative resection with negative margins, no preoperative therapy	7	55	40–81 (range)	NR
Murat Sedef, 2019 [62]	Turkey	Retrospective cohort	Metastatic GC not treated with trastuzumab	10	516	25–85 (range)	NR
Mokdad, 2018 [26]	USA	Retrospective cohort	Gastric adenocarcinoma (all stages)	8	89,098	18 to ≥75	White, Black, Asian, Hispanic, other

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Table 2. Characteristics of the studies on gastric cancer and future therapeutic perspectives (continued)

First Author, year	Country	Study design	Inclusion Criteria	Study duration (years)	Number of patients (N)	Age (mean ± SD or range)	Ethnicity/ Race
Narita, 2023 [71]	Japan	Cohort	Nivolumab-refractory or intolerant advanced GC, ECOG 0–2, scheduled for subsequent cytotoxic chemotherapy, measurable lesions	2.8	199	29–87 (range)	NR
Noh, 2018 [79]	ROK	Nested case-control	Stage I GC, pathologically confirmed, bone mineral density measured just before gastrectomy or endoscopic treatment	6	49	56.5 ± 10.8	NR
Nomura, 2019 [49]	Japan	Retrospective case-control	ESD in remnant stomach vs. intact stomach, Jan 2005–Sep 2017; includes post-gastrectomy (distal, proximal, or pylorus-preserving)	12.7	3,375 (remnant=138; intact=3,237)	Remnant: 71.2 ± 7.3; Intact: 69.6 ± 9.6	NR
Oh, 2021 [57]	ROK	Retrospective observational	GC with curative resection, adjuvant S-1 vs. XELOX	7.5	1,461	<60 or ≥60	NR
Olmi, 2020 [42]	Italy	Retrospective observational	Patients with GC from Jan 2010–Jun 2018, laparoscopic approach with D2 LN dissection & omentum preservation	8.5	138	Mean 70.7 ± 10.1	NR
Oyama, 2013 [38]	Japan	Prospective observational	High or moderate emetic-risk chemotherapy-naïve adults, planned for cisplatin + S-1	NR	53	50–81 (range)	Japanese
Oyama, 2016 [39]	Japan	Observational study	Age ≥20, ECOG PS 0–2, receiving S-1 + cisplatin chemotherapy for GC	1.7	72	Median 65 (range 50–81); 34 <65, 38 ≥66	NR
Petrioli, 2020 [55]	Italy	Prospective observational	Clinical T3–T4 non-metastatic GC, Jan 2010–Dec 2017, comparing NAC with DOC vs. EOF	8	63 (DOC=34, EOF=29)	DOC median=67; EOF median=63	NR
Pyo, 2016 [19]	ROK	Prospective observational	Age >20, newly diagnosed early GC meeting endoscopic resection criteria, no prior GC treatment, curative intent	11	2,563 (ESD=1,290; surgery=1,273)	ESD median ~61; Surgery median ~59	NR
Qiu, 2023 [72]	China	Retrospective cohort	Age ≥18, pathologically confirmed GC, ECOG 0–2, ≥1 measurable lesion (RECIST 1.0), adequate organ function, receiving apatinib second line or beyond	5	92	Mean 62.9 ± 8.7 (range 30–82)	NR
Qiu, 2014 [21]	China	Observational study	Advanced GC, completed 6 cycles of first-line XELOX without progression, developed ≥grade 2 neuropathy, ≥1 measurable lesion, life expectancy ≥3 months	1.9	286 (study group=64; control=222)	Study group: 24–74; Control: 19–82	NR
Rausei, 2015 [54]	Italy	Prospective observational	No distant metastases at laparoscopy, cT ≥ 3 GC (Jan 2010–Dec 2013), comparing NAC + surgery vs. surgery alone	4	71 (NAC + surgery=10; surgery alone=61)	NAC + surgery: mean 66.2; Surgery: mean 72	NR
Saito, 2021 [27]	Japan	Cohort	Unresectable or recurrent GC with peritoneal metastases, age >20, ECOG 0–2, adequate organ function, no other distant metastases (except ovary)	3.2	44	37–77 (range)	NR

(*continued*)

Table 2. Characteristics of the studies on gastric cancer and future therapeutic perspectives (continued)

First Author, year	Country	Study design	Inclusion Criteria	Study duration (years)	Number of patients (N)	Age (mean ± SD or range)	Ethnicity/ Race
Sarriugarte, 2018 [41]	Luxembourg and Spain	Cohort	GC cT1–4 N0–3 M0 located in antrum/body; planned laparoscopic curative R0 gastrectomy	4	67	37–85 (range)	NR
Sato, 2020 [78]	Japan	Observational study	cT2 or deeper GC by endoscopy or CT; no Linitis plastica, no para-aortic LN, no stage IV, no prior staging laparoscopy	NR	1,232–1,322 (approx.)	~69 (29–92) for CE alone, similar in other subsets	Asian (Japanese)
Shi, 2021 [28]	China	Cohort	Age 18–75, metastatic GC with peritoneal metastases, measurable lesion, ECOG 0–1, no prior chemotherapy/radiotherapy/targeted/immunotherapy	2	30	29–74 (range)	NR
Shin, 2024 [76]	Korea	Retrospective cohort	Early papillary GC without LN metastasis, underwent ESD	8	176	71.9 ± 8.7	NR
Tate, 2019 [20]	Australia	Observational study	Gastric lesion >10 mm, T1 lesion (mucosal/submucosal), age ≥18	5.8	121	Overall mean ~72.0 ± 10.6 (subsets ranged 67.4–75.2)	Mixed (Asian, European, etc.)
Terashima, 2021 [83]	Japan	Cohort	Incurable advanced GC with gastric outlet obstruction, age ≥20, ECOG 0–2, adequate organ function, poor/no oral intake	NR	104	Median 68	NR
Trip, 2014 [61]	Netherlands	Observational study	Postoperative chemoradiotherapy for GC (AP-PA vs. 3D-conformal vs. IMRT)	8	87 (AP-PA=31, 3D=25, IMRT=31)	AP-PA: mean 56, 3D: 53, IMRT: 58	NR
Ushiku, 2015 [82]	Japan	Retrospective observational	GC patients who underwent gastrectomy (2005–2010)	6	790	65.2 ± 10.7	NR
Wang, 2017 [58]	China	Prospective cohort	Stage II/III GC post-gastrectomy (D2 LN dissection), comparing chemotherapy alone vs. chemotherapy + CIT	2	159	<60 or ≥60	NR
Wang, 2020 [44]	China	Cohort	Patients undergoing radical gastrectomy (stage I–IV), comparing morning vs. afternoon start	5	117	44 <65 yrs, 73 ≥65 yrs	NR
Yamamoto, 2020 [88]	Japan	Observational study (case-control)	Patients >20 yrs with gastric lesions indicated for ESD, on antithrombotics per JGES guidelines	0.9	166 (vonoprazan=50; historical control=116)	Vonoprazan: 78 (54–87); Control: 75 (59–87)	NR
Yan, 2019 [64]	China	Cohort	D2 laparoscopic radical gastrectomy for GC, ≥18 yrs, no major postoperative complications, ≥5 cycles of chemotherapy	2	108	Group A (S-1): 53.7 ± 6.8; Group B (no S-1): 54.4 ± 7.4	NR
Yang, 2015 [47]	China	Retrospective cohort	Early GC or precancerous lesions treated via ESD	9.2	83	72.7 ± 11.5	NR
Zhang, 2019 [34]	China	Retrospective cohort	GC patients <75 yrs, no severe comorbidities, normal liver/renal function, hemoglobin ≥80 g/L, no severe abdominal pain/distension, body temperature <38°C, comparing IPHP vs. none	2	1,573 (IPHP=134; non-IPHP=1,439)	IPHP: 55.5 ± 10.8; Non-IPHP: 55.4 ± 11.0	NR

(*continued*)

Table 2. Characteristics of the studies on gastric cancer and future therapeutic perspectives (continued)

First Author, year	Country	Study design	Inclusion Criteria	Study duration (years)	Number of patients (N)	Age (mean ± SD or range)	Ethnicity/ Race
Zhang, 2024 [73]	China	Observational study	Advanced GC, treated with anti-PD-1 therapy, Jan 2019–Sep 2023	4.7	158 (low AFP=138; high AFP=20)	Low AFP: <60 yrs=48 (34.8%), ≥60 yrs=90 (65.2%); High AFP: <60 yrs=6 (30%), ≥60 yrs=14 (70%)	NR

AEs, adverse events; AFP, alpha-fetoprotein; AP-PA, anterior-posterior-posterior-anterior radiation technique; ASA, American Society of Anesthesiologists; BSC, best supportive care; CIT, cellular immunotherapy; CT, computed tomography; DOC, docetaxel + oxaliplatin + capecitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; EGJ, esophagogastric junction; EMR, endoscopic mucosal resection; EOF, epirubicin + oxaliplatin + 5-fluorouracil; ESD, endoscopic submucosal dissection ; FOLFOX6, oxaliplatin, leucovorin, and fluorouracil (5-FU); GC, gastric cancer; HIPEC, hyperthermic intraperitoneal chemotherapy; IIC, intraoperative intraperitoneal chemotherapy; IMRT, intensity-modulated radiation therapy; IPHP, intraperitoneal hyperthermic perfusion; IQR, interquartile range; JGES, Japan Gastroenterological Endoscopy Society; KPS, Karnofsky performance status; LAGC, nonmetastatic tumours, subserosal/serosal involvement, with or without lymph node invasion; LN, lymph nodes; LVEF, left ventricular ejection fraction; MET, mesenchymal-epithelial transition; NAC, neoadjuvant chemotherapy; NR, not reported; PD-1, programmed cell death 1; ROK, Republic of Korea; S-1, tegafur/gimeracil/oteracil; SGA, subjective global assessment; SOX, S-1 (tegafur/gimeracil/oteracil) and oxaliplatin; XELOX, capecitabine + oxaliplatin; Yrs, years

The top countries in terms of study origin are China (32.3%), the Republic of Korea (22%), and Japan (17.6%). Most of these studies adopted a prospective or retrospective cohort design (47%), while others used observational (39.7%) or case-control (10.3%) frameworks. The patients' inclusion criteria were based on the tumour stage, the patients' performance status, and their treatment history. Some studies targeted early-stage cases suitable for endoscopic resection [19, 20], whereas others investigated advanced or metastatic disease, including cases refractory to prior treatments [21,22]. Performance status and baseline organ function assessments are nearly universal, with most studies requiring an Eastern Cooperative Oncology Group (ECOG) score of 0-2. Additionally, certain studies explored unique comorbidities or risk factors [23]. The studies' duration ranged from 6 months [24] to a maximum of 13 years [25] and included a wide range of sample sizes. A study in the USA enrolled 89,098 patients with all stages of gastric adenocarcinoma [26]. In contrast, two studies had just 44 and 30 participants in Japan [27] and in China [28], respectively. Age ranges in the included studies reflect the predominance of patients in their 50s and 60s, though some cohorts span from young adults to elderly individuals aged over 90 [25, 29]. All studies included both sexes in varying proportions. When reported, ethnicity or race was often listed broadly, particularly in Asian-based studies. In contrast, a study offered a more diverse representation [26] including White, Black, Asian, Hispanic, and other racial categories across the United States. In Chile, a study evaluated a Latin cohort [30], while Australian-based studies [20, 31] reported a mix of Asian and European participants.

Treatment approaches varied extensively (Table 3). Some studies compared laparoscopic versus open gastrectomy [32, 33], while others examined the role of hyperthermic intraperitoneal chemotherapy [24, 34] or different neoadjuvant and adjuvant regimens [35, 36]. Other studies explored targeted therapies [29] and evaluated HER2-targeted regimens with trastuzumab in a Chinese cohort [37], or focused on supportive or adjunctive measures (e.g., antiemetic control in cisplatin-based chemotherapy) [38, 39] (Table 4).

Minimally invasive or local interventions

Laparoscopic gastrectomy and other minimally invasive surgical approaches have yielded promising outcomes in GC. They could reduce blood loss, diminish postoperative pain, facilitate faster recovery, and improve overall survival (OS)/disease-free survival (DFS) [32, 33]. Performing a laparoscopic gastrectomy may allow for faster initiation of adjuvant chemotherapy [40], especially when combined with D2 lymph node dissection for robust oncological outcomes and low leak risk [41]. Notably, preserving the omentum during laparoscopic surgery appeared feasible and safe for both early and advanced disease. Indeed, patients with omentum preservation had a lower incidence of relapse compared to those with omentectomy (40% vs 57%; p=0.002) [42]. Comparable long-term results were also observed, with reduced blood loss and faster oral intake [43]. However, the timing of surgery might matter: afternoon distal gastrectomies were associated with more bleeding (227.88±181.79 vs 117.93±112.01; p<0.001), slower gastrointestinal recovery, and worse OS [44]. In addition, endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) are effective for early GC or premalignant lesions. Performing EMR/ESD within two

Table 3. Non-pharmacological interventions and adverse events

First Author, year	Non-pharmacological interventions	Adverse events
Ahn, 2014 [53]	Surgery alone (radical gastrectomy with D2)	Death, morbidity (intra-abdominal bleeding, fluid collection, anastomotic leak, pneumonia)
Ali, 2023 [56]	Surgery	NR
Bao, 2017 [32]	Laparoscopic gastrectomy vs open surgery	NR
Beeharry, 2019 [24]	Control group: surgery alone	NR
Chen, 2019 [22]	Supportive therapy	NR
Chen, 2021 [29]	None	NR
Cho, 2020 [51]	TAE	NR
Choi, 2018 [59]	NR	NR
Choi, 2019 [45]	EMR/ESD	NR
Cordova-Delgado, 2021 [30]	Chemotherapy ± radiotherapy ± surgery	Not fully detailed
Deftereos, 2021 [31]	Surgery (open, laparoscopic)	Malnutrition and weight loss: longer stay
Dong, 2016 [35]	Radical D2 gastrectomy (control group)	NR
Dong, 2018 [60]	Chemoradiotherapy	NR
Gamboa-Hoil, 2020 [50]	Radiotherapy (median 50.4 Gy), surgery (subtotal or total)	NR
Garbarino, 2020 [33]	Gastrectomy + D2 LN dissection (lap vs open)	Conversions from laparoscopy to open surgery (n=5)
Guo, 2023 [25]	Surgery (open or laparoscopic)	NR
Han, 2024 [68]	NR	NR
Hao, 2024 [70]	NR	NR
He, 2024 [37]	NR	NR
Hernanz, 2019 [23]	Surgery (Billroth I/II, Roux-en-Y)	NR
Higuchi, 2013 [46]	Possible surgical resection if ESD fails	NR
Hsieh, 2016 [74]	None	NR
Huang (W), 2023 [69]	NR	NR
Huang (K), 2023 [85]	ESD ± radical gastrectomy	NR
Jeong, 2015 [75]	Surgery (open or laparoscopic)	Local: ascites, GI bleeding, anastomotic leak. Systemic: pulmonary complications
Kaito, 2017 [40]	Distal or total gastrectomy (laparoscopic vs open surgery)	Anastomotic leak, pancreatic fistula, bowel obstruction, pneumonia
Kalinka-Warzocha, 2015 [87]	Surgery ± chemotherapy ± radiotherapy	NR
Kang, 2017 [48]	Subtotal/total gastrectomy + D1 + or D2 LN dissection	Not specified
Kim, 2021 [65]	NR	NR
Kim, 2020 [52]	Self-expandable metal stent in EGJ vs pylorus	Bowel perforation, stent migration, bleeding
Kim, 2019 [80]	Subtotal/total gastrectomy	NR
Kim, 2018 [36]	NR	NR
Kim, 2016 [77]	Subtotal gastrectomy	NR
Li (J), 2018 [43]	Robotic or laparoscopic resection ± RFA ± hepatectomy	NR
Li (Q), 2018 [66]	NR	NR
Li, 2020 [67]	NR	NR

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Table 3. Non-pharmacological interventions and adverse events (continued)

First Author, year	Non-pharmacological interventions	Adverse events
Liu, 2015 [81]	Gastrectomy	NR
Martinez-Lago, 2015 [63]	Gastrectomy	NR
Mokdad, 2018 [26]	Surgery	NR
Murat Sedef, 2019 [62]	Surgery	NR
Narita, 2023 [71]	NR	NR
Noh, 2018 [79]	Gastrectomy vs endoscopic treatment	NR
Nomura, 2019 [49]	Possible re-surgery if incomplete ESD	NR
Oh, 2021 [57]	Gastrectomy ± endoscopic approach	NR
Olmi, 2020 [42]	Laparoscopic D2 gastrectomy with omentum preservation	Complications, length of surgery, length of stay
Oyama, 2013[38]	None	NR
Oyama, 2016 [39]	NR	NR
Petrioli, 2020 [55]	Gastrectomy (D2 or D3 LN dissection)	NR
Pyo, 2016 [19]	Endoscopic resection (ESD or EMR) vs surgical resection	Some differences in short-term complications
Qiu, 2023 [72]	NR	NR
Qiu, 2014 [21]	None	NR
Rausei, 2015 [54]	Surgery alone vs NAC + surgery (gastrectomy ± LN dissection)	9 in surgery-only vs 0 in NAC group
Saito, 2021 [27]	Conversion gastrectomy	Post-operational leak
Sarriugarte, 2018 [41]	~95% laparoscopic gastrectomy + D2 LN, Roux-en-Y	Leak, bleeding, infection
Sato, 2020 [78]	None	NR
Shi, 2021 [28]	Conversion surgery (R0, D2 LN)	NR
Shin, 2024 [76]	EMR or ESD	NR
Tate, 2019 [20]	Surgery if incomplete prior resection	NR
Terashima, 2021 [83]	Surgical palliation (distal/total gastrectomy or EGJ)	NR
Trip, 2014 [61]	None (radiologic approaches compared)	NR
Ushiku, 2015 [82]	Gastrectomy	SSI (incisional, organ/space)
Wang, 2017 [58]	D2 gastrectomy	NR
Wang, 2020 [44]	Radical gastrectomy	NR
Yamamoto, 2020 [88]	ESD	NR
Yan, 2019 [64]	Total or distal gastrectomy	NR
Yang, 2015 [47]	Surgery if needed	NR
Zhang, 2019 [34]	Gastrectomy (total/subtotal/palliative) + chemotherapy	NR
Zhang, 2024 [73]	NR	NR

EGJ, esophagogastric junction; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; GI, gastrointestinal; LN, lymph node; NAC, neoadjuvant chemotherapy; RFA, radiofrequency ablation; SSI, surgical site infection; TAE, transarterial embolization

Table 4. Pharmacological interventions, treatment lines and adverse events

First Author, year	Pharmacological interventions	Treatment lines	Adverse events
Ahn, 2014 [53]	NAC: 4 cycles mFOLFOX6 prior to surgery, 4 cycles adjuvant mFOLFOX6 post-surgery	NR	IP bleeding, morbidity, wound problems, fluid collections, anastomotic leak, thrombophlebitis
Ali, 2023 [56]	Adjuvant (CAPOX) or perioperative (ECF/FLOT)	NR	NR
Bao, 2017 [32]	Various chemotherapies: IV 5-FU + cisplatin, oral fluoropyrimidines ± S-1, etc.	NR	Grade 3/4 toxicities (cytopenia, GI)
Beeharry, 2019 [24]	HIPEC (cisplatin 50 mg/m² at 42°C × 60 min)	I	Mild AEs (neutropenia, renal toxicity, hyperbilirubinemia)
Chen, 2019 [22]	Apatinib (250–500 mg/day) + BSC	III+	Appetite decrease, fatigue, anemia (often grade ≥3)
Chen, 2021 [29]	Ramucirumab ± chemotherapy (often paclitaxel)	I–IV	Neutropenia, appetite decrease, hypertension, neuropathy (paclitaxel), ILD/pneumonitis (rare)
Cho, 2020 [51]	NR	NR	Stomach wall perforation (rare)
Choi, 2018 [59]	FOLFIRI, FOLFOX, paclitaxel/cisplatin, etc.	III+	NR
Choi, 2019 [45]	NR	NR	Bleeding (hematemesis, melena)
Cordova-Delgado, 2021 [30]	Multiple regimens: FOLFOX, CAPEOX, CF, DCFm, ECF, FLOT, etc.	I	Neuropathy (common grade 1), neutropenia (grade 3), diarrhea, nausea; DPYD SNPs linked to toxicity
Deftereos, 2021 [31]	NR	NR	NR
Dong, 2016 [35]	NAC: FOLFOX6, SOX, XELOX	I	Leukopenia/neutropenia, nausea/vomiting. FOLFOX6 had more liver dysfunction, constipation/pain vs SOX/XELOX
Dong, 2018 [60]	Various chemotherapies ± platinum ± docetaxel + radiotherapy	IV, locally advanced, recurrent	Mostly hematologic and GI (nausea, vomiting) at grade I–II; low incidence of grade III–IV
Gamboa-Hoil, 2020 [50]	Adjuvant XELOX, CAPEOX, FOLFOX, or capecitabine	NR	NR
Garbarino, 2020 [33]	NR	NR	No major difference in postoperative complications (laparascopic: 2 leaks vs open surgery: 4 canalization delays)
Guo, 2023 [25]	Adjuvant: S-1 alone or combos (SOX, XELOX, FOLFOX)	NR	NR
Han, 2024 [68]	ICIs ± chemotherapy	I+	NR
Hao, 2024 [70]	PD-1 inhibitors	I, II+	Skin rash, nail abnormalities, diarrhea
He, 2024 [37]	Anti-HER2 therapy (trastuzumab ± chemotherapy)	I, II, III+	NR
Hernanz, 2019 [23]	Chemotherapy (adjuvant, neoadjuvant, palliative), PPI therapy	I–IV	NR (not specifically detailed)
Higuchi, 2013 [46]	NR	NR	Delayed hemorrhage, nausea/vomiting, perforation, pneumonia, delirium (mostly grade 1–2, low incidence)
Hsieh, 2016 [74]	Fluoropyrimidine ± platinum (capecitabine+oxaliplatin, S-1, etc.)	I	NR
Huang (W), 2023 [69]	Anti-PD-1/PD-L1 ICIs ± chemotherapy	I, II, III+	NR

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Table 4. Pharmacological interventions, treatment lines and adverse events (continued)

First Author, year	Pharmacological interventions	Treatment lines	Adverse events
Huang (K), 2023 [85]	Chemotherapy (not specified)	NR	NR
Jeong, 2015 [75]	NR	NR	NR
Kaito, 2017 [40]	Adjuvant: S-1, XELOX, S-1+cisplatin, S-1+oxaliplatin (SOX)	NR	NR
Kalinka-Warzocha, 2015 [87]	Various chemo (27 regimens; DCF common). G-CSF prophylaxis studied	I–IV	Some G-CSF-related AEs (bone/back pain, leukocytosis), overall low incidence
Kang, 2017 [48]	NR	NR	NR
Kim, 2021 [65]	Crizotinib (MET inhibitor)	I	NR
Kim, 2020 [52]	Chemotherapy (not specified)	NR	NR
Kim, 2019 [80]	Palliative chemotherapy	I, II	NR
Kim, 2018 [36]	Adjuvant: S-1 vs XELOX	NR	NR
Kim, 2016 [77]	Chemotherapy for *H. pylori* eradication vs placebo	NR	NR
Li (J), 2018 [43]	NR	NR	3 complications in MIS group vs 8 in open surgery
Li (Q), 2018 [66]	Trastuzumab + chemotherapy (platinum-FP or taxane-FP, etc.)	I	Neutropenia, leukopenia most common
Li, 2020 [67]	Trastuzumab + platinum-FP or taxane-FP; maintenance: Trastuzumab alone vs Trastuzumab + single chemotherapy	I–III	Hematologic (neutropenia, thrombocytopenia, anemia), non-hematologic (anorexia, infection)
Liu, 2015 [81]	IIC	NR	Organ/space SSI
Martinez-Lago, 2015 [63]	Radiochemotherapy: 5-FU + leucovorin, then more 5-FU	NR	Neutropenia, anemia, thrombocytopenia, diarrhea, mucositis, hand-foot syndrome (mostly grade II–III, none grade IV)
Mokdad, 2018 [26]	Various chemotherapies ± chemoradiotherapy	NR	NR
Murat Sedef, 2019 [62]	(5-FU + cisplatin) ± taxanes	NR	NR
Narita, 2023 [71]	Cytotoxic chemotherapy: irinotecan, oxaliplatin combos, FTD/TPI, etc.	NR	Neutropenia, thrombocytopenia, anemia, GI issues, neuropathy, rash, hypothyroidism, pneumonitis, etc.
Noh, 2018 [79]	Chemotherapy (not specified)	NR	NR
Nomura, 2019 [49]	Chemotherapy (not specified)	I	Remnant group: 6 bleeds, 3 perforations; Intact group: 174 bleeds, 55 perforations
Oh, 2021 [57]	S-1 monotherapy or XELOX	NR	NR
Olmi, 2020 [42]	NR	NR	34 total complications: 17 surgical (fistulas=7), 19 medical (17 transfusions)
Oyama, 2013 [38]	S-1 + cisplatin, antiemetics (aprepitant, granisetron, dexamethasone)	I	Nausea, vomiting, anorexia
Oyama, 2016 [39]	S-1 + cisplatin; antiemetics (oral aprepitant, IV dexamethasone, palonosetron)	NR	Anorexia, diarrhea, hiccups, constipation
Petrioli, 2020 [55]	Neoadjuvant: DOC or EOF	I	Neutropenia, stomatitis, nausea/vomiting more frequent in EOF

(*continued*)

Table 4. Pharmacological interventions, treatment lines and adverse events (continued)

First Author, year	Pharmacological interventions	Treatment lines	Adverse events
Pyo, 2016 [19]	NR	NR	Early complications higher in ESD (9.0%) vs surgery (6.6%), late complications higher in surgery (2.9% vs 0.5%).
Qiu, 2023 [72]	Apatinib 250–500 mg/day	II+	Hypertension, hand-foot syndrome, proteinuria, fatigue, hematologic
Qiu, 2014 [21]	XELOX induction; maintenance with capecitabine or observation	I	Neutropenia, thrombocytopenia, anemia, leukopenia, fatigue, anorexia, nausea, mucositis, hand-foot syndrome, neuropathy
Rausei, 2015 [54]	NAC regimens: ECF, EOX, or FOLFOX	I	NR
Saito, 2021 [27]	IP paclitaxel (40 mg/m^2 d1,8) + IV oxaliplatin (100 mg/m^2 d1) + S-1 (14 on/7 off)	NR	Leukopenia, neutropenia, anemia, thrombocytopenia, fatigue, anorexia, GI AEs, neuropathy, infection
Sarriugarte, 2018 [41]	Preoperative chemotherapy for cT>1 (FLOT or similar)	NR	NR
Sato, 2020 [78]	NR	NR	NR
Shi, 2021 [28]	IP paclitaxel 40 mg/m^2 d1,8 + IV oxaliplatin 100 mg/m^2 d1 + S-1 80 mg/m^2 (14 on/7 off)	NR	Leukopenia, neutropenia, anemia, thrombocytopenia, neuropathy, diarrhea, nausea, vomiting
Shin, 2024 [76]	NR	NR	Bleeding (main ESD complication)
Tate, 2019 [20]	NR	NR	Delayed bleeding, hospital admission, severe AEs within 30 days
Terashima, 2021 [83]	Postoperative chemotherapy (not specified)	NR	NR
Trip, 2014 [61]	NR	NR	Nephrotoxicity
Ushiku, 2015 [82]	NR	NR	NR
Wang, 2017 [58]	Chemotherapy alone vs chemotherapy + CIT	NR	Few chemotherapy-related myelosuppression with CIT
Wang, 2020 [44]	NR	NR	NR
Yamamoto, 2020 [88]	Vonoprazan 20 mg pre-ESD + IV omeprazole 20 mg same evening	NR	Delayed bleeding incidence
Yan, 2019 [64]	IV chemotherapy (oxaliplatin, leucovorin, tegafur) ± sequential S-1	NR	Anemia, leukopenia, thrombocytopenia, liver dysfunction, diarrhea, GI reaction
Yang, 2015 [47]	NR	NR	Post-ESD bleeding linked to antithrombotic use; low perforation/pneumonia
Zhang, 2019 [34]	IP hyperthermic perfusion (cisplatin 50 mg/m^2 at 42°C × 60 min)	I	Fewer fevers in IPHP group; no increase in major complications
Zhang, 2024 [73]	Combination immunotherapy ± targeted therapy ± chemotherapy, or immunotherapy combos	I, II, III+	NR

AEs, adverse events; BSC best supportive care; CAPOX/ CAPEOX/ XELOX, capecitabine + oxaliplatin; CF, cisplatin + 5-fluorouracil; CIT, cellular immunotherapy; DCFm, docetaxel + cisplatin + 5-fluorouracil; DOC , docetaxel + oxaliplatin + capecitabine; DPYD SNPs, single nucleotide polymorphisms in dihydropyrimidine dehydrogenase gene; ECF, etoposide + cisplatin + 5-fluorouracilo; EMR, Endoscopic mucosal resection; EOF, epirubicin + oxaliplatin + 5-fluorouracil; EOX, epirubicin, oxaliplatin and capecitabine; ESD, submucosal dissection; FLOT, 5-fluorouracil + oxaliplatin + docetaxel + leucovorin; 5-FU, 5-fluorouracil; FOLFIRI, irinotecan, folinic acid, and fluorouracil; FOLFOX/ FOLFOX6, 5-fluorouracil + oxaliplatin + leucovorin; FP, fluoropyrimidine based-therapy; FTD/TPI, trifluridine/ tipiracil hydrochloride; G-CSF, granulocyte colony stimulating factor; GI, gastrointestinal; HIPEC, hyperthermic intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; ICIs, immune checkpoint inhibitors; IIC, Intraoperative intraperitoneal chemotherapy; ILD, interstitial lung disease; IP, intraperitoneal; IV, intravenous; MET, mesenchymal-epithelial transition; MIS, minimally invasive surgery; NAC, neoadjuvant chemotherapy; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PPI, Proton pump inhibitor; RFA, radiofrequency ablation; S-1, tegafur/gimeracil/oteracil; SOX, S-1 (tegafur/gimeracil/oteracil) and oxaliplatin; SSI, surgical site infection; TAE, transcatheter arterial embolization

days was deemed safe and efficient [45], with double-endoscope ESD further enhancing the ability to resect difficult ulcer-scar lesions, albeit at the cost of increased procedural complexity [46]. In older patients, ESD was found to be equally safe, with no major differences in the rate of complications compared with younger patients [47]. ESD can be considered non-inferior to surgery in terms of 10-year OS, although it comes with more early complications [19]. It may be appropriate for larger lesions (over 10–15 mm) under either absolute or expanded criteria [20] and might even extend to certain small mucosal signet-ring carcinomas under strict conditions [48]. In a remnant stomach, however, ESD can take longer (remnant vs intact group: 110.3±63.9 vs 81.9±54.7; p<0.01) and achieve a lower curative resection rate (remnant vs intact group: 77.5, 107 lesions vs. 87.7%, 2,841 lesions; p<0.01), but complication rates remain comparable to those in an intact stomach [49].

Other local interventions address different clinical needs. Surgical margin length, e.g., was found not to influence 5-year OS or recurrence in T2/T3 disease, suggesting a degree of flexibility in margin settings [50]. For patients with acute, uncontrollable bleeding in advanced GC, transarterial embolization was an effective alternative when endoscopic or surgical approaches were not feasible [51]. Stenting offers another local solution, particularly for tumours in the esophagogastric junction (EGJ) or pylorus. Although overall prognosis and complication rates were similar, EGJ stents showed better stability in preventing reobstruction compared to pyloric stents. In fact, the reprocedure average period was longer in the EGJ obstruction group (158.3 ± 42.4 days vs pyloric obstruction 86.0 ± 29.1 days; p=0.022) [52].

Neoadjuvant, adjuvant, or advanced-line chemotherapy

Neoadjuvant (NAC) and adjuvant chemotherapy have demonstrated benefits in survival and surgical outcomes for GC. NAC has been associated with reduced surgical mortality and morbidity, compared to surgery alone [53, 54]. Similarly, NAC with the SOX regimen (S-1 (tegafur/gimeracil/oteracil) and oxaliplatin) achieved over 90% disease control rate and the SOX group had 3.9% metastatic lymph nodes, less than the control (9.9%), FOLFOX6 (6.6%), and XELOX (5.3%) groups [35]. The DOC-based regimen (docetaxel + oxaliplatin + capecitabine) improved 2-year progression-free survival (PFS: 54.1% vs 41.4%; p=0.14) and OS (80.8% vs 58.6%; p=0.05) compared to EOF (epirubicin + oxaliplatin + 5-fluorouracil), with a lower incidence of grade ≥3 neutropenia (23.5% vs 34.4%; p=0.33) [55]. Perioperative chemotherapy also showed a favorable trend for OS and DFS [56]. In the adjuvant context, chemotherapy proved beneficial for stage III disease in elderly patients but not for stage II [25], and XELOX (capecitabine + oxaliplatin) emerged as the recommended regimen in more advanced stages [36, 57]. Beyond these regimens, adding cellular immunotherapy to chemotherapy could further improve 3-year DFS (74.7% vs 60.6%; p=0.036) and OS (83.0% vs 64.9%; p=0.051), particularly in higher-stage disease [58].

Other authors focused on intraperitoneal approaches and hyperthermic intraperitoneal chemotherapy (HIPEC). HIPEC accelerated bowel recovery (42.9 vs 67.8 hours; p<0.05), earlier initiation of a liquid diet (3.03 vs 4.02 days; p<0.05), and reduced hospital stay (8.15 vs 14.08 days; p<0.05) compared to surgery alone [24]. For peritoneal metastases, combining SOX with intraperitoneal paclitaxel proved highly effective, often facilitating conversion surgery [27, 28]. Similarly, intraperitoneal hyperthermic perfusion (IPHP) improved 1-year survival rate (85.5% vs 73.8%; p= .027), exceeding that of non-IPHP treatment, and reduced the 2-year mortality risk by 1.8 times (OR=0.556; p=0.004) without increasing complications [34].

Beyond local or perioperative strategies, several studies highlight the utility of systemic therapy across multiple lines of treatment. Third-line chemotherapy significantly improved survival in metastatic GC, with median OS of 18 vs 8 months (p<0.0001), especially in patients under 70, with good performance status (ECOG 0–1), prior surgery, and combination first-line therapy [59]. Likewise, adding radiotherapy to chemotherapy significantly improved outcomes, with higher remission rates (90.6% vs 73.5%), longer median survival (10.6 vs 6.7 months), and better 6-month (83.3% vs 62%), 1-year (38.2% vs 22.8%), and 2-year (13.7% vs 7.6%) survival rates compared to chemotherapy alone (p<0.05) [60]. Intensity-modulated radiotherapy specifically minimized renal dose, potentially preventing long-term nephrotoxicity [61]. In distal intestinal GC, taxane-containing regimens prolonged PFS and OS by a few months [62], while infusional 5-fluorouracil (5-FU) [63] and sequential intravenous plus S-1 therapy [64] showed favorable tolerance. Maintenance capecitabine after XELOX significantly improved PFS (11.4 vs 7.1 months; p<0.001) and was identified as an independent prognostic factor, with low rates of severe side effects [21].

Targeted therapy and immunotherapy

Research on targeted therapies for specific gastric malignancies has shown how biomarkers can inform treatment strategies. Tumors with MET overactivation and a high stromal proportion had poorer overall outcomes but demonstrated improved responses to MET inhibitors like crizotinib [65]. Similarly, apatinib improved survival in advanced GC patients with poor performance status when combined with best supportive care compared to supportive care alone (4.3 vs 2.1 months; p=0.0004), with common side effects including fatigue (82.6%), appetite loss (73.9%), and anemia (69.6%) [22].

HER2-targeting has impacted on the management of GC, with trastuzumab offering substantial benefits when combined with chemotherapy. One study reported a median PFS of 7.7 months and OS of 16 months for patients receiving trastuzumab plus chemotherapy, though liver metastases or poor performance status negatively affected outcomes [66]. Maintenance therapy with trastuzumab plus single-agent chemotherapy reduced mortality risk by 29% and significantly improved OS in subgroups, including patients with stable disease (Hazard Ratio (HR)=0.084; p=0.004), age >65 (HR=0.4; p=0.015), no liver metastasis (HR=0.271; p=0.008), and fewer than two metastatic organs (HR=0.263; p=0.005). It was also more cost-efficient than trastuzumab alone [67]. Deep-learning models like Nomo-LDLM-2F can predict which patients will benefit the most from HER2-targeted therapies [37]. Furthermore, adding ramucirumab to paclitaxel nearly doubled OS compared to monotherapy (11.0 vs 5.7 months) but was associated with higher rates of grade ≥3 adverse events (60.8% vs 34.2%), particularly neutropenia (49.6% vs 8.9%) [29].

The field of immunotherapy has progressed rapidly, with ICIs becoming a critical treatment option. Multiple studies emphasize the role of predictive biomarkers: a pathomics-driven model effectively identified likely responders to ICIs [68], while a novel CT-based biomarker correlated with innate immune signaling and ICI responses in GC [69]. Interestingly, higher rates of immune-related adverse events were linked to reduced risk of death (HR=0.606, 95% CI: 0.444-0.827), suggesting a paradoxical relationship between toxicity and treatment response [70]. For heavily pretreated patients, post-nivolumab cytotoxic chemotherapy further extended survival [71], with a prognostic index identifying significantly worse outcomes in moderate- and poor-risk groups (HR=1.88 and 3.29, respectively), suggesting a potential synergistic antitumor effect warranting further investigation. Additionally, combining apatinib with p53 expression data resulted in a 17.4% objective response rate and a 79.3% disease control rate [72], while elevated alpha-fetoprotein levels were associated with poorer disease control (50.0% vs 87.7%; p<0.001), shorter PFS (p=0.011), and OS (p=0.036) during ICI therapy [73].

Prognosis, risk factors, quality of life, and supportive care

Numerous studies emphasized the impact of genetic, nutritional, and pathological factors on patient outcomes and postoperative risk. One study found that the DPYD (rs1801159) genotype was linked to a higher risk of grade 3-4 toxicity, improving the overall toxicity-risk modeling [30]. Malnutrition, or a 5% weight loss, was associated with longer hospital stays, although complication rates did not significantly change [31]. Tumour and host-related markers also played crucial roles in predicting survival: a high neutrophil-to-lymphocyte ratio, an elevated modified Glasgow Prognostic Score, poor nutritional status, and peritoneal metastases were all linked to poorer OS. The median OS was 27.6 months for the favorable-risk group, 13.2 months for the intermediate-risk group, and 8.2 months for the poor-risk group. The 2-year survival rates were 52% for the favorable-risk group, 16% for the intermediate-risk group, and 3% for the poor-risk group (p< 0.001) [74]. Logistical factors, such as post-discharge follow-up, were also important, with 16.6% of complications occurring after hospital release, particularly among patients with comorbidities or obesity [75]. In terms of endoscopic procedures, lymphovascular invasion (OR=7.636, 95% CI 1.730 to 22.857; p=0.004) and submucosal involvement (OR=3.735, 95% CI 1.026 to 12.177; p=0.047) were key indicators for lymph node metastasis, although ESD was considered safe [76].

Some studies explored the timing and detection of secondary or missed lesions, as well as other risk factors that may not necessarily affect long-term outcomes. In a large cohort, 61 missed GCs were identified, often associated with Billroth II anastomosis and PPI use. Although these cancers were typically detected at an earlier stage, their OS was similar to that of non-missed cases [23]. Moreover, *H. pylori* eradication after distal gastrectomy did not significantly affect recurrence or survival [77], and additional imaging beyond standard CT did not provide meaningful improvements in detecting advanced T3-T4 disease [78]. Interestingly, even the treatment of early-stage cancer appeared to influence long-term bone density, as patients who underwent surgical treatment experienced greater bone loss compared to those treated endoscopically. In the endoscopic group, BMD changes were –3.30% at the lumbar spine, –1.52% at the femoral neck, and 0.40% at the total hip. The gastrectomy group showed greater reductions: –7.17%, –0.30%, and –3.49%, respectively [79].

Quality of life (QoL) and supportive care measures are essential dimension of GC management. First-line chemotherapy can improve QoL, though direct comparisons among regimens remain inconclusive [80]. Despite its potential benefits in reducing peritoneal recurrence, intraoperative intraperitoneal chemotherapy was associated with a higher rate of organ/space surgical site infections (9.01% vs 3.88%; p=0.002). This results in longer hospital stay in patients who received intra-operative intraperitoneal chemotherapy (mean 20.91 days, 95% CI 19.76-22.06 vs 29.72 days, 95% CI 25.46-33.99; p=0.000) [81]. Various antiemetic strategies also play a role in patient well-being: the addition of aprepitant to cisplatin plus S-1 improved nausea control [38], while palonosetron-based prophylaxis reduced delayed emesis but did not eliminate it [39]. Several factors have been identified as contributing to an increased risk of infection (i.e., open surgery, male sex, splenectomy, higher body mass index, longer operative times) [82].

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Postoperative care significantly impacts outcomes; improving baseline and postoperative QoL, along with adjuvant chemotherapy, led to survival benefits, even in patients with incurable cases [83].

Future directions

A prominent theme emerging from the investigations is the call for larger prospective or randomized trials to better substantiate the efficacy and safety of various therapeutic approaches. The authors underscored the need for more robust trial designs to verify initial findings and address limitations often seen in smaller or retrospective studies [25, 37, 53, 61, 84]. These studies collectively argue that well-powered, multicenter research is crucial for generating stronger evidence and improving clinical decision-making in GC.

A significant concern for many researchers is the optimisation of preoperative strategies. They cautioned against sole reliance on imaging and recommended that, once NAC is completed, proceeding directly to surgery -rather than attempting second-line NAC- may improve outcomes [54]. The importance of enhanced imaging methods for more accurate T staging before NAC initiation was also emphasized [78]. Conversely, Dong (2016) [35] suggested that the SOX regimen is promising as NAC for Chinese patients with advanced GC, highlighting the need to tailor therapeutic interventions to specific demographics.

Several authors underlined the role of endoscopic or local therapies and the importance of close follow-up. Continuing endoscopic surveillance for longer than five years to detect metachronous GC was recommended [85], as well as osteoporosis screening post-endoscopic treatment to preserves bone health [79]. ESD was deemed feasible and safe for older patients [47] but additional research on ESD for small, mucosal signet-ring cell tumours is necessary [48]. To minimize diagnostic oversights, standard definition of missed GC, refined biopsy, ulcer-follow-up protocols, and caution with PPIs or Billroth II anatomy were also recommended [23].

Several studies focused on chemotherapy approaches. The importance of palliative chemotherapy in metastatic disease and ongoing guideline updates were emphasized [26]. It is imperative that a diligent monitoring system be established for the identification of adverse events. This will require the administration of a low-dose apatinib in conjunction with supportive care for patients demonstrating poor performance status [22]. Maintenance capecitabine after induction XELOX was identified as a promising strategy for advanced disease [21]. For those responding to first-line therapy, continued trastuzumab in combination with a single chemotherapy agent was recommended [67]. Similarly, the necessity for enhanced therapeutic interventions for HER2-positive cases that are complicated by liver metastases or poor performance status was underscored [66]. The authors also advocated XELOX-based adjuvant chemotherapy for stage II and for stage 3B/3C disease [36, 57]; a taxane-based triple regimen (e.g., DCF: cisplatin+5FU+docetaxel) for advanced GC was also recommended [62].

Subsequent studies addressed the development of novel therapeutic interventions, with a particular focus on immunotherapy and targeted agents, highlighting the potential for the utilisation of cellular immunotherapy in the treatment of GC and of ongoing trials to provide more definitive evidence regarding its impact [58]. Recent studies confirmed the real-world efficacy and safety of ramucirumab [29] and proposed a pathomics-based model to predict immunotherapy responses [68].

The authors discussed the importance of risk stratification, biomarkers, and supportive care. The development of more robust protocols for the prevention and management of surgical site infection is considered imperative in the event of widespread implementation of intraoperative chemotherapy [81]. A preoperative nutritional intervention to achieve optimal surgical outcomes is also important [31]. A novel surgical site infection risk model that requires validation in larger cohorts was proposed in a study [82]. Regarding molecular and histologic markers, there is a need for validation of a genotype-based nomogram [30].

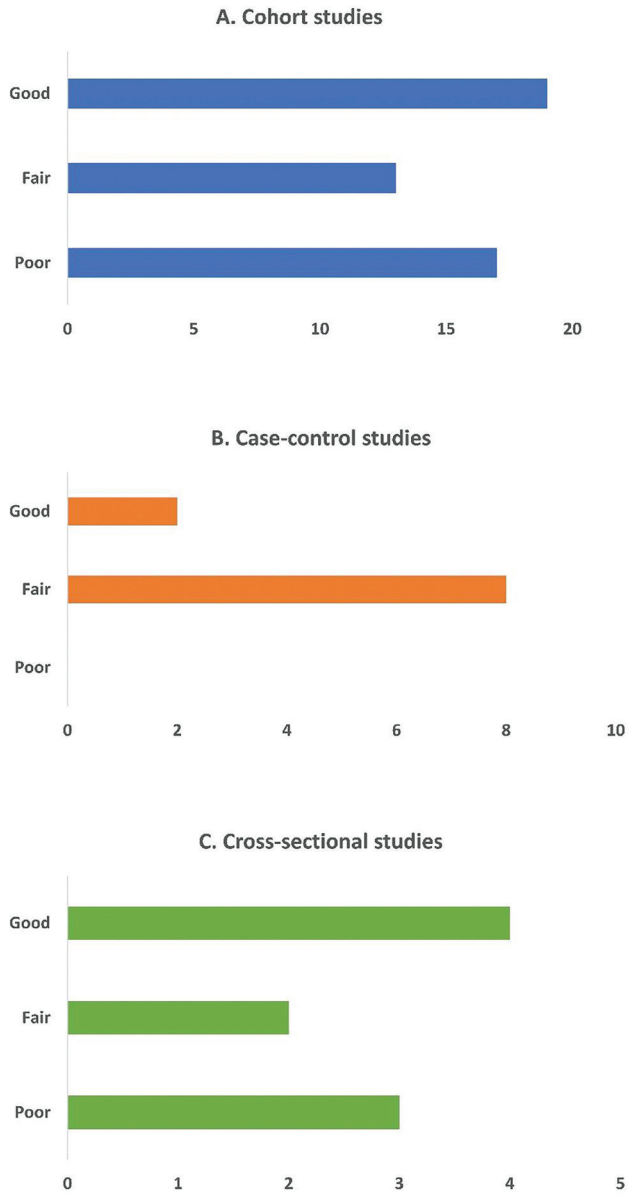
Results of the quality assessment

Of the 68 studies analyzed, 25 (36.8%) were considered to be of higher quality. Forty-nine studies employed a cohort design, with 19 of them rated as good quality, scoring between 6-8 points (Figure 2A). Most of the cohort studies with lower scores did not earn points in the comparability section and lacked representativeness of the exposed cohort. Among the 10 case-control studies (Figure 2B), two were classified as good quality, achieving 7-8 points. The remaining eight studies, rated as "fair," mainly suffered from issues with control selection and definition. The nine cross-sectional studies displayed similar quality, with two receiving low ratings due to the failure to adjust for sex or other demographic factors in the statistical analysis (Figure 2C).

DISCUSSION

The systematic review highlighted recent advances that have been achieved in GC treatment in the last decade. However, continued research and development are essential, as GC remains a significant clinical challenge. Ongoing studies are exploring future therapies, aiming to optimize combinations and sequences of existing treatments while incorporating innovative approaches. Some of the promising areas of investigation are immunotherapy (e.g., checkpoint inhibitors, cancer vaccines), targeted therapy (e.g., HER2-targeted treatments), angiogenesis inhibitors

Figure 2. Quality assessment of the gastric cancer studies



targeting blood vessel formation (e.g., ramucirumab), combination therapies that combine immunotherapy with chemotherapy or targeted therapies to enhance efficacy. In the field of personalized medicine, biomarker-driven approaches are being investigated to tailor treatments based on the genetic and molecular profile of individual tumours, improving treatment effectiveness. Research is also ongoing to evaluate the effectiveness of chemotherapy, radiotherapy, and targeted therapies when given before (neoadjuvant) or after (adjuvant) surgery. These research studies hold promise for enhancing outcomes in GC patients, with ongoing clinical trials being essential for refining and validating these potential therapies [86].

Most authors emphasized the necessity of large randomized controlled trials (RCTs) to validate current findings in GC research [32, 33, 34, 40, 41, 58, 72, etc.]. The recommendation for large RCTs is well-founded, as our review identified variability in participant numbers and study timelines. These differences reflect the diverse objectives of the research, some emphasizing immediate feasibility and early outcomes, while others focus on long-term follow-up and survival analysis. Additionally, variations in surgical techniques, medical environments, and patient conditions contribute to discrepancies in study results, making it challenging to generalize findings across different time periods and geographic regions. To address these challenges, extensive translational research, preclinical investigations, and multi-omics-based clinical trials with extended follow-up are needed to enhance consistency and applicability.

Although numerous studies have explored complex treatment regimens, including mono-immunotherapy, dual checkpoint inhibitors, and biomarker-directed therapies, the challenge of identifying the optimal treatment strategy, particularly for advanced GC, remains unresolved. The emerging therapies for GC offer several advantages and potential improvements over standard treatments but also present unique challenges and side effects. Authors emphasize the need for robust management protocols to enhance patient outcomes [29, 35, 59, 60, 68, 69, 87, 88]. Regular monitoring and supportive care are essential for mitigating side effects, while personalized treatment plans can help minimize risks, particularly for high-risk patient groups [22, 38, 39].

This systematic review has some limitations, primarily the inclusion of records published only between 2013 and 2024. While this may have excluded some relevant studies, our aim was to capture advancements in GC management over the past decade. The selection of English and French was based on the authors' language proficiency; however, as most scientific literature is published in English, no French articles were identified. Additionally, a meta-analysis was not performed due to the high heterogeneity among the studies, making a narrative synthesis a more suitable approach.

In conclusion, current findings highlight a paradigm shift toward more precise, biomarker-guided care in advanced GC, while minimally invasive or localized strategies—alone or combined with neoadjuvant and adjuvant chemotherapy—have shown promise in early GC. Optimized diagnosis and treatment may be achieved through artificial intelligence, enhanced cancer registry databases, and genome analysis to predict cytotoxic drug efficacy, ultimately improving patient prognosis. While emerging therapies offer significant potential, their effectiveness compared to existing treatments remains under investigation. Each therapeutic approach presents unique benefits and risks, underscoring the need for personalized treatment strategies that consider tumor characteristics, patient performance status, and individual preferences. As research advances, integrating these novel therapies into standard GC care could improve survival rates and QoL for patients.

AUTHOR CONTRIBUTION

Conceptualization: IE, BU; Methodology: IE, BU, IG, YLS; Formal analysis: BU, YLS; Investigation: IE, BU, IG, YLS; Writing - Original Draft: BU, YLS, IE; Writing – Review & Editing: BU, YLS, IE, IG; Supervision: BU. All authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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