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Review Article

State of the scientific evidence and recommendations for the management of older patients with gastric cancer

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ABSTRACT

Gastric cancer is one of the most frequent and deadly tumours worldwide. However, the evidence that currently exists for the treatment of older adults is limited and is derived mainly from clinical trials in which older patients are poorly represented.

In this article, a group of experts selected from the Oncogeriatrics Section of the Spanish Society of Medical Oncology (SEOM), the Spanish Group for the Treatment of Digestive Tumours (TTD), and the Spanish Multidisciplinary Group on Digestive Cancer (GEMCAD) reviews the existing scientific evidence for older patients (≥65 years old) with gastric cancer and establishes a series of recommendations that allow optimization of management during all phases of the disease. Geriatric assessment (GA) and a multidisciplinary approach should be fundamental parts of the process. In early stages, endoscopic submucosal resection or laparoscopic gastrectomy is recommended depending on the stage. In locally advanced stage, the tolerability of triplet regimens has been established; however, as in the metastatic stage, platinum- and fluoropyrimidine-based regimens with the possibility of lower dose intensity are recommended resulting in similar efficacy. Likewise, the administration of trastuzumab, ramucirumab and immunotherapy for unresectable metastatic or locally advanced disease is safe. Supportive treatment acquires special importance in a population with different life expectancies than at a younger age. It is essential to consider the general state of the patient and the psychosocial dimension.

1. Introduction

Gastric cancer is one of the most frequent tumours and causes the highest mortality worldwide, affecting more men and older individuals. According to GLOBOCAN 2020 data, it is the fifth most prevalent tumour, the third most prevalent cause of death from cancer, and the sixth most prevalent cancer in patients ≥65 years of age [1,2]. Worldwide, it is estimated that more than one million individuals are diagnosed with gastric cancer each year and in 2020 it caused 768,793 deaths. Although its incidence has decreased in the last 50 years due to advances in *Helicobacter pylori* infection treatments, better food preservation and greater consumption of fresh fruits and vegetables, it continues to be a frequent cancer, especially in older individuals. The mean age of those affected is 68 years, and 6 out of 10 patients are ≥65 years at the time of diagnosis [3]. Despite this, there are few studies on the management of gastric cancer in this population, especially in patients older than 75 years; therefore, the results of clinical trials carried out in younger population groups are used in routine clinical practice, with

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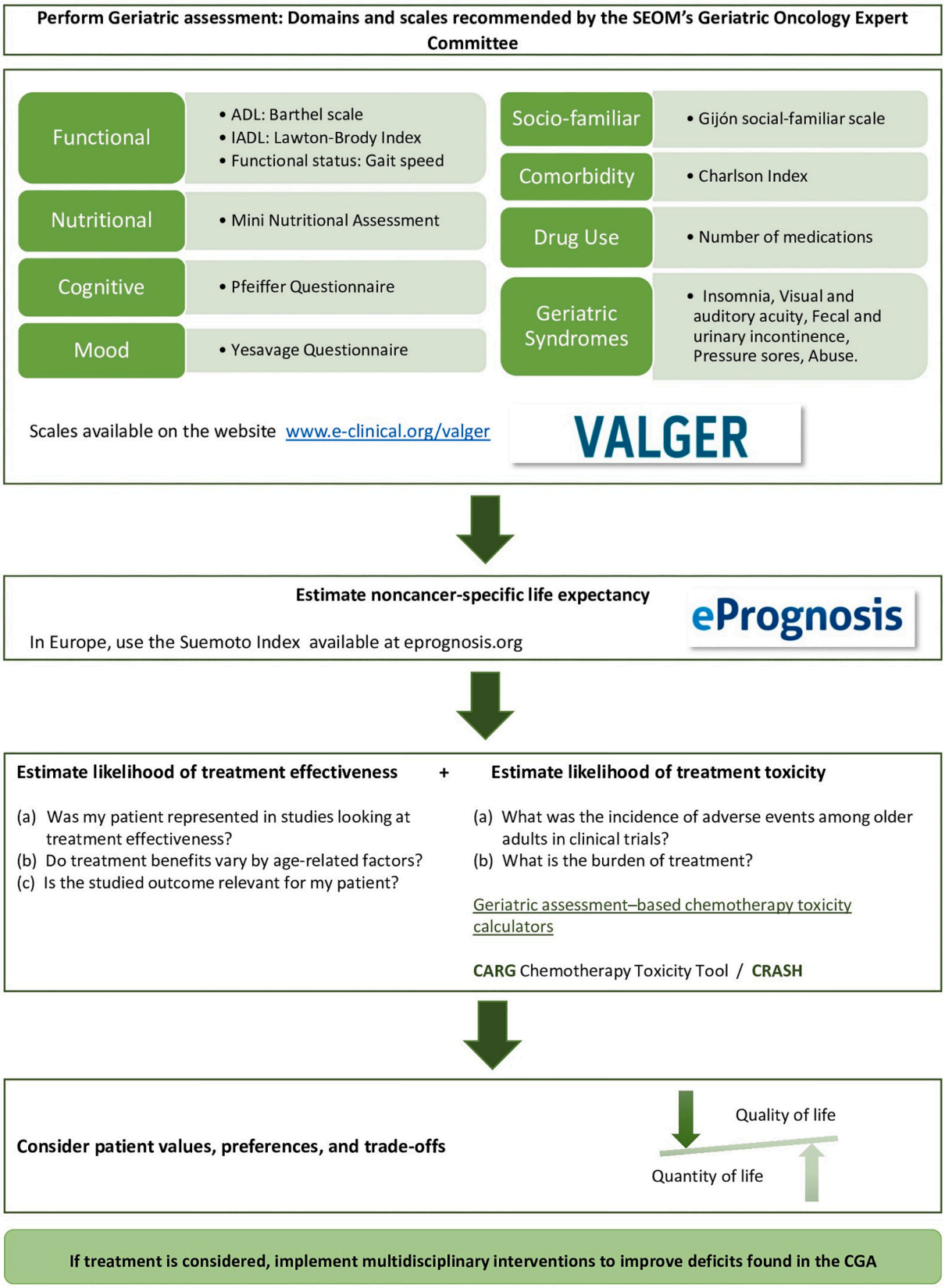

Fig. 1. Application of geriatric assessment [95,96].
ADL: activities of daily living; CARG: Cancer Aging Research Group; CGA: comprehensive geriatric assessment; CRASH: Chemotherapy Risk Assessment Scale for High-Age Patients; GA: geriatric assessment; IADL: instrumental activities of daily living; SEOM: Spanish Society of Medical Oncology.

subanalyses of the included older patients [4].

Given the scant scientific evidence that exists on this topic, a group of experts selected from the Oncogeriatrics Section of the Spanish Society of Medical Oncology (SEOM), the Spanish Group for the Treatment of Digestive Tumours (TTD), and the Multidisciplinary Spanish Group of Digestive Cancer (GEMCAD) has carried out an exhaustive review of the available scientific evidence, including both the results of published clinical trials and of the presentations made at national and international conferences, as well as retrospective and prospective case series. With this information, this group of experts has proposed a series of recommendations to optimize the management of older patients (≥65 years old) with gastric cancer in the different phases of the disease, highlighting the importance of a multidisciplinary approach and the geriatric assessment (GA) of these patients [5–7].

2. Importance of a Comprehensive Geriatric Assessment

Gastric cancer is a disease with a high symptomatic burden and high mortality, even when the disease is localized. Therapeutic decisions for older patients should not be based on chronological age because the available evidence suggests that the benefit obtained from the treatments is similar to that obtained by younger patients, although with a higher risk of complications [8]. Older patients undergoing radical gastrectomy have higher rates of complications related to surgery than younger patients [9]. In the same way, the risk of toxicity secondary to antineoplastic treatments also increases due to the physiological changes associated with aging, comorbidities, and the effects of the disease, such as alterations in gastric absorption, malnutrition, and sarcopenia [10]. An added difficulty in decision-making for these patients is the uncertainty that arises from extrapolating results obtained in clinical trials to the treatment of older adults, which have not been previously validated in that population, and the main objectives of which may not be the most relevant for these patients.

Comprehensive GA is a tool designed to identify and quantify the medical, functional, and psychosocial problems of older patients. In addition to multi-domain assessment, its results are also predictive of potential life expectancy and risk of chemotherapy toxicity, used in tools such as CARG and CRASH scores, which can aid in treatment dose adjustment decisions in older adults with gastric cancer. Use of comprehensive GA allows (i) detecting vulnerabilities that could otherwise go unnoticed in a routine clinical evaluation and that will probably affect the clinical evolution of the patient and the administration of cancer treatments; (ii) weighing more precisely the risks and benefits of cancer therapies based on these vulnerabilities and patient preferences; and (iii) developing interventions aimed at optimizing health and minimizing complications derived from the disease and treatment (Fig. 1).

Physical performance and nutritional status are the aspects that are most related to mortality, postoperative complications, and the effects associated with chemotherapy [10]. In turn, these are the two most prevalent problems in older patients with gastric cancer. Nutritional interventions have been shown to be capable of improving quality of life and reducing postoperative complications in patients with gastric cancer [11]. In the same way, prehabilitation programmes designed to improve the functional capacity of patients before gastrectomy have also proven useful in reducing postoperative complications and hospital stays [12].

A multidisciplinary approach to designing and implementing an intervention plan guided by GA has been shown in recent randomized clinical trials that can improve the health outcomes of older patients. Studies like GAIN, GAP70+, or INTEGRATE showed that the integration of an oncogeriatric care approach into the management of older patients with cancer can lead to clinically meaningful benefits like reduced severe toxicities rates, unplanned hospital admissions, and improved quality of life and healthcare delivery [13–15].

Regarding the impact of GA on cancer outcomes, there are limited data. The phase 3 GO2 clinical trial showed the usefulness of GA as a guide for the selection of the most appropriate treatment [16]. In this trial, the dose intensity of chemotherapy was reduced on the basis of the degree of frailty of the patient as measured by GA without compromising disease control and improving quality of life, as described below.

Therefore, GA should be part of the initial and periodic evaluation of older patients with gastric cancer within a multidisciplinary team [17]. In the coming years, it will be necessary to design more clinical trials that integrate the use of GA in populations that represent the entire older population and in which the preferences and values of each patient are taken into account before making the pertinent therapeutic decisions.

Recommendation:

- GA should be part of the initial and periodic evaluation of older patients with gastric cancer within a multidisciplinary team [IA].

3. Perioperative and Adjuvant Treatment

In Western countries, approximately 40% of gastric adenocarcinomas are diagnosed in localized or locally advanced stages (stages I-III). The treatment plan for these patients must always be evaluated within a multidisciplinary committee [18]. This premise is especially important for older patients. The older population with localized or locally advanced gastric cancer represents a challenge when establishing an optimal treatment because of the heterogeneity of the biological reserve of each patient, the tolerance to treatment, and the diversity of therapeutic objectives that are proposed, which must be individualized for each patient.

In general, except in very early situations in which endoscopic resection is indicated, treatment with intention to cure gastric cancer requires carrying out surgery and, from stage IB, administering a complementary cancer treatment.

3.1. Endoscopic Dissection

Endoscopic submucosal dissection (ESD) is indicated for T1a gastric tumours with good prognostic factors (grade 1–2, ≤2 cm, not ulcerated). In addition, different clinical guidelines consider ESD to be the best option for older patients with high surgical risk, even though they do not strictly conform to the classical criteria required for endoscopic resection. This is the case for T1b tumours in which an ESD could be an appropriate approach depending on the surgical risk of the patient [19]. The complications of ESD described in retrospective series with older patients are similar to those observed in younger patients, with the exception of pneumonia, which was more common among older adults [20,21]. Therefore, ESD is indicated for T1a gastric tumours that have good prognostic factors and for early gastric tumours with expanded criteria that occur in older patients with high surgical risk.

3.2. Surgery

The surgical approach to gastric cancer is to achieve complete resection of the tumour with adequate margins and an appropriate lymphadenectomy; this means D2 lymph node dissection without splenectomy or pancreatectomy whenever possible. Depending on the tumour location, total or subtotal gastrectomy can be performed.

Several issues arise in older patients. The first issue is postoperative morbidity and mortality among older patients compared to those among younger patients and the possibility of predicting them using appropriate tools. A meta-analysis of six studies evaluated the role of GA in predicting postoperative complications in patients with gastrointestinal tumours. A total of 1037, patients were included, and the presence of a Charlson comorbidity index ≥3, polypharmacy (≥5 drugs), and activities of daily living (ADL) dependency were predictors of a greater number of postoperative complications [22]. Postoperative morbidity has been evaluated with different classifications and degrees in different studies. In two clinical trials comparing surgery alone with surgery plus

Table 1
Efficacy of perioperative chemotherapy in older patients with resectable gastroesophageal adenocarcinoma.

Study	N Tumour	Treatment	Age, median (range)	Efficacy	Older patients
Phase 3	$N = 503$	A: ECF + surgery	62	PFS (HR 0.66; $p < 0.001$)	60–69 yr: 37%
MAGIC [24]	Gastroesophageal	B: surgery	(23–81)	OS (HR 0.75; $p = 0.009$)	≥70 yr: 21%
Phase 2–3	$N = 716$	A: FLOT + surgery	62	OS (50 vs 35 m)	60–69 yr: 32%
FLOT4 [23]	Gastroesophageal	B: ECF or ECX + surgery	(54–69)	HR 0.77; $p = 0.012$	≥70 yr: 24%
Phase 3	$N = 224$	A: CF + surgery	63	OS 5 yr (38% vs 24%)	NR
FNCLCC-FFCD[29]	Gastroesophageal	B: surgery	(36–75)	HR 0.69; $p = 0.020$	
Phase 3	$N = 1022$	A: adjuvant CAPOX	59 (52–64)	DFS 3 yr	>65 yr: 20%
RESOLVE [30]	Gastroesophageal	B: adjuvant SOX	59 (53–65)	C vs A: 59.4% vs 51.1% (HR 0.77; $p = 0.028$)	>65 yr: 22%
		C: perioperative SOX	60 (53–66)	B vs A: 56.5% vs 51.1% (HR 0.86; $p = 0.17$)	>65 yr: 26%
Phase 2	$N = 44$	A: FLOT + surgery	70	PFS (21.1 vs 12.0 m)	≥65 yr: 100%
Lorenzen et al. [32]	Gastroesophageal	B: FLO + surgery	(68–75)	HR 2.02; $p = 0.090$	
Phase 2	$N = 83$	A: 2xSC; B: 4xSC	66	pRR: 43% vs 40% vs 29% vs 38%	NR
COMPASS [33]	Gastric	C: 2xPC; D: 4xPC	(32–80)	pCR: 0% vs 10% vs 0% vs 10%	

CAPOX: capecitabine and oxaliplatin; CF: cisplatin and 5-fluorouracil; DFS: disease-free survival; ECF: epirubicin, cisplatin and 5-fluorouracil; ECX: epirubicin, cisplatin and capecitabine; FLO: 5-fluorouracil, leucovorin and oxaliplatin; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; m: month; NR: not reported; OS: overall survival; PC: paclitaxel and cisplatin; pCR: pathological complete response; PFS: progression-free survival; pRR: pathological response rate; SC: S1 and cisplatin; SOX: S1 and oxaliplatin; yr: year.

perioperative chemotherapy in Europe (MAGIC and FLOT4), the morbidity reported for all age groups was 45–50%, and the mortality at 30 days was 3–5% [23,24]. This morbidity and mortality varied depending on whether total gastrectomy was necessary. In a study by the American College of Surgeons (ACS) within the National Surgical Quality Improvement Programme (NSQIP), a significant increase in severe morbidity and mortality was observed in a group of older patients who required total gastrectomy compared to a group of older patients who underwent partial gastrectomy (29.3% vs. 19.9%; $p < 0.001$; and 5.4% vs. 3.4%; $p < 0.015$, respectively). The addition of lymphadenectomy did not increase morbidity or mortality, but it did increase the need for other procedures, such as splenectomy, pancreatectomy, colectomy, or oesophagectomy [25]. There is a need to implement programmes to improve surgical recovery in the older population; postsurgical rehabilitation has been shown to be feasible and effective in multiple studies [26].

Laparoscopic gastrectomy is the most commonly proposed surgery. A meta-analysis that included 11 observational studies with 3,275, patients evaluated its feasibility and safety in older versus younger patients [27]. In the older population, a shorter surgery time, fewer resected lymph nodes, longer time to regain bowel rhythm, longer hospital stay, and higher risk of nonsurgical and pulmonary complications were found. No significant differences were observed in terms of blood loss, infections, and postoperative ileus.

Another meta-analysis of 845 patients concluded that laparoscopic surgery in older patients facilitates a faster recovery, with fewer postoperative complications and less blood loss compared with open surgery [28]. The associated lymphadenectomy must be a D2 lymphadenectomy without splenectomy or pancreatectomy.

Regarding efficacy results, the five-year survival rate after surgery as the only treatment for locally advanced gastric adenocarcinoma is modest. In clinical trials in Europe that included this arm of treatment versus perioperative chemotherapy plus surgery, the five-year survival for the surgery-alone arm was 23–24% [24,29]. This result demonstrates the benefit of adding other complementary treatments.

Thus, the conclusions regarding surgery for older patients are as follows: (i) the morbidity and mortality of gastric cancer surgery for older patients must be evaluated, taking into account patient conditions in a holistic way; (ii) the need for total gastrectomy or resection of adjacent structures increases morbidity and mortality in the older population, but lymphadenectomy does not; (iii) laparoscopic surgery facilitates faster recovery and fewer complications than does open surgery; (iv) laparoscopic surgery in the older population compared to the younger population is associated with a higher percentage of nonsurgical complications, especially pulmonary complications; and (v) programmes to improve surgical recovery in the older population must be implemented.

3.3. Perioperative Chemotherapy

Compared to surgery alone, perioperative chemotherapy treatment improves survival in patients with locally advanced gastric adenocarcinoma. A five-year survival rate of 36% has been achieved with epirubicin, cisplatin, and 5-fluorouracil (ECF), compared to 23% with surgery alone; furthermore, a five-year survival rate of 45% has been achieved with 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT), compared to 36% with ECF or epirubicin, cisplatin, and capecitabine (ECX) (Table 1) [23,24]. However, older adults are underrepresented in these studies, with only 21–24% of patients older than 70 years [23,24,29]. In subgroup analyses of the FLOT4 study, a trend towards a benefit in terms of overall survival (OS) was described in 24% of patients aged 70 years or older (hazard ratio [HR] 0.72; $p = 0.8$) [23].

In addition to efficacy, an important issue in treating older patients is establishing the risk of toxicity in this subgroup. The MAGIC study separated patients into three different subgroups (<60 years old, 60–69 years old, and > 70 years old), without finding differences in the incidence of side effects by age [24]. Neither the FLOT4 study nor the French study with cisplatin and 5-fluorouracil (CF) led by Ychou et al. report toxicity results broken down by age [23,29].

The Asian phase 3 RESOLVE trial evaluated different fluoropyrimidine- and oxaliplatin-based doublet chemotherapy therapeutic strategies in patients with locally advanced gastric cancer who underwent D2 gastrectomy. A clinically significant improvement in terms of disease-free survival (DFS) was observed at three years in the arm that received perioperative S1 and oxaliplatin (SOX) in comparison with the arm treated with adjuvant capecitabine and oxaliplatin (CAPOX) (HR 0.77; 95% confidence interval [CI] 0.61–0.97; $p = 0.028$). On the other hand, adjuvant SOX was non-inferior to adjuvant CAPOX (HR 0.86; 95% CI 0.68–1.07; $p = 0.17$) [30]. Also, the Asian PRODIGY trial compared the perioperative approach (docetaxel, oxaliplatin, and S1 as neoadjuvant treatment followed by adjuvant S1) with adjuvant S1. A benefit in terms of DFS was observed (adjusted HR 0.70; 95% CI 0.52–0.95; stratified log-rank $p = 0.023$). Therefore, the perioperative treatment based on taxanes, platinum and fluoropyrimidine may be considered a new treatment option in these patients [31].

The next level of evidence comes from small phase 2 studies. A German phase 2 study of 44 patients older than 65 years explored tolerance to the perioperative strategy with the FLOT scheme versus the same scheme without taxane (5-fluorouracil, leucovorin, and oxaliplatin [FLO]) [32]. The FLOT scheme resulted in a nonsignificant trend towards better DFS (21.1 vs. 12.0 months; HR 2.02; $p = 0.090$) at the expense of an increase in toxicity associated with chemotherapy. Higher incidences of leukopenia, neutropenia, stomatitis, and nausea were observed. This caused a dose adjustment in 14% of patients under the FLO scheme and 48% of patients under the FLOT scheme ($p = 0.023$).

The postoperative morbidity was 47% for all patients (35% with FLO and 60% with FLOT).

The Japanese phase 2 COMPASS study randomized 83 patients with stage III gastric cancer with a median age of 66 years to receive two or four cycles of perioperative chemotherapy with the S1 and cisplatin (SC) or paclitaxel and cisplatin (PC) [33], showing an increase in the pathological response rate (pRR) in favour of the administration of four versus two cycles, regardless of the scheme used. Additionally, there was no marked increase in toxicities, with grade 3–4 haematological toxicities occurring in <10% of patients. However, the optimal duration of the treatment remains controversial.

There are no phase 3 trials of perioperative chemotherapy performed specifically among older adults. The older population is underrepresented in the most important perioperative chemotherapy clinical trials, but doublet chemotherapy with platinum and fluoropyrimidines has been shown to produce overall benefits. There is limited evidence with regard to the addition of a taxane to a platinum doublet for the older population, as there is a tendency to cause greater toxicity in terms of DFS, but the trend is not statistically significant.

3.4. Radiotherapy

Radiotherapy (RT), as part of the multimodal treatment of gastric adenocarcinoma, has a controversial role, and adjuvant chemoradiotherapy is currently not used. The phase 3 randomized clinical trial (RCT) by MacDonald et al. was widely criticized for the high percentage of patients who did not undergo optimal surgery and for the high grade 3 toxicity of the scheme used [34]. In addition, the phase 3 CRITICS and ARTIST I and II clinical trials showed no benefit when adding postoperative RT to perioperative or adjuvant chemotherapy [35–37]. These toxicity and inefficacy data are especially relevant for the older population.

RT could be part of standard treatment in a preoperative chemoradiotherapy strategy for adenocarcinomas of the gastroesophageal junction. The phase 3 CROSS clinical trial, in which 22% of tumours were at the gastroesophageal junction, showed the effectiveness of RT; however, one of the inclusion criteria was <75 years of age [38]. In a retrospective study, this trimodal therapy approach was analysed in patients >76 years of age, confirming the benefit of this strategy with respect to surgery alone without increasing the mortality rate [39]. In the CROSS study, 8% of participants experienced grade 3–4 haematological toxicity, and 13% experienced nonhaematological toxicity [38]. Therefore, in tumours of the gastroesophageal junction, the administration of perioperative chemotherapy or neoadjuvant chemoradiotherapy can be considered. Preliminary results of the Neo-AEGIS randomized phase 3 trial indicate similar efficacy, without detailed toxicity data [40]. In the older population, the toxicity of trimodal therapy together with the age limitation in the CROSS clinical trial make it a little-explored therapeutic option.

3.5. Adjuvant Chemotherapy

Adjuvant chemotherapy is a standard strategy for the treatment of gastric cancer in Asia; however, clinical trials that have shown its efficacy have not been conclusively reproduced in the West, with perioperative chemotherapy shown to be preferable in our environment [41,42]. However, a meta-analysis that included seventeen clinical trials showed a 6% benefit in five-year survival in Western patients [43]. Therefore, this strategy is recommended in the European guidelines when the patient has not received preoperative chemotherapy [18]. In older patients, a meta-analysis of two Asian clinical trials described significant improvement in DFS with adjuvant chemotherapy versus surgery alone ($p < 0.001$), with a marginal benefit in OS ($p = 0.055$) [44].

In regards to adjuvant chemotherapy, it must be considered that a high percentage of patients fail to complete the schedule. In several pivotal perioperative trials, <50% of patients completed all allocated postoperative chemotherapy, while 90% of patients were able to undergo neoadjuvant treatment [23,24].

Table 2
Efficacy of chemotherapy as first-line treatment in older patients with advanced gastroesophageal adenocarcinoma.

Study	N	Treatment	Age, median (range)	Efficacy	Older or frail patients
Phase 3 studies					
GO2 trial [16]	$N = 514$	A: mCAPOX (100% DI) B: mCAPOX (80% DI) C: mCAPOX (60% DI)	76 (51–96)	B vs. A PFS: HR 1.09; OS: HR 1.09 C vs. A PFS: HR 1.10; OS: HR 1.14	100%
	$N = 45$	C: mCAPOX (60% DI) D: BSC	79 (58–89)	C vs. D OS: HR 0.69; $p = 0.34$	100%
Hwang et al. [47]	$N = 50$	A: Capecitabine B: CAPOX	77 (70–84)	A vs B PFS: (2.1 vs 7.1 m); HR 0.32; $p < 0.001$ OS: (6.3 vs 11.1 m); HR 0.58; $p = 0.108$	100%
Phase 2 randomized studies					
Lee et al. [48]	$N = 91$	A: Capecitabine B: S1	71 (65–82)	PFS A vs. B (4.7 vs 4.2 m) OS A vs. B (9.5 vs 8.1 m) HR 0.90	100%
FLOT65+ [50]	$N = 143$	A: FLOT B: FLO	70 (65–82)	PFS A vs. B (9.0 vs 7.1 m); $p = 0.079$ OS A vs. B (17.3 vs 14.5 m); $p = 0.390$	100%
321GO Trial [51]	$N = 55$	A: EOX B: mCAPOX C: Capecitabine	75 (50–87)	PFS A vs B vs C (5.4 vs 5.6 vs. 3.0 m) OS A vs B vs C (8.1 vs 9.5 vs 3.6 m)	100%
Phase 2 non-randomized studies					
Fonk et al. [45]	$N = 42$	FOLFIRI	77 (70–87)	PFS: 7.0 m OS: 9.0 m	100%
Rivera et al. [46]	$N = 28$	miniDOX	73 (70–87)	PFS: 5.5 m OS: 13.3 m	100%
Kim et al. [55]	$N = 20$	Capecitabine + trastuzumab	79 (75–91)	PFS: 5.2 m OS: 9.3 m	100%
Kimura et al. [57]	N = 51	S1 + trastuzumab	71 (65–85)	PFS: 5.1 m OS: 15.8 m	100%

BSC: best supportive care; CAPOX: capecitabine and oxaliplatin; DI: dose intensity; EOX: epirubicin, oxaliplatin, capecitabine; FLO: 5-fluorouracil, leucovorin and oxaliplatin; FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel; FOLFIRI: folinic acid, fluorouracil and irinotecan; HR: hazard ratio; m: month; mCAPOX: modified CAPOX; miniDOX: reduced dose docetaxel-oxaliplatin-capecitabine; OS: overall survival; PFS: progression-free survival.

Recommendations:

- Endoscopic resection is indicated for T1a gastric tumours with good prognostic factors (grade 1–2, ≤2 cm, nonulcerated) and for early tumours with expanded criteria in patients with high surgical risk [IIIB].
- GA allows the prediction of postoperative complications in patients with gastrointestinal tumours [IIA].
- Laparoscopic surgery facilitates faster recovery and fewer complications than does open surgery in the older population [IIB].
- The associated lymphadenectomy must be a D2 lymphadenectomy without splenectomy or pancreatectomy [IIB]
- Surgical recovery improvement programmes must be implemented in the older population [IIIB].
- Perioperative chemotherapy: doublets with platinum and fluoropyrimidines have shown global benefits. There is little evidence for the addition of a taxane to a platinum doublet in the older population, and it causes greater toxicity [IIB].
- RT could be part of treatment in a preoperative chemoradiotherapy strategy for adenocarcinomas of the gastroesophageal junction [IIC].
- Adjuvant chemotherapy based on platinum and fluoropyrimidines is an option if perioperative chemotherapy has not been administered [IIB].

4. First-Line Treatment of Metastatic Disease

Given that advanced gastric cancer is associated with poor survival, even with the most active treatment regimens, the choice of treatment for older patients should lead to tolerable toxicity and preserve quality of life.

First, clinicians must be agreed upon whether patients are candidates for active treatment or best supportive care (BSC). An RCT of non-inferiority phase 3 GO2 was carried out in the United Kingdom with patients not eligible to receive the standard regimen, i.e., epirubicin, oxaliplatin, and capecitabine (EOX), but who could receive reduced intensity chemotherapy (Table 2). The study included older individuals, without an age limit [16]. Overall treatment utility (OTU) was measured, including efficacy, toxicity, quality of life, and patient acceptability at nine weeks. Two cohorts were analysed. One cohort of randomized patients received a dose intensity of 60% of CAPOX or BSC, and a nonsignificant trend in favour of chemotherapy in terms of OS was observed (HR 0.69; 95% CI 0.35–1.48). Both quality of life and fatigue were better in the chemotherapy arm despite higher toxicity. In the arm treated with CAPOX at 60% dose intensity (DI), 70% had severe frailty (≥3 domains), 13% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) >2, and 9% had a body mass index (BMI) < 18.5. In patients with an estimated glomerular filtration rate (eGFR) of 30–50 ml/min or bilirubin 1.5–2 times the upper limit of normal (ULN), the dose (60% DI) was reduced by 75%. It was concluded that in older patients who want active treatment, chemotherapy can be administered if the GA conducted by the oncologist indicates that the patient can tolerate it.

Second, the chemotherapy regimen must be selected. Several non-randomized phase 2 trials have evaluated chemotherapy regimens with a single agent (fluoropyrimidine), doublets with platinum or irinotecan and fluoropyrimidine, and triplets with docetaxel at reduced doses (miniDOX) [45,46]. Currently, there are two phase 3 clinical trials and three randomized phase 2 clinical trials comparing these strategies (Table 2).

A Korean phase 3 study was interrupted early due to superiority in terms of OS of CAPOX versus capecitabine in patients >70 years in the first interim analysis [47]. The second phase 3 GO2 RCT, previously mentioned, compared modified CAPOX (mCAPOX) with the same scheme with a DI of 80% and 60% [16]. Notably, 60% DI is approximately 40% of the standard DI. This study showed that reducing the DI of chemotherapy by up to 60% reduced toxicity and improved quality of life and OTU without a significant detriment to OS (HR 1.14; 95% CI 0.92–1, 41) or progression-free survival (PFS) (HR 1.10; 95% CI 0.90–1.33). Only 32% of those who started a full dose of mCAPOX were able to receive three cycles of treatment without reduction or interruption, compared to 58% of those who received a 60% DI. Initial frailty, quality of life, and the neutrophil to lymphocyte ratio were predictive factors for OUT. Therefore, these variables can help clinicians make good therapeutic decisions.

In a Korean phase 2 RCT, the administration of capecitabine was compared with S1 in patients older than 65 years, without finding differences in efficacy and toxicity. None of the potential prognostic factors that were evaluated were statistically significant predictors of efficacy, including age (> 70 versus ≤70 years) [48]. The median time to progression (TTP) and OS were 4.2 months versus 4.7 months (HR 1.0; 95% CI 0.6–1.6) and 9.5 months versus 8.1 months (HR 0.9; 95% CI 0.5–1.4) for capecitabine and S1, respectively. However, the age used to define older patients (> 65 years), the use of S1 in a mainly Asian population, and the evidence established in other randomized clinical trials favouring the administration of doublets with platinum and fluoropyrimidines limited the applicability of these chemotherapy regimens as monotherapy.

The German FLOT65+ phase 2 RCT was based on the premise that oxaliplatin is better tolerated and more effective than cisplatin in older patients when taking into account the results of a previous phase 3 RCT of the same population [49], and it compared the administration of FLOT with FLO in patients ≥65 years [50]. The addition of docetaxel to the scheme significantly increased toxicity and impaired quality of life in a relevant proportion of patients without offering a clear impact on PFS (9.0 vs. 7.1 months; $p = 0.079$) and OS (17.3 vs. 14.5 months; $p = 0.390$).

The English phase 2 321GO RCT, a prelude to the phase 3 GO2 RCT, included patients with advanced gastroesophageal cancer in whom the oncologist considered the administration of a standard chemotherapy scheme inappropriate due to the frailty of the patient but in whom the administration of chemotherapy with reduced DI was feasible [51]. Instead of a breakdown of toxicities, tolerability, and quality of life, functional and OTU metrics were collected at 12 weeks to better describe the impact of treatment on patients. Patients were randomized to receive EOX, CAPOX, or capecitabine with a DI of 80%; the PFS was 5.4, 5.6, and 3.0 months, respectively; the median OS was 8.1, 9.5 and 3.6 months, respectively; and the OTUs were 18%, 32% and 17%, respectively. Because of the worse results for EOX compared to those for CAPOX, the value of anthracyclines as part of combination chemotherapy in patients with advanced gastroesophageal cancer is questioned, and the combination of platinum with fluoropyrimidines is reinforced.

In summary, CAPOX with a DI of 60% is an active regimen in first-line treatment and is associated with a favourable tolerance profile and improved quality of life in older patients with advanced gastroesophageal adenocarcinoma who are not candidates for standard treatment. The combination of folinic acid, fluorouracil, and irinotecan (FOLFIRI) may be an alternative for patients who are not candidates to receive platinum (Table 2) [16,17,45]. The addition of anthracyclines can be deleterious, and docetaxel is associated with a tendency towards greater OS but with an increase in toxicity and a negative impact on quality of life (Table 2) [46,50,51].

Despite the decline in the immune system with age, current evidence shows a similar benefit of immunotherapy in the first-line treatment of multiple types of cancer in older patients and in younger populations [52]. In advanced gastroesophageal adenocarcinoma with a combined positive score (CPS) of the programmed death ligand-1 (PD-L1) ≥5 and in patients with ECOG 0–1, the phase 3 CheckMate-649 RCT confirmed the benefit of adding nivolumab to oxaliplatin and fluoropyrimidine-based chemotherapy, without differences in the results obtained for patients ≥65 years (42%) versus <65 years (HR 0.72; 95% CI 0.57–0.92; $p = 0.85$) [53]. Furthermore, the phase 3 Keynote-859 RCT

Table 3
Efficacy of chemotherapy as second and successive lines of treatment in older patients with advanced gastroesophageal adenocarcinoma.

Study	N (% Asians) Tumour	Treatment	Age, median (range)	Efficacy	Older patients N (%)
Second-line treatments					
Phase 3 Thuss-Patience et al. [60]	40 (0%) Gastroesophageal	A: Irinotecan B: BSC	58 (43–73) 55 (35–32)	OS A vs B (4.0 vs 2.4 m) HR 0.48; $p = 0.012$	NR
Phase 3 Kang et al. [61]	$N = 202$ (100%) Gastric	A: Chemotherapy B: BSC	56 (31–83)	OS A vs B (5.3 vs 3.8 m) HR 0.66; $p = 0.007$	NR
Phase 3 COUGAR-02[62]	$N = 168$ (0%) Gastroesophageal	A: Docetaxel + ASC B: ASC	65 (28–84)	OS A vs B (5.2 vs 3.6 m) HR 0.67; $p = 0.01$	>70 yr: 23%
Phase 3 WJOG 4007[63]	$N = 219$ (100%) Gastric	A: Paclitaxel B: Irinotecan	65 (37–75)	OS A vs B (9.5 vs 8.4 m) HR 1.13; $p = 0.38$ PFS A vs B (3.6 vs 2.3 m) HR 1.14; $p = 0.33$	>65 yr: 50%
Phase 3 TCOG-GI-0801/BIRIP [66]	$N = 130$ (100%) Gastric	A: Irinotecan, cisplatin B: Irinotecan	66 (29–80) 67 (49–78)	OS A vs B (10.7 vs 10.1 m) HR 1.00; $p = 0.982$ PFS A vs B (3.8 vs 2.8 m) HR 0.68; $p = 0.040$	>70 yr: 33%
Phase 3 REGARD [64]	$N = 355$ (8%) Gastroesophageal	A: Ramucirumab B: Placebo	60 (52–67) 60 (51–71)	OS A vs B (5.2 vs 3.8 m) HR 0.78; $p = 0.047$ PFS A vs B (2.1 vs 1.3 m) HR 0.483; $p < 0.0001$	>65 yr: 36%
Phase 3 RAINBOW [65]	$N = 665$ (30%) Gastroesophageal	A: Ramucirumab + paclitaxel B: Paclitaxel	61 (25–83) 61 (24–84)	OS A vs B (9.6 vs 7.4 m) HR 0.807; $p = 0.017$ PFS A vs B (4.4 vs 2.8 m) HR 0.635; $p < 0.0001$	>65 yr: 37%
Phase 2 DESTINY-Gastric02 [68]	$N = 79$ (5%) Gastroesophageal	A: DS-8201	61 (52–68)	ORR: 42% PFS: 5.6 m OS: 12.1 m	>65 yr: 42%
Third-line and successive treatments					
Phase 3 Li et al. [69]	$N = 267$ (100%) Gastroesophageal	A: Apatinib B: Placebo	58 (23–71)	OS A vs B (6.5 vs 4.7 m) HR 0.709; $p = 0.016$ PFS A vs B (2.6 vs 1.8 m) HR 0.444; $p \leq 0.001$	>65 yr: 14%
Phase 3 TAGS [70]	$N = 507$ (16%) Gastric	A: TAS-102 + BSC B: BSC	64 (56–70) 63 (56–69)	OS A vs B (5.7 vs 3.6 m) HR 0.69; $p < 0.001$	>65 yr: 45%
Phase 3 Kang et al. [71]	$N = 493$ (100%) Gastroesophageal	A: Nivolumab B: Placebo	52 (54–69) 61 (53–68)	OS A vs B (5.3 vs 4.1 m) HR 0.63; $p < 0.001$	>65 yr: 24%
Phase 2b Shitara et al. [72]	$N = 187$ (100%) Gastric	A: DS-8201 B: Chemotherapy	65 (28–82)	OS A vs B (12.5 vs 8.4 m) HR 0.59; $p = 0.01$ PFS A vs B (5.6 vs 3.5 m) HR 0.47	NR

ASC: active symptom control; BSC: best supportive care; DS-8201: trastuzumab deruxtecan; HR: hazard ratio; m: month; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; TAS-102: trifluridine/tipiracil; yr: year.

demonstrated significantly improved OS with pembrolizumab and chemotherapy (CF or CAPOX) compared with chemotherapy alone in previously untreated patients with locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma. This benefit was observed in patients with an ECOG PS of 0–1 and PD-L1 CPS ≥1 and ≥ 10. In the PD-L1 CPS ≥1 population, the median OS was 13.0 months (95% CI 11.6–14.2) with pembrolizumab and chemotherapy compared with 11.4 months (95% CI 10.5–12.0) with chemotherapy alone (HR 0.74; 95% CI 0.65–0.84; $p < 0.0001$). In the PD-L1 CPS ≥10 population, the median OS was 15.7 months (95% CI 13.8–19.3) with pembrolizumab plus chemotherapy compared with 11.8 months (95% CI 10.3–12.7) with chemotherapy alone (HR 0.65; 95% CI 0.53–0.79; p < 0.0001). Specific data for older adults have not yet been published [54]. Therefore, immunotherapy can be added to chemotherapy for older patients with a good performance status without contraindications. However, it would be beneficial to have evidence from a larger sample of older patients [17].

In patients with gastric cancer and with human epidermal growth factor receptor 2 (HER2) overexpression and adequate cardiac function, trastuzumab combined with fluoropyrimidine- and platinum-based chemotherapy increased survival, and the result was inferior when only trastuzumab and fluoropyrimidine were administered (Table 2) [55–57]. In a subgroup analysis of OS in the TOGA phase 3 RCT with trastuzumab, cisplatin, and fluoropyrimidine, the benefits were similar between patients ≥60 years of age and younger patients (HR 0.66; 95% CI 0.49–0.88) [58]. Because of the risk of cardiotoxicity with trastuzumab in older patients with poorly controlled cardiovascular disease or left ventricular ejection fraction (LVEF) < 50%, administration should be avoided because these populations were excluded from the TOGA RCT [58]. Although cisplatin-based chemotherapy was used in the TOGA trial, there are several series and some randomized phase 2 studies that have shown the efficacy and safety of oxaliplatin-based regimens, although not specifically in older patients [58].

Therefore, in older patients with gastric cancer with *HER2* overexpression, LVEF >50% and controlled cardiovascular disease, the regimen of choice is trastuzumab, oxaliplatin, and fluoropyrimidine [17].

The addition of pembrolizumab to trastuzumab and chemotherapy resulted in a substantial and statistically significant increase in the objective response rate (ORR) compared to trastuzumab and chemotherapy alone as first-line treatment for patients with HER2+ metastatic gastric or gastroesophageal junction cancer. Additionally, an increase in terms of PFS, one of the primary endpoints, has been confirmed; although there were no statistically significant differences in terms of OS, the other co-primary endpoint. Specific data on older adults have not been reported so far and will be crucial to ascertain mature survival data [59].

Recommendations:

- In older patients who are not candidates for standard treatment, CAPOX with DI at 60% is recommended [IA].
- FOLFIRI is recommended for patients who are not candidates to receive platinum [IIIA].
- Immunotherapy can be added to chemotherapy for older patients with a good performance status without contraindications [IIA].
- Trastuzumab, oxaliplatin and fluoropyrimidine is recommended if the patient is HER2+, has an LVEF >50% and has controlled cardiovascular disease [IIA]. The addition of pembrolizumab may be considered as an alternative.

5. Second-Line and Successive Treatments of Metastatic Disease

For second-line treatment, after failure with platinum- and fluoropyrimidine-based chemotherapy, there are at least seven RCTs that compare a treatment scheme versus BSC or two treatment schemes with each other (Table 3) [60–66].

Five studies had the primary objective of showing differences in OS, and in two studies, PFS was the primary outcome. Except in one study, statistically significant differences were observed in favour of chemotherapy; however, in some, the HR was somewhat higher than the established objective [60–63]. Today, these treatments (irinotecan, paclitaxel, and docetaxel as monotherapy) have been approved and are considered options for these patients. Notably, these studies have certain limitations. Some were carried out exclusively in the Asian population; none are focused on older patients; GA was not performed; patients >65 years of age account for a small percentage of participants (Table 3); and the patients were not stratified by age, nor does age appear as a prognostic factor. Furthermore, HR data for OS by age subgroup are not available, but in no study is age correlated with a higher incidence of toxicity. Therefore, whether benefits are different in the older population than in the younger population cannot be confirmed.

The other two second-line RCT studies evaluated the role of ramucirumab. The REGARD study evaluated the use of ramucirumab as monotherapy versus placebo, and the RAINBOW study evaluated the addition of ramucirumab to paclitaxel versus paclitaxel as monotherapy [64,65]. Both studies reported an increase in OS, subsequently leading to drug approval. A subsequent analysis evaluated the results of these two studies by age group [67]. For the REGARD study, the HR data for OS were greater than or equal to the target in each age group, confirming that the benefit of ramucirumab is not dependent on age. For the RAINBOW study, compared with that in the control group, there was an increase in OS in the group that received treatment with ramucirumab and paclitaxel, with an HR of 0.75 when stratified by prognostic factors. However, only in the group of patients <65 years was the HR maintained at 0.75. In the other age subgroups (> 65, < 70 and > 75), the HRs were 0.88, 0.88 and 0.98, respectively, which were higher than the target set; therefore, the benefit of administering the drug combination in these subgroups of patients has not been confirmed. When comparing the grade 3–4 toxicity in the REGARD and RAINBOW studies in the subgroup of young patients with those >65 years of age, the incidence was similar; therefore, it can be concluded that ramucirumab is safe in the older population [64,65].

Recently, trastuzumab-deruxtecan has been approved for second-line treatment of patients with HER2-positive gastric cancer previously treated with trastuzumab due to the results of the DESTINY-Gastric02 trial. Even though it was a phase 2 trial with 79 patients, it reported a confirmed ORR of 42%, a median PFS of 5.6 months, and a median OS of 12.2 months [68].

Regarding third-line treatment, there are four randomized studies comparing chemotherapy with placebo [69–72]. A phase 3 study evaluating the use of apatinib versus placebo conducted in China showed a statistically significant increase in OS (6.5 vs. 4.7 months; HR 0.709; 95% CI, 0.537–0.937; $p = 0.016$) [69]. Although patients >65 years old only represented 14% of the total number of patients in the study, the HR was higher (HR 0.55; 95% CI 0.26–1.19 vs. HR 0.75; 95% CI 0.75–1.02), suggesting that apatinib may be a good treatment for older adults.

In the TAGS study, the administration of trifluridine/tipiracil (TAS-102) was compared with placebo, and age > 65 years appeared to be a poor prognostic factor in the multivariate analysis [70]. The study showed OS benefits, with an HR adjusted for prognostic factors of 0.69. Patients >65 years old represented 45% of the total sample, but with an HR of 0.73, the maintenance of the benefits of the drug in this age group cannot be confirmed.

In the study carried out with nivolumab versus placebo in the Asian population, a benefit in OS was observed when reaching the target HR of 0.65 [71]. The group >65 years represented 24% of all patients, and the HR for this group was better than that for the younger population (0.53 vs. 0.76), suggesting another treatment option for the older population. However, its use is now preferred in the first line associated with chemotherapy. On the other hand, the study, conducted in patients with *HER2*-positive gastric cancer that evaluated the administration of

trastuzumab deruxtecan (DS-8201) versus routine chemotherapy showed any improvement in OS although the percentage of patients >65 years among the total sample was not indicated in the original publication [72].

In conclusion, for second-line treatments, there are insufficient data from RCTs to ensure that the benefits obtained with chemotherapy in the general population are maintained in the older population; however, the benefits of ramucirumab as monotherapy has been confirmed in the older population [67]. For third-line treatment, both apatinib and nivolumab have been shown to provide benefits to this subgroup of patients, but these drugs are not approved in Spain. Nivolumab has also shown a benefit in older patients and could be offered if it has not been used before as a first line treatment.

Recommendations:

- Second-line treatment options include (i) ramucirumab [IIB]; (ii) paclitaxel-ramucirumab [IIC]; (iii) paclitaxel, irinotecan, and docetaxel as monotherapy [IIC]; and (iv) DS-8201 [IIC].
- Third-line and subsequent treatment options include (i) TAS-102 [IIC]; (ii) apatinib and nivolumab [IIB]; and (iii) DS-8201 [IIC].

6. Supportive Treatments for Older Patients

Chemotherapy is the standard treatment for advanced disease. However, it is often inadequate in relieving local symptoms such as pain and intestinal obstruction, which in turn can lead to dysphagia, vomiting or nausea, or digestive bleeding. There are several therapeutic options aimed at alleviating these symptoms that should be considered, taking into account the objective of treatment, the evolution of the disease and life expectancy.

6.1. Radiotherapy

RT is a noninvasive and effective therapeutic option with few side effects, but the volume and anatomical location of the tumour must be taken into account because of the risk of secondary enteritis. The study by Tey et al. showed the benefits of administering RT for the control of symptoms (pain, bleeding, and obstruction); in this study, the mean age of the patients included was 77 years [73]. For obstructive symptoms, RT has the added advantage over other therapeutic options of reducing the tumour burden and bleeding while relieving symptoms; however, the effect is transitory.

6.2. Palliative Surgery

The absence of a survival benefit from palliative gastrectomy for advanced disease has been shown with the REGATTA trial [74]. In the study by Kim et al., the results obtained in octogenarian and non-octogenarian patients after gastrectomy were compared, and older patients had lower survival and higher morbidity and postoperative mortality [75].

For obstructions, surgical bypass (open or laparoscopic gastrojejunostomy) may be considered, especially in patients in whom longer survival is expected [76].

6.3. Endoscopic Treatment

Endoscopic therapy, despite not being as well studied as RT, can be an effective option for controlling bleeding in highly selected patients, especially when the vital prognosis is not very limited and the tumour burden, especially remotely, is low [77]. For obstructive symptoms, stenting has a similar success rate to surgical bypass but with lower morbidity, mortality, and cost [78]. However, its disadvantage is the high rate of late complications due to migration or obstruction. Another more recent option is endoscopic gastrojejunostomy.

6.4. Nutrition

Malnutrition in older patients with cancer is associated with a worse prognosis [79]. When oral intake is not possible, due to disease or treatment, enteral or parenteral feeding may be considered if RT enteropathy or malabsorption syndrome is developed [80,81].

However, there are both potential risks and benefits of parenteral nutrition. The aim of nutritional therapy is to improve the nutritional status, metabolism, incidence of postoperative complications, adherence to anticancer therapies, quality of life (QOL), and survival. Both the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend oral or enteral feeding whenever possible. Any postoperative complications may delay this approach and diminish predefined caloric uptake. In this case, parenteral nutrition (peripheral or total) can improve the nutritional status of malnourished patients with gastric cancer. However, it should be considered that parenteral nutrition may cause various impairments of host defense mechanisms, including gut immunity, systemic mucosal immunity, hepatic immunity, and peritoneal host defense. In addition, it requires a central vein catheter which is associated with additional risks [82–86].

7. Further Research and Future Needs

Currently, there are multiple lines of active research that include older patients with gastric cancer. On the digital platform clinicaltrials.gov (last accessed October 12, 2022), 55 clinical trials address different aspects of treatment specifically in older patients with this pathology [87]. Studies that stand out include researching the usefulness of GAs in the management of metastatic patients (NCT04618809), comparing the open or laparoscopic approach in the localized or locally advanced stage (NCT03564834), comparing D1 or D2 lymphadenectomy in patients with high-risk gastric adenocarcinoma who are older than 75 years with a Charlson index >5 (NCT03051152), multimodal prehabilitation for surgery in the frail older patients (NCT05352802), assessing the value of neoadjuvant chemotherapy versus entry surgery (NCT04677673), comparing the second-line treatment of metastatic disease with ramucirumab with or without paclitaxel (NCT03760822), and the SOAR study on GA, physical exercise and health education for twelve weeks via telematics in different stages of the disease (assessing the effects on quality of life and toxicity of the treatments administered) (NCT05509751).

Compared to other pathologies, clinical trials in progress for gastric cancer in older adults are scarce, which is an indicator of unmet needs in an increasing population in an aging society [88,89]. The ideal would be to design specific studies for the older population, where studies on surgical approaches would be most feasible. Regarding pharmacological treatments, a good strategy to increase scientific evidence would be not to limit the maximum age of patients in the inclusion criteria of clinical trials, to use GA routinely for older patients during all stages of the treatment and assess its impact, to carry out pharmacodynamic and pharmacokinetic studies of drugs in this population before their commercialization and, once approved, to support the results of studies with real world evidence (RWE), which can be a source of valuable information [90–92]. Regarding supportive treatment, there are several groups that are applying and researching the value of physical prehabilitation, and the results obtained with this intervention should be disseminated as soon as possible.

Emerging biomarkers such as Claudin18.2 (CLDN18.2) or fibroblast growth factor receptor 2b (FGFR2b) are highly prevalent in metastatic gastric cancer and new specific targeted drugs are expected to be available soon, also for older patients. These will be added to established biomarkers such as HER2, microsatellite instability (MSI) or PD-L1. Apart from pembrolizumab, which is indicated for patients with MSI high or deficient mismatch repair (dMMR), zolbetuximab in combination with chemotherapy could be a new therapeutic option in patients

with CLDN18.2 positive and HER2 negative advanced gastric cancer [93,94].

8. Final Conclusions and Recommendations

Gastric cancer is a frequent pathology in the older patients. The recommendations for treatment are generally derived from clinical studies not specifically focused on the older population and therefore have a low level of evidence. Table 4 gives a series of management recommendations developed by this working group and Table 5 explain the meaning of the levels of evidence and grades of recommendation. To improve daily clinical practice with these patients, a series of approaches should be considered: (i) a multidisciplinary approach, ideally within a tumour committee with the participation of a geriatrician who takes into account the perspective of age, supportive treatment, and preservation of quality of life in these patients, who tend to have different expectations about their cancer treatment than younger patients; (ii) perform GA for all patients after a positive screening test such as G-8 or VES-13, and repeat them throughout all stages of treatment; (iii) include older patients in clinical trials and, if possible, conduct trials only with the older population, for example, as the GO2 study; (iv) consider and even anticipate a probable greater surgical morbidity and mortality in these patients after gastrectomy; (v) although current evidence indicates that older patients obtain the same benefit as younger patients with systemic treatments, consider the possibility of reducing the dose or DI of chemotherapy to achieve better tolerance with similar efficacy; (vi) collect RWE through multicentre registries of tumours in older patients; and (vii) promote specific clinical trials in the older population that take into account their medical as well as their social needs. With this in mind, the Oncogeriatrics Section of the SEOM, like other scientific associations, has launched different projects aimed at increasing the evidence and improving the treatment of gastric cancer in older individuals, such as the MULTIFRAG study (Evaluation of the usefulness of various frailty scales in the older patients with cancer treated with chemotherapy) and the National Registry of Tumours in the Elderly [88,89].

Table 4
Summary of recommendations for the management of gastric cancer in older patients according to levels of evidence and grades of recommendation described in Table 5.

Recommendations at different stages	LOE/ GOR
GA should be part of the initial and periodic evaluation of older patients with gastric cancer within a multidisciplinary team.	IA
Endoscopic resection is indicated for T1a gastric tumours with good prognostic factors (grade 1–2, ≤2 cm, nonulcerated) and in older patients with high surgical risk.	IIIB
GA can predict postoperative complications in patients with gastrointestinal tumours.	IIA
Laparoscopic surgery facilitates a faster recovery and fewer complications than does open surgery in the older population.	IIB
The associated lymphadenectomy must be a D2 lymphadenectomy without splenectomy or pancreatectomy.	IIB
Surgical recovery improvement programmes must be implemented in the older population.	IIIB
Perioperative chemotherapy (preferably over adjuvant chemotherapy): The doublet with platinum and fluoropyrimidines has shown benefits. The addition of a taxane to a platinum doublet in the older population has limited evidence, as it causes greater toxicity.	IIB
RT could be part of treatment in a preoperative chemoradiotherapy strategy for adenocarcinomas of the gastroesophageal junction.	IIC
Adjuvant chemotherapy:	
Platinum- and fluoropyrimidine-based if perioperative chemotherapy has not been administered.	IIB
First-line treatment:	
- In older patients who are not candidates for standard treatment: CAPOX with DI at 60%	IA
- FOLFIRI for older patients who are not candidates for platinum	IIIA
- Immunotherapy can be added to chemotherapy for older patients with a good performance status without contraindications	IIA
- Trastuzumab, oxaliplatin and fluoropyrimidine (if *HER2* +, LVEF >50% and controlled cardiovascular disease)	IIA
Second-line treatment:	
- Ramucirumab	IIB
- Paclitaxel-ramucirumab	IIC
- Paclitaxel, irinotecan, and docetaxel as monotherapy	IIC
- DS-8201	IIC
Third-line and subsequent treatments:	
- TAS-102	IIC
- Apatinib	IIB
- Nivolumab	IIB
- DS-8201	IIC

CAPOX: capecitabine and oxaliplatin; DI: dose intensity; DS-8201: trastuzumab deruxtecan; FOLFIRI: folinic acid, fluorouracil and irinotecan; GA: geriatric assessment; GOR: grade of recommendation; HER2: human epidermal growth factor receptor 2; LOE: level of evidence; LVEF: left ventricular ejection fraction; RT: radiotherapy; SOX: S1 and oxaliplatin; TAS-102: trifluridine/tipiracil.

Table 5
Levels of evidence and grades of recommendation [17].

Levels of evidence
I. Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity.
II. Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity.
III. Prospective cohort studies.
IV. Retrospective cohort studies or case–control studies.
V. Studies without control group, case reports, experts' opinions.
Grades of recommendation
A. Strong evidence for efficacy with a substantial clinical benefit, strongly recommended.
B. Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.
C. Insufficient evidence for efficacy or benefit, does not outweigh the risk or the disadvantages (adverse events, costs), optional.
D. Moderate evidence against efficacy or for adverse outcome, generally not recommended.
E. Strong evidence against efficacy or for adverse outcome, never recommended.

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Authors' Contributions

All authors contributed to the study conception and design. All authors participated in the writing of the first draft of the manuscript, commented on following draft versions and approved the final version of the manuscript.

Ethical Statement

The study has been performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. This article does not contain any studies with human participants or animals performed by any of the authors.

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