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REVIEW

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Comparative analysis of systemic oncological treatments and best supportive care for advanced gastresophageal cancer: A comprehensive scoping review and evidence map

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Abstract

Objective: To identify, describe, and organize the available evidence regarding systemic oncological treatments compared to best supportive care (BSC) for advanced gastresophageal cancer.

Methods: We conducted a thorough search across MEDLINE (PubMed), EMbase (Ovid), The Cochrane Library, Epistemonikos, PROSPERO, and Clinicaltrials.gov. Our inclusion criteria encompassed systematic reviews, randomized controlled trials, quasi-experimental and observational studies involving patients with advanced esophageal or gastric cancer receiving chemotherapy, immunotherapy or biological/targeted therapy compared to BSC. The outcomes included survival, quality of life, functional status, toxicity, and quality of end-of-life care.

Results: We included and mapped 72 studies, comprising SRs, experimental and observational designs, 12 on esophageal cancer, 51 on gastric cancer, and 10 both locations. Most compared schemes including chemotherapy (47 studies), but did not report therapeutic lines. Moreover, BSC as a control arm was poorly defined, including integral support and placebo. Data favor the use of systemic oncological treatments in survival outcomes and BSC in toxicity. Data for outcomes including quality of life, functional status, and quality of end-of-life care were limited. We found sundry evidence gaps specifically in assessing new treatments such as immunotherapy and important outcomes such as functional status, symptoms control, hospital admissions, and the quality of end-life care for all the treatments.

Conclusions: There are important evidence gaps regarding new for patients with advanced gastresophageal cancer and the effect of systemic oncological treatments on

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important patient-centered outcomes beyond survival. Future research should clearly describe the population included, specifying previous treatments and considering therapeutic, and consider all patient-centered outcomes. Otherwise, it will be complex to apply research results into practice.

KEYWORDS
drug therapy, esophageal neoplasms, immunotherapy, molecular targeted therapy, review, stomach neoplasms

1 | INTRODUCTION

Esophageal and gastric cancers are significant public health problems worldwide. Their combined mortality has exceeded 1.2 million in 2020, and they have become the second most common cause of cancer-related deaths after lung cancer.[1] Both types of cancers are often diagnosed in advanced stages, due to their aggressive nature, typically have a poor prognosis.[2,3] In a metastatic stage, gastresophageal cancers (GEC) have less than 30% survival at one year and less than 5% at 5 years.[4]

For patients in advanced stages, systemic oncological treatments (SOTs) including chemotherapy (CT), targeted/biological therapy, and immunotherapy are currently the classical therapeutic approaches, and their use has increased as more potentially effective drugs have been developed. Nevertheless, they are also associated with notable toxicity that may impact patient's quality of life (QoL), and what entails their prescription could be an indicator, in some cases, of poor-quality and aggressiveness of care.[5,6] Best supportive care (BSC), in contrast, is focused on symptom control and improvement in patients' QoL, including a variety of treatments given by highly personalized multidisciplinary teams to on-demand consultations.[7–9] It is widely accepted that BSC has a role as a complementary treatment, but it is uncertain if it could be a reasonable alternative when the disease is more advanced.[10]

Our previous study recently found that the methodological quality of guidelines for advanced GEC was heterogeneous, and many of the recommendations were still not based on systematic reviews (SR) but on individual primary studies, sometimes with nonexperimental designs.[11] Despite the number of recommendations on advanced GEC treatment,[12,13] very few clinical guidelines considered other important outcomes beyond survival.[14–17] For instance, QoL, functional status, hospital admissions, symptom control, and quality of end-life care were all outcomes that should be considered into treatment discussions with patients.

Besides guidelines, it was crucial to analyze the whole body of available evidence identifying possible knowledge gaps to better guide future research and ultimately translate into better patient care. Scoping review was a useful tool in the ever-increasing arsenal of evidence synthesis approaches.[18] It might be conducted to "map the literature on a particular topic or research area and provide an opportunity to identify key concepts; gaps in the research; and types and sources of evidence to inform practice, policymaking, and research."[19] In this context, we conducted a scoping review to identify, describe, and organize the available evidence about the efficacy of SOTs compared to BSC for patients with advanced GEC, with the purpose to identify evidence gaps that require further research.

2 | METHODS

2.1 | Protocol and registration

Our review was conducted in accordance with the guidance provided by the JBI Scoping Review Methodology Group.[20–22] The reporting of the review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guideline, as well as the methodology proposed by Global Evidence Mapping Initiative[23,24] (PRISMA_ScR checklist is available in Supplementary Material 1). Methods for determining the scope of a content area[25–27] consist of the following: (1) establish the boundaries and context of the subject area in question; (2) search and selection of relevant studies; and (3) report on the performance and characteristics of the study. The protocol for this study was prospectively registered and is openly accessible on Open Science Framework.[28] This study is part of a broader project (ASTAC-Study) that aims to describe and assess the available evidence on the efficacy and appropriateness of SOT in advanced nonintestinal digestive cancers (including advanced hepatobiliary, gastresophageal, and pancreatic cancer). Here, we report the results of the scoping review and evidence mapping on advanced GEC.

2.2 | Eligibility criteria

We used the PCC framework (Population, Concept, and Context) to guide our review question and eligibility criteria.[20] According to this framework, our review question was: "What research has been conducted to assess the efficacy of SOTs compared to BSC for patients with advanced GEC considering patient-centered outcomes?" Supplementary Material 2 presents inclusion and exclusion criteria.

2.2.1 | Population

Adult patients (over 18 years), with esophageal or gastric cancers, including gastresophageal junction (GEJ), either primary or recurrent, either adenocarcinoma or squamous cell carcinoma, in stages IIIb, IIIc, or IV,[29] or described as advanced or metastatic stage by study authors at the moment of the intervention. We excluded lymphatic, stromal, and neuroendocrine cancers.

2.2.2 | Concept

We included studies that compared SOTs with BSC. For SOT, we considered any CT (either monotherapy or in combination), biological/targeted therapy (BIO/TT), or immunotherapy, whether individual or combined, with or without supportive care. We excluded studies that solely examined surgical or radiotherapy intervention, as well as studies that considered CT solely as adjuvant or neoadjuvant therapy.

For BSC, we included any supportive treatment aimed at symptomatic or palliative control. This encompassed both usual treatment approaches and BSC.[8] Studies that did not explicitly define the control groupt's intervention or studies where the control group received a placebo were also included. Exclusions were made for studies in which the control group received any form of CT, biological/targeted therapy, or immunotherapy. Additionally, interventions with nonpalliative intent, such as curative surgery or radiotherapy, were excluded.

Supplementary Material 3 presents other patient-centered outcomes considered in addition to survival. Overall survival (OS), QoL, functional status, and toxicity were considered as primary outcomes, which were visually mapped.

2.2.3 | Context

We considered studies in any clinical setting.

2.2.4 | Type of studies

We included primary research—randomized controlled trials (RCTs), quasi-experimental studies (QEx), and observational studies (OBS)—and SRs according to the recommendations of JBI Scoping Review Methodology Group.[30] We defined an SR as any form of secondary research that met the following criteria: (I) explicit eligibility criteria or research question; (II) structured search strategy involving explicit search terms and data framework in at least two databases; (III) clearly defined screening methods; (IV) explicit assessment of methodological quality or risk of bias of each included study; and (V) explicit approach to data analysis and synthesis.[31,32] For RCTs, we considered any experimental primary study that employed a random allocation of interventions. Study protocols of RCTs were also included in our analysis. In the case of QEx studies, we incorporated experimental studies with an inadequate process of randomization or specific study designs utilizing a nonrandomized allocation of interventions, such as interrupted time series or before-after studies. OBS encompassed case-control and cohort studies. We included OBS as long as they were controlled and consisted of a minimum of 30 patients.

We excluded studies with no control group, clinical practice guidelines, case reports, nonsystematic reviews (such as narrative reviews), and qualitative studies.

We did not apply any language or publication date restrictions except for SRs, for which we included only those published from 2008 onward.

2.3 | Search methods for identification of studies

We conducted thorough electronic searches across multiple databases to ensure a comprehensive coverage of the relevant literature. The following five databases were included MEDLINE (accessed via PubMed), EMbase (accessed via OVID), the Cochrane Database of Systematic Reviews (CENTRAL), and Epistemonikos. from inception until April, 2022 (date of search). To tailor our search strings to the specific requirements of each database, we combined controlled vocabulary and relevant search terms related to the key concepts of our clinical question. The search strategy for MEDLINE (PubMed) can be accessed in the Open Science Framework repository (https://osf.io/c6vxp). Search strings were common for the whole ASTAC-Study and included different cancer locations: gastresophageal, pancreatic, and hepatobiliary cancer.

In addition to the database search, we also explored PROSPERO and Clinicaltrials.gov to identify any protocols of potentially eligible studies. To further ensure inclusivity, we reached out to experts in the field to inquire about any relevant studies. It is worth mentioning that we did not employ any other strategies specifically targeting the retrieval of grey literature.

2.4 | Selection of studies

Initially, two reviewers independently evaluated the titles and abstracts of the search results, ensuring a comprehensive screening. In instances where discrepancies occurred, a third reviewer was consulted to resolve any disagreements and ensure consensus. Subsequently, two reviewers independently conducted a detailed full-text screening of the selected articles, rigorously assessing their eligibility for inclusion in the study. Any discrepancies that arose during this stage were resolved through consultation with a third author, ensuring a thorough and unbiased evaluation of the articles. To facilitate this systematic process and enhance efficiency, we utilized Covidence,[33] a web-based software platform that streamlines the production of evidence synthesis.

2.5 | Data extraction

Data extraction was carried out by two reviewers independently using a pre-tested data extraction sheet in Google Forms. The extraction sheet was carefully piloted prior to use. For each included study, the following information was extracted: year of publication, country, study design, conflict of interest, number of studies included answering our review question (for SRs), number of patients included (for primary studies), interventions assessed (CT, BIO/TT, immunotherapy), comparators (BSC, placebo, or nonspecified), outcomes reported, and direction of effect classified as "favors intervention," "favors comparison," or "no differences."

2.6 | Data synthesis and analysis

We conducted a descriptive analysis, reporting frequency counts and proportions of studies, populations, interventions, and outcomes assessed. The results were presented both narratively and in a tabular form, enabling the classification of studies based on cancer type, intervention type, methodological design, and the direction of the effect.

To visually represent evidence, we utilized the *evimappr* library,[34] an R package specifically designed for creating evidence maps. For each cancer type, we generated bubble plots as evidence maps. These maps were structured as a grids, with rows representing the different type of SOT and columns representing the outcomes assessed, including survival, QoL, functional status, and toxicity. Within each intersection of the grid, corresponding studies were populated and classified on their study design (SR, RCT, QEx, OBS). We identified an evidence gap if an intersection had no primary studies included.

3 | RESULTS

3.1 | Searching articles

Following the removal of duplicates, our comprehensive search yielded a total of 50,601 records encompassing various cancer locations, including gastresophageal, pancreatic, and hepatobiliary cancers. Subsequent screening of titles and abstracts led to the exclusion of 47,667 references. Among the remaining 2934 references, we were not able to retrieve 106 reports. consequently, we conducted a full-text review of 2828 articles, ultimately including a total of 185 studies that covered all cancer locations, of which 72 were related to advanced GEC (Figure 1).

3.2 | Characteristics of the included studies

Of the 72 included studies, 22 were SRs,[35-49] 21 were RCTs,[50-70] 4 were QEx studies,[71-74] 21 were OBS studies,[75-96] and 4 were RCT protocols.[97-100] Eleven studies focused on esophageal cancer, 51 on gastric cancer and 10 addressed both locations. Table 1 summarizes the characteristics of the included studies. Out of the total studies, 56 (77.8%) were published in the past 10 years and were published in English. The published studies were distributed among 23 different countries worldwide. China had the highest number of publications,[15] followed by Japan,[10] South Korea,[8] and the Netherlands.[6] The rest of the countries had fewer than 5 published studies.

Among the 11 studies on advanced esophageal cancer,[40,51,59,67,72,76,79,85,89,90,94] only three were RCT[51,59,67] including between 20 and 156 participants. All studies assessed the effect of CT. Most of the schemes included *5-Fluorouracil* (7 studies), *Cisplatin* (5 studies), *Docetaxel* (3 studies), and/or *Doxorubicin* (1 study). Most studies did not report the line of therapy (7 out of 11), and among those who did, two included SOT as first-line therapy and two second or further therapy lines. One study assessed BIO/TT, considering *Gefitinib* and *Ramucirumab* as second, third, or more lines.[40] No study assessed the effect of immunotherapy compared to BSC in advanced esophageal cancer.

Among the 51 studies including patients with advanced gastric cancer,[35-37,39,43,55-58,78,80-84,98,101-103] only 15 were RCT[55–58,60–66,69–71,103] including between 40 and 656 participants, and 31 studied the effect of CT. Most of the schemes included *5-Fluorouracil* (15 studies), *Irinotecan* (9 studies), *Docetaxel* (7 studies), and *Leucovorin* (7 studies). Many CT studies did not report the line of therapy (12 out of 31), and among those who did, nine included SOT as first-line therapy and 13-s or further therapy lines. Nineteen studies assessed BIO/TT considering *Apatinib* (13 studies), *Ramucirumab* (8 studies), and *Everolimus* (7 studies) mostly as second or more line of therapy (16 out of 19). Five studies assessed immunotherapy, considering *Ipilimumab, and Nivolumab* as second, third, or more lines of therapy.

Among the 10 studies including patients with both esophageal and gastric cancer,[42,45,46,52,53,68,77,99,100,104] only three were RCT[52,53,68] including between 45 and 449 participants, and nine studied the effect of CT. Most of the schemes included *Doxorubicin* and/or *Irinotecan*. Patients in their first, second, third, or more lines of therapy were considered, but three studies did not report this information. Three studies assessed BIO/TT, considering *Apatinib*, *Everolimus, Gefitinib*, *Ramucirumab*, *Regorafenib*, and *Marimastat* as first, second, third, or more lines of therapy. One study assessed immunotherapy with *Nivolumab* but did not report the lines of therapy.

Conflicts of interest (COI) were not reported in 29 (40.3%) studies. Of the 43 studies that included COI disclosures, 16 had at least one author reporting COI with industry.

3.3 | Outcomes

Figures 2 and 3 show an overall summary of the evidence retrieved for esophageal and gastric cancers, classified by type of SOT and reported outcomes. Table 2 provides details about the direction of the effect

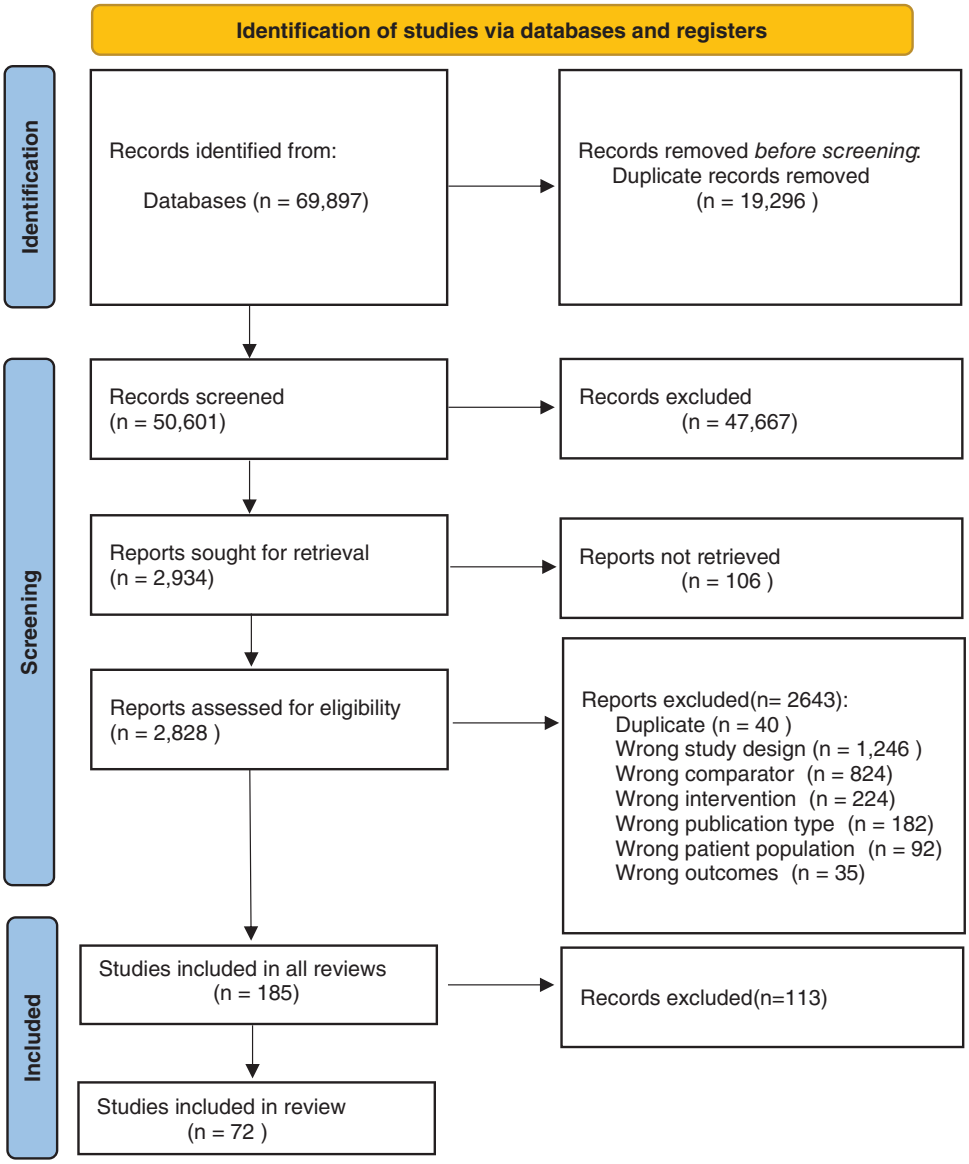

FIGURE 1 PRISMA flowchart.

reported by each study for all patient-centered outcomes considered in this scoping review.

Evidence regarding esophageal cancer comes mostly from SR assessing CT. The most reported outcomes were those related to survival, especially in the form of time-to-event survival. Although 19 studies reported survival outcomes in favor of SOT, eight studies (1 SR, 6 RCT and 1 observational study) did not find differences between SOT and BSC or placebo. For QoL outcomes, most studies (11 studies) did not show significant differences between SOT and BSC or placebo, although some (eight studies) reported favoring results for SOT. All but one study reporting toxicity (14 studies) found favorable results for BSC or placebo. There were evidence gaps regarding the effects of immunotherapy for all outcomes and the effects of any SOT in outcomes such as functional status, symptoms, admissions to hospital, or quality of end-life care.

Evidence regarding gastric cancer was mostly from RCT assessing CT. The most reported outcomes were survival-related, especially time-to-event survival. Most studies showed a trend favoring SOT in terms of survival outcomes (45 studies), although 14 studies on CT and BIO/TT (5 SRs, 9 RCT, and 1 OBS) did not find differences in survival between SOT and BSC or placebo. For QoL outcomes (15 studies), about half of the studies did not show a significant difference between SOT and BSC or placebo (8 studies) and the other half reported favoring results for SOT (7 studies). Regarding toxicity (24 studies), most studies (20 studies) found favorable results for BSC or placebo, although three RCTs did not find differences between BIO/TT and BSC or placebo, and one RCT found favorable results for immunotherapy. There were evidence gaps regarding the effect of immunotherapy for all outcomes, and the effect of any SOT in outcomes such as functional status, symptoms, admissions to hospital and quality of end-life care.

TABLE 1 Characteristics included studies ($n = 72$).

Study	Country	N[a]	Design	Location	Intervention	Scheme use	Line	Comparison	Outcome	Conflicts
Adenis 2010[76]	France	284	OBS	Esophageal	CTX	NS/NC	NS/NC	NS/NC	OS	NS/NC
Alberts 1992[51]	South Africa	20	RCT	Esophageal	CTX	5-FU, CIS	NS/NC	NS/NC	OS	NS/NC
Baumgartner 2020[76]	Austria	244	OBS	Esophageal; Gastric	CTX	5-FU, CAPE, CIS, DOC, EPI, OXA, Leucovorin	NS/NC	BSC	OS	Industry
Bernards 2013[77]	Netherlands	4797	OBS	Gastric	CTX	NS/NC	NS/NC	NS/NC	OS	No
Bernards 2016[78]	Netherlands	710	OBS	Esophageal	CTX	NS/NC	NS/NC	NS/NC	OS	No
Chan 2017_a,[b, 36]	China	5 of 5	SR	Gastric	CTX	DOC, IRI	2nd, 3rd or more	BSC, PLB	OS	No
					BIO/TT	Apatinib, EVE, RG			OS, PFS, Toxicity	
Chan 2017_b,[b, 35]	Australia	4 of 15	SR	Gastric	BIO/TT	Apatinib, Ramucirumab, RG	2nd, 3rd or more	PLB	OS, PFS, QoL	Industry
Chen 2018[102]	China	2 of 13	SR	Gastric	BIO/TT	Apatinib	3rd line	PLB	OS, PFS, Toxicity	No
Chen 2019_a,[b, 37]	China	2 of 9	SR	Gastric	IM	Ipilimumab, NIVO	2nd	BSC, PLB	OS, PFS	No
Chen 2019_b,[b, 80]	China	64	OBS	Gastric	BIO/TT	Apatinib	3rd or more	BSC	OS	No
Chua 2019[99]	Australia	.	PT	Esophageal; Gastric	CTX	RG	2nd, 3rd or more	PLB	OS, PFS, QoL	NS/NC
Ciardiello 2019[98]	Italy	136	PT	Gastric	CTX	Pamiparib	1st	PLB	OS, PFS	NS/NC
Ciliberto 2015[38]	Italy	3 of 22	SR	Gastric	BIO/TT	Apatinib, EVE, Ramucirumab	3rd or more	BSC, PLB	OS, PFS	No
Cordero-Garcia 2019[80]	Costa Rica	168	OBS	Gastric	CTX	5-FU, CAPE, CIS, Epirubicin, OXA, PAC, Leucovorin	NS/NC	NS/NC	OS, PFS	No
Dutton 2014,[b, 52]	UK	449	RCT	Esophageal; Gastric	BIO/TT	Gefitinib	2nd, 3rd or more	BSC, PLB	OS, PFS, QoL, Symptoms, Toxicity	Industry
EudraCT 2014,[b, 100]	Italy	.	PT	Esophageal; Gastric	CTX	RG	2nd	PLB	.	NS/NC

(Continues)

TABLE 1 (Continued)

Study	Country	N[a]	Design	Location	Intervention	Scheme use	Line	Comparison	Outcome	Conflicts
Ford 2014[53]	UK	168	RCT	Esophageal; Gastric	CTX	DOC	2nd, 3rd or more	BSC	OS, QoL, Symptoms, Toxicity	Industry
Fuchs 2014,[b, 103]	USA	355	RCT	Gastric	BIO/TT	Ramucirumab	NS/NC	BSC, PLB	OS, PFS, QoL, Toxicity	Industry
Glimelius 1997[55]	Sweden	61	RCT	Gastric	CTX	5-FU, EPEG, Leucovorin	NS/NC	BSCkorea	OS, QoL	NS/NC
Hayashi 2019[81]	Japan	681	OBS	Gastric	CTX	5-FU, IRI, Platin, Taxane, Trastuzumab	NS/NC	BSC	OS	No
Hwang 2014[82]	South Korea	68	OBS	Gastric	CTX	5-FU, CIS, DOC, IRI, OXA, PAC, Leucovorin	NS/NC	BSC	OS	NS/NC
Iacovelli 2014[39]	Italy	5 of 5	SR	Gastric	CTX	DOC, IRI	2nd	BSC, PLB	OS	No
					IM	Ramucirumab				
					BIO/TT	EVE				
Janmaat 2017,[b, 40]	Netherlands	5 of 11	SR	Esophageal	CTX	5-FU,CIS, DOC, DOX, CP	1st, 2nd	BSC	OS, PFS, QoL, Toxicity	NS/NC
					BIO/TT	Ramucirumab, Gefitinib	2nd	BSC	OS, PFS, QoL, Toxicity	
Jiang 2012[72]	China	99	Q-Exp	Esophageal	CTX	5-FU, CIS	NS/NC	NS/NC	Admission, FS, OS, Toxicity	NS/NC
Kang 2012[56]	South Korea	202	RCT	Gastric	CTX	5-FU, CAPE, CIS, DOC, Epirubicin, IRI	2nd, 3rd or more	BSC	OS	No
Kang 2017,[b, 70]	South Korea	493	RCT	Gastric	IM	NIVO	3rd or more	PLB	OS, PFS, Toxicity	NS/NC
Kang 2019,[b, 57]	South Korea	460	RCT	Gastric	BIO/TT	Apatinib	3rd or more	PLB	OS, PFS	NS/NC
Kano 1982[84]	Japan	196	OBS	Gastric	CTX	MITO, FT	NS/NC	NS/NC	OS	NS/NC
Kawamoto 2018[85]	Japan	70	OBS	Esophageal	CTX	5-FU, CIS	1st	NS/NC	Symptoms	No
Khatri 2019[58]	India	51	RCT	Gastric	CTX	5-FU, EPEG, Leucovorin	NS/NC	BSC	OS, QoL	NS/NC
Kozaczka 1990[73]	Poland	100	Q-Exp	Gastric	CTX	5-FU, CP, MTX, Lederfolin	NS/NC	NS/NC	OS	NS/NC
Kundel 2020,[b, 41]	Israel	1 of 5	SR	Gastric	IM	NIVO	3rd or more	PLB	OS, PFS	Industry
Lee 2012[74]	South Korea	372	Q-Exp	Gastric	CTX	NS/NC	2nd	BSC	OS	NS/NC
Lee 2016[86]	South Korea	1871	OBS	Gastric	CTX	NS/NC	NS/NC	NS/NC	OS	No
Levard 1998[59]	France	156	RCT	Esophageal	CTX	5-FU, CIS	NS/NC	NS/NC	OS, Symptoms, Toxicity	NS/NC

(Continues)

TABLE 1 (Continued)

Study	Country	N[a]	Design	Location	Intervention	Scheme use	Line	Comparison	Outcome	Conflicts
Li 2013,[b, 60]	China	141	RCT	Gastric	BIO/TT	Apatinib	3rd or more	PLB	OS, PFS, QoL	No
Li 2016,[b, 61]	China	267	RCT	Gastric	BIO/TT	Apatinib	3rd or more	PLB	OS, PFS, QoL, Toxicity	Industry
Lin 2008[87]	China	389	OBS	Gastric	CTX	5-FU	NS/NC	NS/NC	OS	NS/NC
Liu 2018,[b, 129]	China	3 of 8	SR	Gastric	BIO/TT	Apatinib, Ramucirumab, RG	2nd, 3rd or more	PLB	OS, PFS	No
Liu 2020[42]	China	4 of 7	SR	Esophageal; Gastric	CTX	DOC,IRI	NS/NC	BSC, PLB	OS, PFS, Toxicity	No
					IM	NIVO				
Moon 2010[88]	Korea	532	OBS	Gastric	CTX	5-FU, ADM, CAP, DOC, DOX IRI,OXA,PAC, S1	1st, 2nd, 3rd or more	BSC	OS	No
Moriwaki 2014[89]	Japan	111	OBS	Esophageal	CTX	DOC	2nd	BSC	OS	No
Murad 1993[75]	Brazil	40	Q-Exp	Gastric	CTX	5-FU, DOX, Leucovorin, MTX	1st	BSC	OS	NS/NC
Nomura 2016[90]	Japan	283	OBS	Esophageal	CTX	5-FU, DOC, Fluorouracil, PAC, Platin, Taxane, INDs, IRI, S1	3rd or more	BSC	OS, PFS, Toxicity	No
Oba 2013[43]	Japan	1 of 22	SR	Gastric	CTX	5-FU, EPEG, Leucovorin	NS/NC	BSC	OS	No
Ohtsu 2013,[b, 62]	Japan	656	RCT	Gastric	BIO/TT	EVE	2nd, 3rd or more	PLB	OS, PFS, Toxicity	Industry
Park 1997[91]	Korea	409	OBS	Gastric	CTX	5-FU, DOX, MITO	1st	NS/NC	OS	NS/NC
Park 2008[96]	South Korea	254	OBS	Gastric	CTX	NS/NC	2nd	BSC	OS	NS/NC
Park 2011[63]	South Korea	193	RCT	Gastric	CTX	DOC, IRI	2nd	BSC	OS	NS/NC
Pavlakis 2016,[b, 64]	Australia	147	RCT	Gastric	BIO/TT	RG	2nd, 3rd or more	PLB	OS, PFS, QoL, Symptoms, Toxicity	Industry
Pyrhönen 1995[65]	Finland	41	RCT	Gastric	CTX	5-FU, Epirubicin, MTX, Leucovorin	1st	BSC	Admission, OS, PFS, Toxicity	NS/NC
Qi 2014[44]	China	2 of 7	SR	Gastric	BIO/TT	Apatinib, Ramucirumab	2nd	PLB	OS, PFS	No
Qin 2014[71]	China	270	RCT	Gastric	BIO/TT	Apatinib	NS/NC	PLB	OS, PFS	NS/NC
Shitara 2018,[b, 66]	Japan	507	RCT	Gastric	CTX	Tipiracil, Trifluridine	3rd or more	PLB	FS, OS, PFS, QoL, Symptoms, Toxicity	Industry

(Continues)

TABLE 1 (Continued)

Study	Country	N[a]	Design	Location	Intervention	Scheme use	Line	Comparison	Outcome	Conflicts
Schmid 1993[66]	South Africa	86	RCT	Esophageal	CTX	5-FU, Trimetrexate, Ifosfamide, Mesna, Leucovorin	NS/NC	NS/NC	OS, Symptoms	NS/NC
Sugimoto 2017[96]	Japan	47	OBS	Gastric	CTX	NS/NC	1st	BSC	OS	NS/NC
Sugimoto 2019[95]	Japan	141	OBS	Gastric	CTX	NS/NC	1st, 2nd	BSC	OS	No
					BIO/TT	Ramucirumab, Trastuzumab	1st			
Swinson 2019[67]	UK	45	RCT	Esophageal; Gastric	CTX	CAPE, OXA	NS/NC	BSC	OS	NS/NC
TerVeer 2016_a[45]	Netherlands	7 of 29	SR	Esophageal; Gastric	CTX	DOC, IRI	2nd, 3rd or more	BSC	OS, PFS, Toxicity	Industry
					BIO/TT	Apatinib,EVE, Ramucirumab, RG			OS, PFS, Toxicity	
TerVeer 2016_b[46]	Netherlands	2 of 65	SR	Esophageal; Gastric	CTX	Anthracycline, CIS, Fluoropyrimidine, IRI, OXA, MTX, taxane	1st	BSC	OS, PFS	Industry
Thuss-Patience 2011,[b,69]	Germany	40	RCT	Gastric	CTX	IRI	2nd	BSC	OS	No
Tsavaris 1999[93]	Greece	260	OBS	Gastric	CTX	5-FU, Carboplatin, Epirubicin, MITO	NS/NC	NS/NC	OS	NS/NC
van Kleef 2020[104]	Netherlands	7 of 43	SR	Esophageal; Gastric	CTX	5-FU, DOC, EPEG, Leucovorin	1st, 2nd, 3rd or more	BSC, PLB	OS, QoL, Symptoms	Industry
					BIO/TT	Apatinib, EVE, Gefitinib, Ramucirumab, RG, Marimastat			OS, QoL, Symptoms	

(Continues)

TABLE 1 (Continued)

Study	Country	N[a]	Design	Location	Intervention	Scheme use	Line	Comparison	Outcome	Conflicts
Wagner 2017[47]	Switzerland	2 of 64	SR	Gastric	CTX	5-FU, ADM, Epirubicin, MTX	1st	BSC	OS	Industry
Wallis 2019,[b, 48]	Canada	1 of 23	SR	Gastric	IM	NIVO	NS/NC	PLB	OS	Industry
Wang 2017[49]	China	3 of 10	SR	Gastric	BIO/TT	Apatinib, EVE, Ramucirumab	2nd	PLB	OS	No
Wong 2017[94]	USA	155	OBS	Esophageal	CTX	NS/NC	NS/NC	NS/NC	OS	No
Xie 2017[130]	China	2 of 23	SR	Gastric	BIO/TT	Bevazicumab, Cetuximab, EVE, Lapatinib, Nimotuzumab, Onartuzumab, Panitumumab, Ramucirumab, Sunitinib, Trastuzumab, Endostar, Matuzumab	NS/NC	PLB	OS, PFS	No
Xue 2018[131]	China	2 of 7	SR	Gastric	BIO/TT	Apatinib	3rd or more	PLB	OS, PFS	No
Zeng 2014[132]	China	1 of 8	SR	Gastric	CTX	IRI	NS/NC	BSC	OS	NS/NC
Zhu 2017,[b, 133]	Canada	5 of 8	SR	Gastric	CTX	CIS, DOC, IRI, PAC	2nd, 3rd or more	BSC, PLB	OS	Industry
					BIO/TT	EVE, Ramucirumab				

5-FU: fluorouracil; ADM: adriamycin; BIO: biological; BSC: best supportive care; CAPE: capecitabine; CIS: cisplatin; CP: cyclophosphamide; CTX: chemotherapy; IM: immunotherapy; NS/NC: not specified/not clear; OBS: observational study; PT: protocol; Q-Exp: quasi-experimental study; RCT: randomized clinical trial; SR: systematic review; TT:target therapy; DOC: docetaxel; DOX: doxorubicin; EPEG: etoposide; EVE: everolimus; FT: tegafur; GEM: gemcitabine; INDs: investigative new drugs, IRI: irinotecan; NIVO: nivolumab; MITO: mitomycin; MTX: methotrexate; OXA: oxapalatin; PAC: paclitaxel; RG: regorafenib; FS: functional status; OS: overall survival; PFS: progression-free survival; QoL: quality of life.

[a]Number of included participants for primary studies and number of included studies relevant to our clinical question/total of included studies for systematic reviews.

[b]Includes the GEJ.

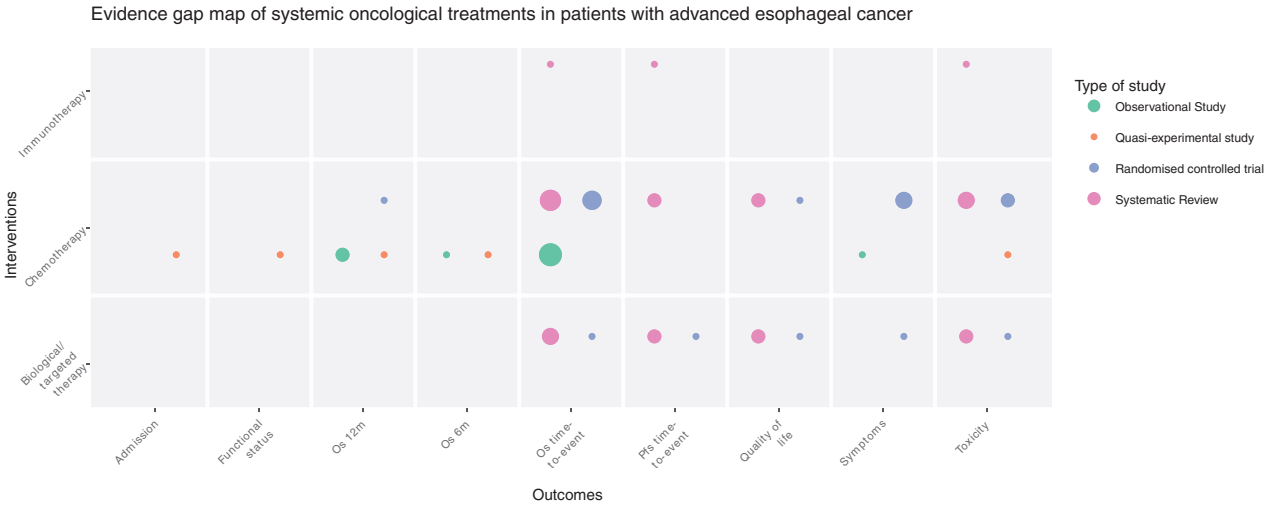

FIGURE 2 Evidence map of systemic oncological treatment in patients with advanced esophageal cancer.

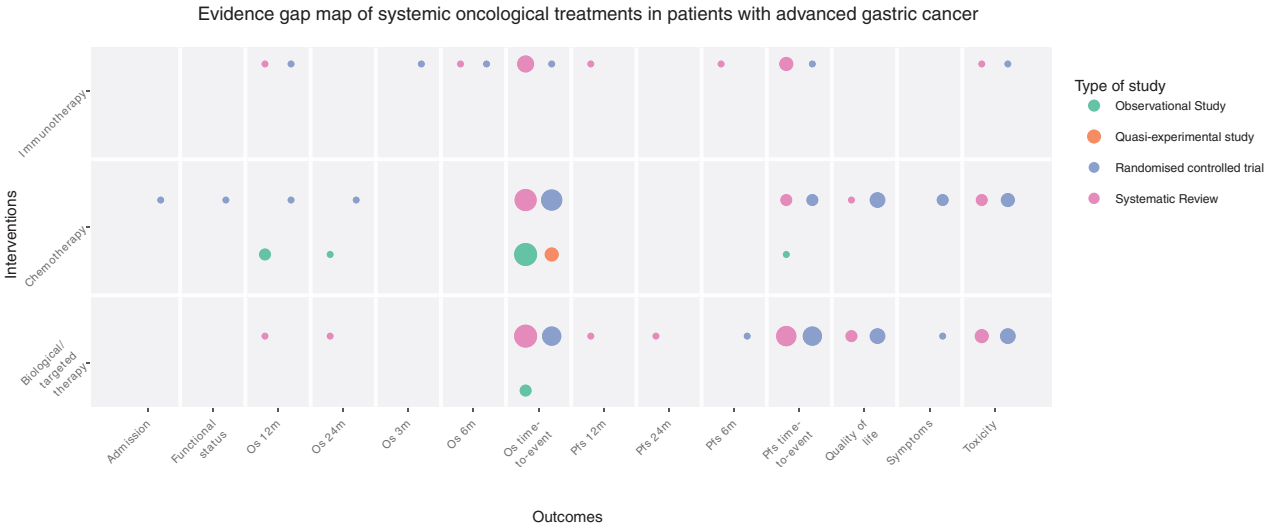

FIGURE 3 Evidence map of systemic oncological treatment in patients with advanced gastric cancer.

4 | DISCUSSION

4.1 | Summary of findings

This scoping review comprehensively identified the currently available evidence about the efficacy and safety of SOT compared to BSC for patients with advanced GEC. Two evidence maps presented the results from 72 studies, including SRs, experimental and observational designs in similar proportions. Regarding population, we identified diverse inclusion criteria in terms of anatomic location and cancer stages. Regarding the intervention, most studies did not report therapeutic lines. So, this heterogeneity in relation to patientt's prognosis might lead to think they were treating advanced cancer for the first time, which was probably not true. Moreover, BSC as a control arm was poorly defined, sometimes including integral support and sometimes including placebo. As a result of this lack of rigor in study designs, results might be biased over or underestimating the potential benefits of SOT and BSC leading to flawed conclusions.

Most studies reported survival outcomes favoring the use of SOT, although some did not find differences between SOT and BSC or placebo for either advanced gastric and esophageal cancer. Among the few studies that reported other outcomes, most found no differences or better results for SOT in terms of QoL, and favorable results for BSC or placebo regarding toxicity. It was noteworthy that only slightly more than a quarter of the included studies reported on QoL, when preserving QoL was one of the main objectives when treating patients with advanced cancer.[105,106]

Aside from survival, QoL, and toxicity outcomes, we found sundry evidence gaps specifically in assessing new treatments such as immunotherapy and important outcomes such as functional status,

symptoms control, hospital admissions and quality of end-life care for all the treatments.

4.2 | Results in context

To our knowledge, this was the first scoping review and evidence mapping assessing SOT versus BSC on patient-centered outcomes for advanced GEC. Our research identified the quantity, design, and characteristics of research conducted in a broad topic area, such as advanced cancer, in contrast to SR, which usually addressed narrowly-focused research questions.[24] However, scoping reviews have been used in the oncology arena to identify the evidence on a particular topic and point out new lines of research that need to be developed. For example, they had been used to identify breast cancer-related lymphedema treatments, gastrointestinal stromal tumors (GIST) and cancer-related fatigue interventions.[107–109]

Interestingly, we found that China, Japan and South Korea, three Asian countries, lead research in this topic area. This apparent interest could be explained by the fact that more than 75% of esophageal cancers and deaths in the world occur in Asia,[1] and highest incidence of gastric cancer had been reported from some eastern Asian countries such as China, Korea and Japan[1]; China for instance was part of the so-called Asian belt of esophageal cancer,[110] an area with the highest incidence.

Our results confirmed that research on advanced GEC had ignored some dimensions of care that had proven important in the last phase of life, such as symptom control, hospital admissions, and quality of death and dying.[111] In this sense, the Core Outcome Measures in Effectiveness Trials (COMET) initiative, which advocated for the development of outcome standardization through the development of Core Outcome Sets (COS), could help to fill the information gap that exists for some important outcomes. COS was an agreed minimum set of important outcomes that should be measured and reported in clinical research and those were relevant for either patients or healthcare professionals.[111] Although there were COS for esophageal cancer resection surgery trials,[112] gastric cancer surgery trials,[113] and a patient-reported core set of general symptoms for cancer treatment trials,[114] there was still no specific COS available for research on advanced cancer. Some authors were working on developing a COS for best care of patients at high risk of dying. Although this set would be useful for patients with advanced cancer, it would only cover the end phase of the process through which these patients pass through.[115]

In addition, it was important to consider the clinical decision-making process regarding medical treatment in an end-of-life context. In this sense, involving patients in the process and considering their values and preferences was needed to reach truly patient-centered care.[116,117] This was especially important in complex scenarios such as treating patients with advanced GEC, where benefits and risks were closely balanced. It was known that patient preferences and the importance and value they give to different outcomes varied across patients and differed from healthcare professionals.[118–120] However, to consider patient values and preferences and involve patients in the decision-making process, it was necessary to provide sufficient information on the effects of intervention in all patient-relevant outcomes. This review showed a lack of evidence in many patient-important outcomes, which hindered the correct decision-making process.

Another important finding of this scoping review was that the third part of published studies assessing the effectiveness of SOT versus BSC in advanced GEC did not provide information on the line of treatment of included patients. As the expected benefit of SOT on survival outcomes could be different in patients in their second or more lines of therapy compared to those on their first line,[47] it was crucial that study authors provided detailed information on included participants so their results could be useful for the decision-making process.

On the other hand, this scoping review revealed that 40% of included studies did not report potential conflicts of interest. The reporting of funding and other support was incorporated in 2010 in the CONSORT checklist for reporting RCT[120] and had been considered in the PRISMA statement for reporting systematic reviews since 2004.[121] All SRs identified in this scoping review were published after the PRISMA statement was available, and all but two reported conflicts of interest. Regarding RCT, most were published from 2011 on, when the CONSORT 2010 statement included the disclosure of conflicts of interest, but six of them still did not report them. Previous studies had shown that research sponsored by the pharmaceutical industry reports better results for the drug being tested than research funded by other sources,[122-124] but other studies found no differences in positive outcomes between industry-funded and nonfunded RCT.[125,126] As the role of industry in oncology research had expanded over the last decades,[127] adhering to available reporting checklists and informing about sources of funding, conflicts of interest, and industry collaboration was mandatory for granting transparency and enabling readers to assess studies properly.[126]

4.3 | Strengths and limitations

Our study had several strengths. As previously stated, it was the first scoping review regarding SOT compared to BSC in advanced GEC. Also, we made an effort to include all potentially patient-centered outcomes beyond survival. We undertook a comprehensive search in five databases without any language or date restriction (except for SRst' date of publication) to minimize selection bias. The screening process and data extraction was performed by two independent reviewers to minimize errors. We also designed and created a graphical display in which we used thought-colored bubbles to map available evidence in a reader friendly way.

This research, however, was subject to possible limitations. First, a limitation of scoping reviews (and other knowledge synthesis products) was that we could not exclude a potential publication bias. However, we tried to minimize it by searching in public registries (PROSPERO and clinicaltrials.gov) and by asking experts in the field for relevant unpublished studies. Second, the pragmatic decision of including SR

TABLE 2 Effect direction reported outcomes of the published studies on systemic oncological treatment in patients with advanced gastresophageal cancer ($n = 68$).

Study	Design	Location	Therapy	Admission	FS	OS time-to event	OS 3 m	OS 6 m	OS 12 m	OS 24 m	PFS time-to-event	PFS 6 m	PFS 3 m	PFS 12 m	PFS 24 m	Symptoms	QoL	Toxicity
Adenis 2010[76]	OBS	Esophageal	CTX	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Alberts 1992[51]	RCT	Esophageal	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baumgartner 2020[77]	OBS	Esophageal; Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bernards 2013[78]	OBS	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bernards 2016[79]	OBS	Esophageal	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chan 2017_a,[a, 36]	SR	Gastric	CTX	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chan 2017_a,[a, 36]	SR	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	FC
Chan 2017_b[a, 35]	SR	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	FI	NR
Chen 2018[102]	SR	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	FC
Chen 2019_a,[a, 37]	SR	Gastric	IM	NR	NR	FI	NR	FI	FI	NR	NR	NR	NS	FI	NR	NR	NR	NR
Chen 2019_b,[a, 80]	OBS	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ciliberto 2015[38]	SR	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
Cordero-Garcia 2019[81]	OBS	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
Dutton 2014,[a, 52]	RCT	Esophageal	BIO/TT	NR	NR	NS	NR	NR	NR	NR	FI	NR	NR	NR	NR	FI	NS	NS
Ford 2014[53]	RCT	Esophageal; Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	FI	NS	FC
Ford 2014[53]	RCT	Esophageal	CTX	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	FI	NS	FC
Ford 2014[53]	RCT	Gastric	CTX	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	FI	NS	FC
Fuchs 2014,[a, 103]	RCT	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NS	NS
Glimelius 1997[55]	RCT	Gastric	CTX	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	FI	NR
Hayashi 2019[82]	OBS	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hwang 2014[83]	OBS	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Iacovelli 2014[39]	SR	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

(Continues)

TABLE 2 (Continued)

Study	Design	Location	Therapy	Admission	FS	OS time-to event	OS 3 m	OS 6 m	OS 12 m	OS 24 m	PFS time-to-event	PFS 6 m	PFS 3 m	PFS 12 m	PFS 24 m	Symptoms	QoL	Toxicity
Iacovelli 2014[39]	SR	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Iacovelli 2014[39]	SR	Gastric	IM	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Janmaat 2017[40]	SR	Esophageal; Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	FI	FC
Janmaat 2017[40]	SR	Esophageal	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NS	FC
Janmaat 2017[40]	SR	Esophageal; Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	NS	NR	NR	NR	NR	NR	FI	FC
Janmaat 2017[40]	SR	Esophageal	BIO/TT	NR	NR	FI	NR	NR	NR	NR	NS	NR	NR	NR	NR	NR	FI	FC
Jiang 2012[72]	Q-Exp	Esophageal	CTX	FC	FI	NR	NR	FI	FI	NR	NR	NR	NR	NR	NR	NR	NR	FC
Kang 2012[56]	RCT	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kang 2017,[a, 70]	RCT	Gastric	IM	NR	NR	FI	FI	FI	FI	NR	FI	NR	NR	NR	NR	NR	NR	FI
Kang 2019,[a, 57]	RCT	Gastric	BIO/TT	NR	NR	NS	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
Kano 1982[84]	OBS	Gastric	CTX	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	FI	NR	NR	NR
Kawamoto 2018[85]	OBS	Esophageal	CTX	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	FI	NR	NR
Khatri 2019[58]	RCT	Gastric	CTX	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	FI	NR
Kozaczka 1990[73]	Q-Exp	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kundel 2020,[a, 41]	SR	Gastric	IM	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
Lee 2012[74]	Q-Exp	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lee 2016[86]	OBS	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Levard 1998[59]	RCT	Esophageal	CTX	NR	NR	NR	NS	NR	NS	NR	NR	NR	NR	NR	NR	NS	NR	FC
Li 2013,[a, 59]	RCT	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NS	NR
Li 2016,[a, 61]	RCT	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NS	FC

(Continues)

TABLE 2 (Continued)

Study	Design	Location	Therapy	Admission	FS	OS time-to event	OS 3 m	OS 6 m	OS 12 m	OS 24 m	PFS time-to-event	PFS 6 m	PFS 3 m	PFS 12 m	PFS 24 m	Symptoms	QoL	Toxicity
Lin 2008[87]	OBS	Gastric	CTX	NR	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR
Liu 2018,[a, 129]	SR	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
Liu 2020[42]	SR	Esophageal; Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	FC
Liu 2020[42]	SR	Esophageal; Gastric	IM	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	FC
Moon 2010[88]	OBS	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Moriwaki 2014[89]	OBS	Esophageal	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Murad 1993[75]	Q-Exp	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nomura 2016[90]	OBS	Esophageal	CTX	NR	NR	FI	NR	FI	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR
Oba 2013[43]	SR	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ohtsu 2013,[a, 62]	RCT	Gastric	BIO/TT	NR	NR	NS	NR	FI	NR	NR	NS	NR	NR	NR	NR	NR	NR	NS
Park 1997[91]	OBS	Gastric	CTX	NR	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR
Park 2008[97]	OBS	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Park 2011[63]	RCT	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pavlakis 2016,[a, 63]	RCT	Gastric	BIO/TT	NS	NR	NS	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NS	FC
Pyrhönen 1995[65]	RCT	Gastric	CTX	NS	NR	FI	NR	NR	FI	FI	FI	NR	NR	NR	NR	NR	NR	FC
Qi 2014[65]	SR	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
Qin 2014[71]	RCT	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
Shitara 2018,[a, 66]	RCT	Esophageal; Gastric	CTX	NR	FI	NS	NS	NR	NR	NR	FI	NR	NR	NR	NR	NS	NS	FC
Shitara 2018,[a, 66]	RCT	Gastric	CTX	NR	FI	FI	NS	NR	NR	NR	FI	NR	NR	NR	NR	NS	NS	FC
Schmid 1993[67]	RCT	Esophageal	CTX	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NS	NR	NR

(Continues)

TABLE 2 (Continued)

Study	Design	Location	Therapy	Admission	FS	OS time-to event	OS 3 m	OS 6 m	OS 12 m	OS 24 m	PFS time-to-event	PFS 6 m	PFS 3 m	PFS 12 m	PFS 24 m	Symptoms	QoL	Toxicity
Sugimoto 2017[96]	OBS	Gastric	CTX	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sugimoto 2019[95]	OBS	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sugimoto 2019[95]	OBS	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Swinson 2019[68]	RCT	Esophageal; Gastric	CTX	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
TerVeer 2016_a[45]	SR	Esophageal; Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
TerVeer 2016_b[46]	SR	Esophageal; Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	FC
TerVeer 2016_b[46]	SR	Esophageal; Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	FC
Thuss-Patience 2011,[a, 69]	RCT	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tsavaris 1999[93]	OBS	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
van Kleef 2020[104]	SR	Esophageal; Gastric	BIO/TT	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	FI	FI	NR
van Kleef 2020[104]	SR	Esophageal; Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	FC	FI	NR
Wagner 2017[47]	SR	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wallis 2019,[a, 48]	SR	Gastric	IM	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wang 2017[49]	SR	Gastric	BIO/TT	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wong 2017[94]	OBS	Esophageal	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Xie 2017[130]	SR	Gastric	BIO/TT	NR	NR	NR	NR	NR	NS	NS	NR	NR	NR	FI	FI	NR	NR	NR
Xue 2018[131]	SR	Gastric	BIO/TT	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
Zeng 2014[132]	SR	Gastric	CTX	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zhu 2017,[a, 133]	SR	Gastric	BIO/TT	NR	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zhu 2017,[a, 133]	SR	Gastric	CTX	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

FI: favor intervention; FC: favor comparison; NS: no significance difference; NR: not reported.
[a] Includes the GEJ.

published after 2008 could be seen as a flaw, but as we did not apply date restrictions for primary studies, we were confident to have localized all available evidence that could be included in old SR. Third, because of the study design, we had not assessed the methodological quality of included studies and had not analyzed the magnitude of effect sizes nor the certainty of the evidence. Nevertheless, it was not the goal of a scoping review, so we suggested the interpretation of the effect of interventions on different outcomes should be cautious.

4.4 | Future perspectives

The breadth of our scoping review identifies evidence gaps and may guide future research efforts in advanced GEC. The finding of knowledge gaps regarding the effectiveness of SOT on other patient-centered outcomes beyond survival ones precludes conducting a trustworthy trade-off between the potential survival benefits of SOT and their potentially negative effects on other important outcomes such as toxicity, symptoms control, hospital admissions, functional status and quality of end-of-life in patients with advanced GEC. These uncertainties claim for the conduction of high-quality research (mainly RCT and SR) comparing SOT with BSC on all other patient-centered outcomes to provide enough evidence to guide clinical guideline recommendations, facilitate clinical decision-making and provide truly patient-centered care. Therefore, our group (ASTAC) plans to conduct de novo high-quality SRs to update previous ones and include all available RCTs assessing SOT versus BSC.

It is essential for future studies to specify previous treatments and to objectify those patients that do not receive treatment or those in who failed. Otherwise, it is very difficult to extrapolate the results to practice.

Finally, funding agencies may use our results to access completed or ongoing studies in advanced GEC. Also, researchers and experts in the field can use these evidence maps to inform and prioritize their own research decisions and study designs to avoid duplicities and fill knowledge gaps.

In conclusion, our scoping review identifies the current research in advanced GEC and recognizes important evidence gaps regarding new interventions such as immunotherapy and the effect of SOTs on important patient-centered outcomes needed for decision-making. Future research should clearly describe the population included, specifying previous treatments and considering therapeutic lines, and consider all patient-centered outcomes. Otherwise, it will be complex to extrapolate the results into practice.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Appendices and the datasets generated and/or analyzed during the current study are available in the Open Science Framework repository (https://doi.org/10.17605/OSF.IO/7CHX6).[28]

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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