Real-world challenge for clinicians treating advanced gastroesophageal adenocarcinoma (Review)

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Abstract. Gastroesophageal adenocarcinoma (GOA) is a disease of older people. Incidence is rising in the developed world and the majority of patients present with advanced disease. Based on clinical trial data, systemic chemotherapy in the advanced setting is associated with improvements in quality of life and survival. However, there is a recognised mismatch between trial populations and the patients encountered in clinical practice in terms of age, comorbidity and fitness. Appropriate patient selection is essential to safely deliver effective treatment. In this narrative review, we discuss the challenges faced by clinicians when assessing real-world patients with advanced GOA for systemic therapy. We also highlight the importance of frailty screening and the current available evidence we can use to guide our management.

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Abbreviations: CARG, Cancer and Aging Research Group; CGA, comprehensive geriatric assessment; CRASH, Chemotherapy Risk Assessment Scale for High-Age patients; ED, emergency department; ECOG, Eastern cooperative oncology group; EOX, epirubicin/oxaliplatin/capecitabine; FFS, failure-free survival; GOA, gastroesophageal adenocarcinoma; GORD, gastroesophageal reflux disease; GP, general practice; HR, hazard ratio; HRQoL, health-related quality of life; ICI, immune checkpoint inhibitor; LV function, left ventricular function; MDT, multi-disciplinary team; OS, overall survival; OTU, overall treatment utility; OX, oxaliplatin/capecitabine; PFS, progression-free survival; PS, performance status; RR, response rate; SACT, systemic anticancer therapy; UK, United Kingdom; 5FU, 5-fluorouracil

Key words: advanced gastroesophageal cancer, frailty, geriatric oncology, real-world, reduced performance status

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1. Introduction

The two major histological subtypes of gastroesophageal cancer are adenocarcinoma and squamous cell carcinoma. Gastroesophageal adenocarcinoma (GOA) is the most common histological subtype in developed countries and the incidence of GOA has markedly increased in the Western world in the last 40 years due to a rise in gastroesophageal reflux disease (GORD) and obesity (1).

GOA is a disease affecting older-aged individuals (2,3). In the United Kingdom (UK), the median age at diagnosis is 74 years and there are approximately 15,000 cases diagnosed annually (2). As the population ages, this figure is projected to continue to rise, particularly in patients aged ≥80 years (4).

Patients with GOA often have a high symptom burden and frequently have a reduced performance status and features of frailty (3,5,6). It is therefore becoming crucial to understand how to best tailor treatments for the older-aged, frail patients with GOA in clinical practice.

Between 60 and 80% of patients with GOA present with advanced stage disease not amenable to curative treatment approaches with surgery or definitive chemoradiotherapy, or present when curative treatment is not possible due to medical co-morbidities or frailty (7,8). The focus of treatment in these patients is disease control and the palliation of symptoms. There is ample evidence to suggest that systemic anticancer therapy in the form of chemotherapy can achieve this. Systemic treatment has also been shown to improve the health-related quality of life (9). However, at diagnosis,

less than half of patients are assessed as being fit to receive palliative systemic therapy (10).

The median overall survival (OS) is approximately 3 months with the best supportive care (9,11) and reported as 9-11 months with chemotherapy, extending to 16 months with the addition of trastuzumab to the subgroup (approximately 20%) of patients whose tumours are human epidermal growth factor receptor 2 (HER2)-positive (12,13). Emerging data suggest a role for immune checkpoint inhibitors (ICIs) in selected patients, which may provide more durable responses and result in a prolonged treatment duration, particularly in patients with an increased programmed death-ligand 1 (PD-L1) expression or mismatch repair deficiency (14,15).

In those patients with advanced GOA who are deemed fit for systemic therapy, there is often a mismatch between their clinical phenotype and that observed in trial populations on which treatment guidelines are based. Clinicians are therefore required to apply information extrapolated from clinical trials in which patients are younger, fitter and have fewer comorbidities (16). This creates uncertainty around regime and dose due to concerns regarding the risk of toxicity with age-related changes to pharmacokinetics and pharmacodynamics. Ultimately this can result in the undertreatment of a patient and/or excess morbidity and mortality (17).

Despite this, trial data suggest that older-aged patients with advanced GOA can tolerate and benefit from systemic chemotherapy (18). As such, chronological age should not by itself preclude the use of anticancer therapy. Rather, a global picture of the patient's health should be considered, including functional status, comorbidities and social support. Frailty screening and comprehensive geriatric assessment (CGA) along with allied healthcare professional involvement should be part of this process (19).

The present narrative review discusses the challenges associated with the assessment of older-aged patients with advanced GOA and frailty that is commonly encountered in real-world clinical practice, the importance of frailty assessment and the current evidence which underpins our treatment decisions.

2. Patient experience and the role of the multi-disciplinary team

At diagnosis, the patient population with advanced GOA is characterised by an older age, a high symptom burden and a poor prognosis. For patients not fit to receive systemic treatment, the median OS is poor, estimated at 3 months (11). Contributing factors include the stage of disease and performance status; however, age does not appear to have an impact (18).

For patients who receive systemic therapy, there is a median OS benefit of approximately 6.7 months over supportive measures alone (20) and evidence to support improvement in symptoms (9). However, >50% of patients require at least one treatment-related hospital admission, and 96% report fatigue (21). In all patients, there is a fine balance between the palliation of symptoms, improving survival and the risk of toxicity negatively impacting the quality of life.

Due to the nature of the disease, patients of all ages have often had a period of nutritional deficit. This, coupled with the high catabolic state of advanced disease, can result in malnutrition, immunodeficiency, an impaired quality of life and worse clinical outcomes (22). The impact is more evident in older-aged patients where age-related nutritional consequences, such as sarcopenia and osteoporosis are more common (23) and where other comorbidities are prevalent (24). In adults aged ≥60, the prevalence of malnutrition varies according to the setting, estimated at 3.1% in the community to 28.7% in long-term care (25). This has important implications when assessing a patient's suitability for treatment. The treatment of advanced GOA therefore requires a multidisciplinary approach (Table I) with specific focus on input from palliative care, physicians with geriatric expertise (if available), general practice (GP), dietetics, occupational therapy and physiotherapy (26).

The medical team. Patients experience a high symptom burden in their final year of life (5). Symptoms related to tiredness, well-being and appetite become more severe earlier in the disease course, whereas symptoms related to drowsiness, pain and shortness of breath become more severe closer to death (5). The impact of symptom burden on both patients and the health service, was demonstrated by a study in Scotland, which found that 75% of patients with upper gastrointestinal cancer use GP out-of-hours services in the last year of life with a further 7.8% using hospital emergency departments (EDs) and 22.6% using both GPs and EDs (27). In addition, patients with advanced GOA who survive <7 months following diagnosis, have an association with several indicators of low-quality end-of-life care (28).

Outpatient palliative care initiation has been shown to be associated with a decrease in symptoms and early palliative care involvement improves the quality of life at the end stages of life and reduces hospital visits (29). This highlights the importance of early cross-speciality collaboration.

Allied healthcare professionals. Cancer and its treatment can have an impact on a number of domains of a patient's health. It is therefore essential to assess for and address any functional, social or cognitive deficits early in the patient cancer journey. This can be done using frailty screening tools and a CGA, which will be discussed in detail below.

An example is the impact of cancer on the metabolic state of a patient, exacerbated in GOA by dysphagia. Systemic therapy can compound this further by causing symptoms, such as nausea, vomiting, mucositis and diarrhoea. The consequence is malnutrition, which in turn can influence the effectiveness of chemotherapy (30). A proportion of patients will require stent insertion to maintain oral intake, but all patients should receive regular nutritional assessments and dietetics input, as this has been shown to improve the quality of life and outcomes (31). In those who undergo stent insertion, close nutritional observation is required due to post stent pain.

Physical activity following a diagnosis of advanced cancer has the potential to prevent or reverse functional decline, control cancer-related symptoms and help maintain independence, thus improving outcomes (32). Older-aged patients with cancer are at an increased risk of falls compared to the general population (33) and prior falls are associated with a risk of

Table I. Key elements of a patient's cancer journey, which require regular re-evaluation.

Factors	Elements
Aims/goals of treatment	Improved survival
	Improved/maintained quality of life
	Minimise toxicity
	Improve symptoms
Patient factors	Symptoms
	Disease burden
	Performance status/fitness
	Age
	Frailty status
	Nutritional status
	Organ function
Treatment options	Chemotherapy
	Radiotherapy
	Targeted therapy
	Immune checkpoint inhibitors
	Clinical trial
	Procedural e.g., stenting
	Best supportive care
MDT involvement	Oncologist
	Surgeons
	Palliative care
	Geriatrics
	General practice
	Allied healthcare professionals
	Cancer nurse specialists

Goals of care, patient factors, MDT involvement and available treatment options interact to create a plan of management. MDT, multi-disciplinary team.

chemotherapy toxicity and survival (34,35). Chemotherapy in advanced GOA can contribute to an increased risk of falls; for example, dehydration may result in orthostatic hypotension or neurotoxicity, thus affecting balance. The involvement of physiotherapy and occupational therapy at an early stage can reduce the risk of adverse outcomes by facilitating strength and balance training, implementing home exercise programmes and providing a home safety evaluation.

The review of a patient by allied health professionals prior to treatment is part of prehabilitation. Prehabilitation is now widely practiced prior to GOA cancer surgery with significant outcome benefits related to nutrition, length of stay and improved complication rates (36-38). However, evidence relating to treatment outcomes with prehabilitation in advanced GOA is limited. Nevertheless, it has been demonstrated that individualised exercise and nutritional programmes for patients with advanced GOA result in significant improvements in functional and symptomatic domains (39). It stands to reason that enabling these improvements will reduce frailty and therefore improve tolerance of treatment.

3. Treatment challenges in advanced gastroesophageal adenocarcinoma

General considerations. Central to the process of decision-making are the wishes of the individual patient. Recent reports by Cancer Research UK and from North America highlight the importance of clear communication regarding the risks of treatment, and also demonstrate that the majority of older-aged cancer patients value quality of life over length of life (40,41). These studies included patients with advanced GOA and highlight the importance of a personalised approach to management.

With improvements in medical care, life expectancy is increasing worldwide. As a result of this changing demographic, there is an increasing proportion of cancers diagnosed in the >65 age group. Within the UK, a third of all cancer diagnoses and half of all cancer-related deaths occur in the >75 age group (42).

The evidence for systemic anticancer therapy (SACT) in older populations is often extrapolated from retrospective and subgroup analyses of clinical trials in younger patients. Caution therefore needs to be applied and consideration given to altered physiology and drug pharmacology. Age alone is not an exclusion from chemotherapy as agents appear equally efficacious regardless of age (43). However, age-related changes in pharmacokinetics and pharmacodynamics often lead to increased toxicity when older and frailer patients are treated with doses established from clinical trials in younger, less frail patients (18,44). Treatment decisions must be made in the context of life expectancy.

Frailty. Frailty is defined as a state of increased vulnerability toward stressors due to a multisystem reduction in reserve capacity (45). It is linked to both chronological age and the presence of comorbidities, but is considered a distinct concept.

Frailty is common in cancer, both due to the association of cancer with certain comorbidities and the increasing age, but also as the cancer itself places a physiological strain on the health of an individual. There are different models of the concept of frailty and no single diagnostic test. This means it is not possible to state an exact prevalence of frailty in older-aged patients with cancer.

A systematic review in 2015 evaluated data from 2,916 participants in 20 studies of frailty in older cancer patients (6). Studies were included if they used one or more of the established frailty models (phenotype model, cumulative deficit model or CGA). They found that the median reported prevalence of frailty and pre-frailty was 42% (6-86%) and 43% (13-79%), respectively. Only a median of 32% (11-78%) were classified as fit. Importantly, few patients included in the review had GOA and there is therefore a paucity of data relating specifically to prevalence of frailty in advanced GOA. Patients deemed frail or pre-frail were at increased risk of chemotherapy toxicity and intolerance as well as all-cause mortality.

Consequently, screening for frailty prior to commencing therapy is a useful step to identify a population that is at higher risk for toxicity. This screening should prompt more detailed investigation of specific patient needs. This is usually done by CGA, which not only identifies issues but also involves the intervention and follow-up.

Traditionally, oncologists have used the Eastern Cooperative Oncology Group (ECOG) performance status (PS) or the Karnofsky performance scale as measures of fitness and frailty. Although very quick to do, they were validated in younger populations and do not take into account contributing domains of frailty such as medications, comorbidity and cognition (34) or interuser variability (46). They have also been shown to be inferior to other frailty screening tools and therefore should not be used alone (47).

Due to time limitations in clinical practice, a number of screening tools for frailty have been developed and validated with a focus on identifying patients who require a more in-depth assessment in the form of a CGA.

The Clinical Frailty Scale (48) also known as the Rockwood Score, is the most commonly used tool in the UK due to its ease of use and availability. It is based on clinical assessment using knowledge of cognition, social support, comorbidity and function. The patient is assigned a score between one and nine based on activity, function and disability. Other screening tools used in a cancer setting are the Geriatric 8 (G8) (49), Vulnerable Elders Survey-13 (50), the abbreviated CGA (51) and the Groningen Frailty Indicator (GFI) (52).

A screening tool may prompt the implementation of a CGA. This is used to identify causes of frailty, and target interventions appropriately (53). It is a detailed process with interdisciplinary input, which assesses multiple domains to create a problem list and subsequent plan of management. Although it is a strong predictor of adverse events with chemotherapy (19), its use in clinical practice is limited by time-constraints and the need for a physician with geriatric expertise. The implementation of CGA in gastrointestinal cancer has been shown to improve tolerance to chemotherapy, reduce dose modifications and lower rates of grade 3-5 toxicity (54,55). A CGA should therefore be a standard of care for patients with advanced GOA deemed to have features of frailty.

Drug-related issues

Age-related changes. Physiology changes with age. This can have an impact on drug pharmacokinetics and pharmacodynamics (56). The age-related decline in renal function, as well as liver volume and blood flow impact the excretion and metabolism of drugs. In gastroesophageal cancer, this can be compounded by reduced gastric motility and absorption. A further complication is the age-associated reduction in lean body weight and muscle mass, which can impact the volume of distribution of lipid-soluble drugs. Taken together, these factors render the older-aged population more prone to drug-related side-effects, particularly when symptom control becomes a priority at the end of life.

Polypharmacy. Patients with advanced GOA, prior to their diagnosis, will often have multiple co-morbidities with associated prescribed medications. A UK study in patients with advanced cancer found the median number of medications was 7 (57). In that study, the median age and PS were 73 years and 2 respectively, similar to the advanced GOA population which is encountered.

In the context of SACT, a number of regimes involve the prescription of drugs that are inherently toxic and have narrow therapeutic windows. In addition, regimes often have supportive medications adding to the medication burden. This can potentially lead to poor adherence or inappropriate medication use (58). In advanced GOA, a good example of a common drug interaction is the reduction in the efficacy of capecitabine if co-prescribed with a proton pump inhibitor (59). This has been shown to impact both progression-free survival (PFS) and OS. It is therefore vital to rationalise medications whenever possible.

Nutritional support. Malnutrition is an important prognostic factor in all cancer patients. Approximately 10-20% of cancer-related deaths can be predominantly attributed to malnutrition as a consequence of the cancer itself (60,61). A poor nutritional state is associated with poorer outcomes, such as lower response rates and survival, increased toxicity and a reduced quality of life (62-64). An age >70 years is associated with a 2-fold increased risk of cancer mortality and severe malnutrition a 2.5-fold increased risk (61).

Advanced GOA can significantly affect nutrition with dysphagia and anorexia being common symptoms. In a study on 1,000 cancer outpatients, the median percentage weight loss for oesophageal and gastric cancers was 15.9 and 11.0%, respectively (65). In these patients, weight loss was associated with anorexia and was greater in those with more advanced disease and with compromised performance status.

The recognition and management of nutritional issues is of particular importance in older-aged patients as they are predisposed to age-related reductions in lean muscle mass (sarcopenia) (66), as well as reduced gastrointestinal absorption (67). There is an additional challenge of delineating normal age-related changes from pathological cancer-related changes. In advanced gastric cancer, there is evidence that malnutrition exists in over half of patients and that it is associated with greater stage, elevated inflammatory markers and significantly lower survival (68). Nutritional assessment and subsequent intervention have been observed to improve survival.

Chemotherapy risk assessment tools. Chemotherapy toxicity can have a significant impact on a patient's quality of life. Toxicity occurring in the first cycle of treatment can predict those patients who will develop severe toxicity (69). Toxicity can result in reduced survival as a consequence of reduced dose intensity. The ability to predict which patients are more likely to develop side effects would facilitate a proactive approach, either dose reduction or the initiation of supportive measures. The goal for clinicians is to maintain efficacy of treatment, while minimising the negative impact on quality of life.

In advanced GOA, in a standard of care epirubicin/oxaliplatin/capecitabine (EOX) arm of the REAL2 trial (13), 42% of patients required a dose reduction and 50% of patients required at least one dose delay due to treatment-related toxicity (13). In the GO2 trial in a frail population, even with a 60% dose, 86% of patients experienced some form of toxicity and 37% experienced grade ≥3 toxicity (70).

At present, there is no validated chemotherapy toxicity tool specifically for advanced GOA. There are two tools in general use that have been validated in a range of solid and haematological malignancies, the Cancer and Aging Research Group (CARG) tool and Chemotherapy Risk Assessment Scale for High-Age patients (CRASH) score. The CARG tool and CRASH score were developed as tools to predict severe

toxicity in older-aged patients (34,71). They use baseline patient and treatment factors to calculate a risk score and are more predictive of toxicity than age or performance status.

Although validated (72), their use is limited in advanced GOA due to a lack of agreement in which factors are important, the wide range of chemotherapy regimes and settings included and the low numbers of GOA patients. These limitations, coupled with the knowledge that the GOA population differ from other tumour types, highlight the need for a toxicity prediction tool specific to advanced GOA.

4. Trial evidence for practice

There have been a limited number of oncology studies focused on an older, frailer population treated with chemotherapy. The majority of the data used in clinical practice comes from retrospective data collection or sub-analysis of larger trials which included older patients within their eligibility criteria (Table II). When applying these data, consideration should also be given to the end points used, the traditional endpoint of OS may be less appropriate in an older population. Other outcomes, such as quality of life, the maintenance of a functional status and cognition may be as relevant or even more relevant than survival (73).

First-line chemotherapy. In advanced GO cancer, a standard of care chemotherapy in younger patients with a good PS (PS 0-1) was established by the REAL2 trial (13). In that trial, the median age of the EOX arm was 62 years and 90% of patients had PS 0 or 1. In patients with features of frailty and reduced PS, a standard of care was established by the recently presented GO2 trial (70).

Prior to the GO2 trial, there was a lack of data in elderly, frail patients. Several phase I/II studies were conducted in the 1990s/early 2000s to investigate the use of chemotherapy in older patients with gastric cancer. Overall response rates (RRs) ranged from 29 to 45%, with median PFS 4.2-5 months (74-77).

The only large, randomised trial in advanced GO cancer was the COMBAT study (78). That study tested the addition of mitomycin C to infusional 5-fluorouracil (5FU), demonstrating no statistically significant advantage in the primary endpoint, failure-free survival (FFS). The median age was 72, 32% were PS 2 and the median OS was 6.3 months.

A pooled analysis in 2006 of three UK clinical trials in advanced GO cancer compared outcomes in patients aged >70 years to younger patients (18). A total of 1,080 patients were included, of whom 257 (23.8%) were >70 years of age. No significant differences in RR, survival or toxicity were observed. A further study by the North Central Cancer Treatment Group (NCCTG) in which 154 patients were aged >65 years, found that although OS and RR were similar, the rates of toxicity were higher than those compared to patients younger, <65 years of age (79).

In 2015, the Phase II TTD 08-02 study assessed the use of a triplet regime in the form of reduced dose docetaxel with oxaliplatin and capecitabine in 42 'sub-optimal' patients. These patients were defined as those with PS 2, weight loss 10-25% and/or aged ≥70 years. Although the median OS was 13.4 months, the rate of grade 3-5 toxicity was 76%, with 3 (7%) patients suffering a sudden death (80). Due to the high toxicity, this regime has not been adopted.

These studies suggested that three drug platinum-based chemotherapy often provided an unequal balance of toxicity over efficacy for older and frailer patients. This opinion was reflected in guidelines for GOA (81), and despite the lack of randomised trial evidence oncologists commonly made empirical dose reduction to chemotherapy in those older and frailer patients for whom there was concern that they would not tolerate standard dose three drug regimens.

To address the question of appropriate dosing in a frailer population a Phase II feasibility study in the UK, 321GO, was undertaken (16). It concluded that it was feasible to recruit older and/or frail patients with advanced GO cancer to a randomised clinical trial and that OX (oxaliplatin/capecitabine) was the preferred regimen for further study. That study also supported the use of the novel composite endpoint, overall treatment utility (OTU), including both patient-reported and clinical indices. This was initially used in the FOCUS2 trials in colorectal cancer (82) and reflects whether either or both the patient and clinician were pleased with the decision to proceed with chemotherapy (Table III).

The subsequent GO2 trial (70) aimed to establish the optimum dose-intensity (100, 80 or 60%) of two-drug OX palliative chemotherapy in patients who are considered unsuitable for triplet EOX chemotherapy. The goal was to achieve the best balance of cancer control, toxicity, patient convenience, acceptability and quality of life. That study also aimed to establish pre-treatment patient characteristics which predict for better or worse outcomes with chemotherapy at different dose intensities.

A total of 517 patients were recruited, and the population appeared representative of real-world experience, median age 76 years, 31% PS ≥2 and >50% classified as very frail. The 60% dose was found to be non-inferior to 100% dose [median OS, 7.6 vs. 7.5 months; hazard ratio (HR), 1.10] with reduced toxicity (grade 3+ adverse events, 37 vs. 56%) and better OTU (good OTU, 43 vs. 35%). On sub-analysis, no group was found to benefit from the higher dose, and the fittest patients benefited most from dose reduction. Age and PS were not predictive of OTU; however, this may be due to higher numbers of fit elderly patients and unfit younger patients within the trial.

As a result of that trial, the new 'full dose' standard of care treatment for patients with advanced GOA and features of frailty is 60% of the dose of oxaliplatin and capecitabine used in the REAL2 trial. Of note, in a sub-study of the GO2 trial, which recruited 45 patients in whom there was doubt over the benefit of giving chemotherapy, there was no significant survival advantage for single drug capecitabine over best supportive care (median OS, 6.1 vs. 3.0 months; HR, 0.64; P=0.34) (11).

Subsequent chemotherapy. When disease progression occurs during or following first-line treatment, only approximately 50% of patients are fit to receive further therapy (83). These patients are often frail as a result of their disease progression (3). In this setting, fewer older-aged patients are offered further treatment compared to younger patients (84). Second line chemotherapy options for advanced GOA include irinotecan, docetaxel and weekly paclitaxel administration.

Table II. Practice changing clinical trials in advanced GOA, which included patients of an older age and with a higher performance status.

	Trial overview				Relevant data for older adults/frailty/increased PS		
Trial/(Refs.), year	Regime	Population	Median age (range), years	Patient fitness	PFS	OS	Toxicity
First line chemotherapy							
REAL2 (13), 2008	EOX vs. ECX vs. ECF vs. EOF	n=239 in EOX (87.4% GOA)	62 (25-80)	PS 0/1: 90% PS 2: 10%	No data published data regarding PS 2 and age.		
TTD08-02 (80), 2015	Mini-DOX	n=42 'sub-optimal patients' defined as PS 2+, >70 years or weight loss 10-25%	73.3 (40.2-87.7); 65% >70 years	PS 2: 27%; 53% had weight loss of 10-25%	5.5 Months (3.8-7.2)	13.4 Months (7.7-19.6)	76.2% Grade 3-5 toxicity; prophylactic G-CSF introduced for last 33 patients.
GO2 (70), 2019	OX Level A (100%)	170	76	PS: ≥2 31%	4.9 Months	7.5 Months	Grade 3+ toxicity 56%
	Level B (80%)	171	76	≥2 32%	4.1 Months	6.7 Months	56%
	Level C (60%)	173	77	≥2 31%	4.3 Months	7.6 Months	37%
Subsequent line chemotherapy							
COUGAR-02 (88), 2014	Docetaxel vs. BSC	GOA (n=84 and 84)	65 (28-84) vs. 66 (36-84) Age >70: 23 (27%) vs. 16 (19%)	Docetaxel: PS 0/1/2=28/55/17%	ITT: 12.2 weeks. No breakdown for PS or age	ITT: 5.2 vs. 3.6m HR for OS: PS 0=1.0, PS 1=2.0, PS 2=2.16	21% Grade 4 toxicity
German AIO (87), 2011	Irinotecan vs. BSC	Gastric (n=21 and 19)	58 (43-73) and 55 (35-72)	PS 0/1: 17 (81%) and 14 (74%) PS 2: 4 (19%) and 5 (26%)	Irinotecan ITT: 2.6 months	4.9 vs. 2.4 months; HR PS 0/1 vs. PS 2=0.53, P=0.1	26% Grade 3 diarrhoea 16% grade 3+ neutropenic fever
WGOJ4007 (101), 2013	Paclitaxel vs. irinotecan	Gastric (n=108 and n=111), Asian population	64.5 (37-75) and 65 (38-75)	PS 0/1: 104 (96.3%) and 107 (96.4%) PS 2: 4 (3.7%) and 4 (3.6%)	3.6 vs. 2.3 months; HR, 1.14; P=0.33	9.5 vs. 8.4 months (HR, 1.13, P=0.38); HR ≥65, 0.97 HR PS 2: 7.27 (0.79-66.6) favouring paclitaxel	No breakdown by age or performance status

Table II. Continued.

Trial/(Refs.), year	Trial overview				Relevant data for older adults/frailty/increased PS		
	Regime	Population	Median age (range), years	Patient fitness	PFS	OS	Toxicity
Targeted therapy							
TOGA (12), 2010	CX + herceptin vs. CX alone in 1st line	GO cancer (n=294 and n=290)	59.4 (1.08) and 58.5 (11.2) 305 patients >60 years	PS 0/1: 264 (90%) and 263 (91%) PS 2: 30 (10%) and 27 (9%)	6.7 vs. 5.5 months (HR, 0.71, P=0.0002)	PS of 2 (HR 0.96), therefore no OS advantage For those aged 60+, OS HR 0.66	Grade 3+ toxicity 68% both groups; toxicity similar across ages
RAINBOW (92), 2014	Ramicirumab + paclitaxel vs. paclitaxel alone in 2nd line	GO cancer (n=330 and n=335)	61 (25-83) and 61 (24-84) >65 years: 126 (38%) and 123 (37%)	PS 1: 213 (65%) and 191 (57%). No PS 2. Weight loss >10%: 53 (16%) and 47 (14%).	4.4 vs. 2.9 months (HR 0.635, P<0.0001)	9.6 vs. 7.4 months (HR, 0.807, P=0.017) PS 0 and weight loss <10% were among predictors of survival.	Grade 3+ toxicity 83 vs. 65%
REGARD (91), 2014	Ramicirumab vs. BSC	GO cancer (n=238 and n=117)	60 (52-67) and 60 (51-71)	PS 1: 171 (72%) and 85 (73%). Only 1 patient was PS 2; weight loss >10%: 41 (17%) and 20 (17%)	2.1 vs. 1.3 months (HR, 0.483; P<0.0001)	5.2 vs. 3.8 months (HR, 0.767; P=0.047)	Grade 3+ toxicity 57 vs. 58%
Immune checkpoint inhibitors							
KEYNOTE-062 (14), 2020	Pembrolizumab vs. pembrolizumab + CTx vs. CTx alone	1st line GO cancer (n=256, 257, 250)	ITT: 62 (20-87) 216 patients >65	PS 1: 48.8% vs. 53.7% vs. 54% No patients with PS 2		No survival advantage for age ≥65 with addition of pembrolizumab in any group	Grade 3+ toxicity: 16.9% vs. 73.2% vs. 69.3%; immune-mediated adverse events: 21% vs. 24% vs. 8%; no data for age

Table II. Continued.

Trial overview					Relevant data for older adults/frailty/increased PS		
Trial/(Refs.), year	Regime	Population	Median age (range), years	Patient fitness	PFS	OS	Toxicity
Immune checkpoint inhibitors							
CheckMate 649 (15), 2020	Nivolumab + CTx vs. CTx	1st line GO cancer (n=789, 792)	63 (18-88) and 62 (23-90)	PS 1: 59 and 58%	CPS ≥5: 7.7 vs. 6.0 months (HR, 0.68, P<0.0001) All: 7.7 vs. 6.9 months (HR, 0.77)	CPS ≥5: 14.0 vs. 11.3 months (HR, 0.71, P<0.0001); PS 0: 17.6 months PS 1: 12.6 months; no difference in OS between <65 and ≥65 years	Grade 3+ toxicity: 59% vs. 44%

PFS, progression-free survival; OS, overall survival; PS, performance status; ITT, intention to treat; BSC, best supportive care; CX, cisplatin/capecitabine; GO, gastroesophageal; EOX, epirubicin/oxaliplatin/capecitabine; ECF, epirubicin/cisplatin/5-fluorouracil; ECX, epirubicin/cisplatin/capecitabine; EOF, epirubicin/oxaliplatin/5-fluorouracil; DOX, docetaxol/oxaliplatin/capecitabine; CPS, combined positivity score.

There is limited trial evidence for those who are older or of reduced performance status; however, extrapolated data exists that, for those who have PS 2, and to a certain extent 1, the efficacy of further systemic therapy is minimal (85). In the second line COG study which did not stratify according to performance status, the median OS was 6.07, 3.93 and 1.97 months for patients with PS 0, 1 and 2, respectively (86) highlighting the poor survival in those with a reduced PS.

The German AIO trial (87) and the COUGAR-02 trial (88) demonstrate efficacy from cytotoxic agents, such as irinotecan and docetaxel, respectively in the second line setting. However, the benefits of these treatments in the population as a whole were minimal and the toxicity was significant.

The German study of irinotecan included only 9 patients with a performance status of 2. Despite this fact, these patients had a poorer outcome than those with PS0 or 1 (HR, 0.53). The COUGAR-02 trial included 39 patients aged ≥70 and 26 patients with PS 2. Patients with a performance status of 0 had a better OS than those with a performance status of 1 [HR, 2.00; 95% confidence interval (CI), 1.35-2.96] or 2 (HR, 2.16; 95% CI, 1.27-3.66). On the whole, this supports the lack of efficacy of subsequent line therapy in frailer patients with a poor PS.

Beyond second line, the recently published TAGS trial (89) demonstrated a 2.1 month median OS advantage for lonsurf (trifluridine/tipiracil) when compared to supportive care. Lonsurf has now been licenced in the third line setting in the UK. However, only patients with PS 0 or 1 were recruited and the median age of patients recruited was 63. The grade 3+ toxicity rate was 53% and patients aged >65 who received Lonsurf (n=154), although trending for a survival advantage did not meet significance (HR, 0.73; 95% CI, 0.52-1.02).

Targeted agents. In HER2-positive advanced GOA, following the results of the ToGA trial, there is the option to add trastuzumab to a chemotherapy backbone if left ventricular (LV) function permits (12). This is an important consideration in elderly patients, as LV function decreases with age (90). Within the ToGA trial, 57 patients had a PS of 2 and 305 patients were aged >60 years of age. There was no survival advantage for those with a PS of 2 (HR, 0.96), but a significant survival advantage for those aged ≥60 years (HR, 0.66). This supports the hypothesis that age alone should not be used as the deciding factor in treatment decisions. Toxicity was similar according to age. Despite the low incidence of cardiac events within the trial, all patients require baseline cardiac imaging prior to starting trastuzumab in addition to ongoing monitoring.

Another licenced targeted agent is the vascular endothelial growth factor receptor (VEGFR)-2 monoclonal antibody, ramucirumab. The REGARD (91) trial demonstrated a survival benefit for ramucirumab over supportive care in the second line setting of 1.4 months. The majority of patients in the trial were performance status 1; only 1 patient was PS 2 and they did not receive the trial drug. However, given that clinicians were prepared to randomise to supportive care and only 35% of patients went on to receive subsequent therapy, PS may not provide an accurate representation of the frailty of the cohort. Therefore, although the survival benefit is minimal, the toxicity profile of ramucirumab is favourable, rendering this a more feasible option for subsequent therapy in frail patients,

Table III. OTU scored after 9 weeks.

Good OTU	Intermediate OTU	Poor OTU
All of: - Clinician score 'benefit' - Patient satisfied - No major toxicity - No drop in QoL	Either: - Clinician score 'no benefit' but patient satisfied and no major toxicity or QoL drop Or - Either patient dissatisfied or major toxicity or QoL drop, but clinician scores 'benefit'	Both: - Clinician score 'no benefit' And any of - Patient dissatisfied - Major toxicity - QoL deterioration Or - Patient has passed away

Clinician scores 'benefit' indicates no clinical or radiological evidence of cancer progression. A drop in QoL is defined as a fall of ≥2 on 12-point EORTC global QoL scale. Decision rules ensure OTU can be scored in 100% of patients. OUT, overall treatment utility; QoL, quality of life. The table was provided by PSH.

particularly as the PFS and OS benefit was preserved for both PS and age. Of note, toxicity according to age was similar apart from an increased incidence of hypertension in the >65 age group.

The RAINBOW trial subsequently examined ramucirumab in addition to paclitaxel in the second line setting compared to paclitaxel alone (92). The addition of ramucirumab significantly improved OS (9.6 vs. 7.4 months, P=0.017) with only a minimal increase in toxicity. Again, only PS 0 or 1 patients were included but the PFS and OS was again preserved for PS and age. Of note, rates of neutropenia were higher for those aged >65. Taken together, the REGARD and RAINBOW trials provide an option for subsequent line therapy in those patients in whom there are concerns over toxicity.

Immune-checkpoint inhibitors. The advent of immune-checkpoint inhibitors has altered the treatment paradigm for several tumour groups. These agents have a more favourable toxicity profile than traditional chemotherapy in an older population with preserved efficacy (93).

Evidence for their use in advanced GOA is increasing; however, similar to trials with chemotherapy, there is a mismatch between real-world and trial populations. An example is the recent Keynote-061 trial in advanced GO cancer where no patients >70 years of age were included and the only patient with PS 2, did not receive the trial drug (94).

In the first-line setting, the Keynote-062 trial included no patients with PS 2 and >50% had PS 0 (14). Of note, 216 patients were aged ≥65 years and there did not appear to be a survival advantage in this group with the addition of pembrolizumab. Importantly, despite this apparently fit population, grade 3+ toxicity was 69% with chemotherapy and 73% with the addition of pembrolizumab.

Likewise, the CheckMate 649 trial did not include patients with PS 2 and the median age was 63 years. Of the patients included, 59% had PS 1 and the median OS was 12.6 months, compared to 17.6 months in patients with PS 0. Again, grade 3+ toxicity was high at 59% in the combination arm (15).

This highlights the challenge of combination therapy which will likely have important implications in real-world clinical practice.

Radiotherapy. The recently published ROCS study (95) investigated the role of palliative radiotherapy in patients who had had a self-expanding oesophageal stent inserted for dysphagia. The median age was 72 years in the radiotherapy group and only 10% of patients had PS 0. No improvement in time to dysphagia deterioration or overall survival was observed with the addition of radiotherapy compared to the usual care group. However, for patients considered to be at high risk of bleeding, concurrent palliative radiotherapy may reduce bleeding risk.

Early supportive care. As mentioned above, advanced GOA is a high burden disease. This disease burden can impact not only on quality of life but also the tolerance of treatment. A recent study in China demonstrated that the early integration of nutritional and psychological support alongside SACT provided a survival advantage in advanced GO cancer (14.8 vs. 11.9 months; HR, 0.68; P=0.021) (96). No difference in frequency of adverse events was observed. Where available, early supportive care should therefore be offered to patients.

5. Future direction

For all patients, both cancer and the systemic treatments offered by oncologists are significant stressors that have the potential to challenge physiological reserve. For those patients with advanced disease, the delivery of treatment can be challenging, and the impact of treatment can be unpredictable and significant.

There is a recognised mismatch between the age of patients with advanced GOA encountered in clinical practice (median age, 74 years) and trial populations (REAL2 trial; median age, 63 years) (13). There is similar but less measurable mismatch in other measures such as frailty, performance status and co-morbidity. This issue is not unique to upper gastrointestinal cancer. The ageing population in the Western world can be expected to lead to a marked increase in the number of older patients seeking systemic anticancer therapy over the coming decades (97).

A lack of evidence in older-aged frail patients across tumour groups impacts negatively upon treatment delivery and effectiveness, as well as health-related quality of Life

(HRQofL). These factors lead to uncertainty in selecting optimal regimens to achieve the best balance of cancer control, toxicity, patient acceptability and quality of life in older and frailer patients.

With the emerging role of immune checkpoint inhibitors and other targeted therapies in advanced GOA, it is important to include patients who represent our real-world patients in terms of age and frailty in prospective trials.

To address this issue, the inclusion of frailer patients in clinical trials, who more resemble those encountered in practice, as well as the incorporation of appropriate endpoints has been highlighted as a priority for the American Society of Clinical Oncology (ASCO), the International Society of Geriatric Oncology (SIOG) and the European Organization for Research and Treatment of Cancer (EORTC). They have produced reports on the topic (73,98-100) and have suggested removing the upper age limit of trials and the design of specific trials for older patients where standard therapy is not feasible with integrated appropriate measures of outcome.

Consideration should be given to identifying relevant clinical and translational questions and designing trials appropriately to address them. With an older, frailer population, these questions may involve issues relating to dose de-escalation to achieve a balance of efficacy and toxicity or validating novel endpoints. In the complex world of geriatric oncology where there is huge variation in patient fitness and circumstances, communication with patients and families is essential. The GO2 trial is an exemplar of this approach. The data from the GO2 trial offers the opportunity to develop a decision aid based on objective assessments of frailty and both clinical and patient reported outcomes.

In the absence of evidence from clinical trials, the role of real-world data should not be ignored. These data can provide insight into outcomes post-drug approval in patient groups not adequately represented in clinical trials. This can aid clinical decision making but also accelerate progress in developing appropriate future studies.

6. Conclusion

The real-world patient cohort of patients with advanced GOA differs from traditional trial populations. Palliative chemotherapy is effective in older and frail patients, but it is vital to monitor patients closely for toxicity. The proper selection of patients is paramount, and this highlights the importance of integration of frailty screening and geriatric assessment, multi-disciplinary team (MDT) input and toxicity prediction tools into decision making. In the future, there should be a move to make clinical trials more applicable to real-world populations.

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Authors' contributions

MAB and SOH developed the concept for the study. MAB, SOH and RDP drafted the manuscript. RDP, PSH and DS reviewed and edited the manuscript. All authors read and approved the final draft. MAB and RDP confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

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