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TITLE: CHALLENGES IN THE TREATMENT OF GASTRIC CANCER IN THE OLDER PATIENT

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CHALLENGES IN THE TREATMENT OF GASTRIC CANCER IN THE OLDER PATIENT

ABSTRACT:

Gastric cancer is considered an age-related disease, with the majority of new cases in the UK diagnosed in individuals over the age of 75. At present most guidance related to the management of gastric cancer is based on trials undertaken in the fit, younger patient. Historically the elderly have been underrepresented in clinical trials, which frequently have a restricted inclusion to an upper age limit of 75. The European Society for Medical Oncology (ESMO) recommends use of a geriatric assessment to determine functional age when initiating treatment in elderly patients with gastric cancer, which has been shown to be a better predictor of treatment response than chronological age. The physiological changes that occur with age, including reduced organ function and pharmacokinetic and pharmacodynamic variability, together with impaired functional status, necessitate a more individualised approach to treatment decisions in the older patient to provide them with the same advantages from radical treatment and palliative chemotherapy as younger patients. This review summarises the current evidence extrapolated from trial data on how best to optimise treatment for elderly patients with gastric cancer.

Key words: gastrointestinal cancer, elderly, esophageal, gastric, colorectal

INTRODUCTION:

Age is one of the biggest risk factors for cancer, and most solid tumours are considered age-related diseases. In the UK, more than a third of all new cancer diagnoses each year are in people aged 75 years and over, and the number of older people living with cancer is set to treble from 2010 to 2040 (1). Gastro-oesophageal cancers account for 13.5% of all cancer mortality worldwide (2) and remains a huge contributor to the global burden of cancer (3). It is largely a disease of the older person, with incidence rates in the UK highest in people aged 85-89(4). Current guidelines for the management of gastric cancer are predominantly based on evidence from clinical trials frequently performed in younger patients, however the older cancer patient has been shown to have poorer overall survival (OS) outcomes (5). This review summarises the evidence available for treating the older patient with gastric cancer, to help guide a more individualised approach to their management.

DISEASE BIOLOGY OF OLDER PATIENTS WITH GASTRIC CANCER

Five year overall survival in older adults with gastric cancer has been shown to be significantly lower than their younger counterpart (29.4% versus 32.9%, $p<0.001$), which may be secondary to reduced receipt of standard recommended treatment modalities, but also in part due to possible differences in disease biology (6, 7). There has been shown to be a male predominance in the elderly patient with gastric cancer, compared to a 1:1 gender split in the young (8), with cancers of the distal third of the

stomach and well/moderately differentiated cancer more common than in younger age groups (7, 9, 10). Histologically, elderly gastric cancer patients mainly have an intestinal type of tumour (11) by Lauren's criteria, and more typically papillary adenocarcinoma by the 2010 WHO classification (12). These cancers have frequently been shown to metastasise to the liver, with peritoneal metastases less common (13). Gastric cancers in those of a younger age however, have been suggested to be a more aggressive phenotype, with a higher prevalence of linitis plastica or diffuse type cancer, which have an associated poor prognosis. The differences in disease biology therefore may not play a significant role in accounting for the lower survival seen in the elderly, although the evidence for the effect of disease biology on age and survival have been contradictory(14). It is also important to note that most studies comparing the clinic-pathological characteristics of gastric cancer patients by age have been conducted in Asia.

More generally progressive physiological changes occur with increasing age, including an impairment of organ function and body composition, with possible effects on the pharmacokinetics and pharmacodynamics of anticancer therapies, and a theoretical increased risk of toxicity (15). A large proportion of the elderly present with comorbidities, which pose the challenge of a potential higher risk of complications from surgery or systemic therapies. Therefore, with an increasingly ageing population, a better understanding of how best to treat elderly patients with gastric cancer is required.

IDENTIFYING FRAIL OLDER PATIENTS

Huge variability exists amongst those traditionally defined as old, with chronological age a poor predictor of frailty or fitness. Functional age may be a better prognostic and predictive marker of treatment response, and may improve the treatment decision-making process than reliance on chronological age alone (16)

The Comprehensive Geriatric Assessment (CGA) is an established, validated score of functional status in both the geriatric and oncological settings. It has been shown to identify frail, vulnerable patients at risk of morbidity or mortality (17), taking into account comorbidities, cognitive impairment, functional difficulties and social circumstances, and therefore can help to risk stratify patients when making clinical decisions (18). Studies have shown that use of a geriatric assessment (GA) tool can influence oncological treatment decisions by 40-50% (19, 20), including choice of chemotherapy regime. The CGA has been criticised for the time and resource intensity required to complete it, however shorter frailty tools, including the vulnerable elders survey-13 (VES-13) and geriatric 8 (G8), have been developed to identify patients at risk (21). The vulnerable elders survey (VES-13) is a 13-

item self-administered scoring tool, which considers age, self-rated health, limitations in physical function and functional disabilities, to identify individuals over the age of 65 considered vulnerable. Individuals scoring 3 or more are considered vulnerable, and have been demonstrated to have a 4.2 times increased risk of death or functional decline over a 2 year period compared to those with a score of <3 (22). The eight item G8 questionnaire covers multiple domains of cognition, depression, comorbidities, nutrition and disability, scoring individuals between 0-17, and has been shown to be a simple and useful tool to adequately screen elderly patients who may benefit from a CGA (scores of ≤14) (23). The International Society of Geriatric Oncology (SIGO) have highlighted that geriatric assessments can predict the risk of severe treatment-related complications and overall survival in a number of tumours, although there is no current consensus on which GA tool to implement (24). In the setting of a busy clinical practice, use of brief screening tools such as VES-13 or G8, are recommended to identify vulnerable patients who may benefit from a more comprehensive assessment (25).

A meta-analysis of 6 studies including 1,037 participants found that comorbidity, polypharmacy and activities of daily living (ADL) dependency components to the CGA were predictive factors for postoperative complications in gastrointestinal cancer patients (with cognition, nutritional status, depression and instrumental ADLs showing no conclusive relationship) (26). There have been limited studies evaluating the role of a GA in predicting outcomes specifically in gastro-oesophageal cancers, with most small retrospective cohort studies (27). The largest of these reviewed279 patients, in a single US centre, who had undergone gastrectomy for adenocarcinoma and in whom a GA had been performed within 30 days of surgery. Functional status measured by performance status (PS) greater than zero (OR 2.3, 95% confidence interval (CI) 1.2–4.6), polypharmacy of ≥5 medications (OR 2.4, 95% CI 1.1–5.2) and pain score >0 (OR 3.8, [1.6–8.7]), were found to be predictive of major postoperative morbidity (28). The European Society for Medical Oncology (ESMO) recommends use of a geriatric assessment to determine functional age when initiating treatment in elderly patients with gastric cancer, rather than sole consideration using PS, which may not have much greater ability to predict chemotherapy tolerance than chronological age (29).

THE MANAGEMENT OF THE OLDER PATIENT WITH GASTRIC CANCER IN THE RADICAL SETTING

Surgery

The main stay of potentially curative treatment for locally advanced gastric cancer is surgical resection, although the vast majority of patients still relapse. Very early T1a staged gastric cancers typically undergo endoscopic resection, either by an endoscopic mucosal resection (EMR) or endoscopic

submucosal dissection (ESD) (29). However a more multidisciplinary combined modality approach to treatment is essential to improve prognosis in cancers staged > IB (29). Radical gastrectomies are associated with a high risk of morbidity, and therefore careful selection of appropriately fit candidates is essential. As overall life expectancy continues to rise, opportunities for treatment of elderly patients increase.

Currently an assessment of exercise tolerance, such as cardiopulmonary exercise testing (CPEX), together with review of comorbidities, provides a good indication of perioperative risk and postoperative morbidity. Scoring systems like the American Society of Anaesthesiologists (ASA) physical status score allows stratification of patients prior to a gastrectomy to determine suitability for surgery. The Charlson Comorbidity Index (CCI) is a validated numerical measure of the burden of chronic disease, originally developed to predict prognosis of patients with comorbidities. The age-adjusted CCI (ACCI) has been demonstrated to predict the incidence of postoperative complications following radical gastrectomy for gastric cancer, with a high ACCI score an independent risk factor for the long-term prognosis of gastric cancer patients after surgery (30). This could prove a useful measure in the decision to undergo surgery and to plan the therapeutic strategy by the multidisciplinary team. A number of risk models have been developed, using data from national databases in Japan (n=20,000-33,000 gastric cancer cases), including age, ASA, ADL dependency and haematological/biochemical variables to predict surgical outcomes following gastrectomy and therefore appropriateness for surgery (31, 32), and validating these or similar models in the Western world could be a useful tool to risk stratify these patients.

Sub-group analyses of data from prospective randomised trials conducted in Western countries of surgical resection of gastric cancer have suggested poorer survival in older patients. The MRC study comparing D1 (limited lymph-node dissection) and D2 (extended lymphadenectomy) resections found that 5 year survival in those patients over 60 was significantly worse than those under 60 (hazard ratio (HR) 1.03, 95% CI 1.01-1.04, p=0.0001), with similar results in those aged 60-69 and those over 70 (33). In an Italian trial, irrespective of type of resection (D1 or D2), a similarly increased HR for survival was seen in those patients aged 70 years or above (1.03, 95% CI 1.00-1.05, p=0.033) compared to those ≤69 years (34). 5 year survival in an equivalent Dutch trial was between 38-40% in those over 65 years and 54-55% in those under 65 (35), with significantly higher morbidity and mortality in those over 70 (36). Further analysis of results from the Italian study suggested a disease-specific survival benefit for patients aged 70 years or over who had a D1 gastrectomy (75% versus 51% for D2 resection; p=0·018), corroborated in a further Dutch study (37). Based on evidence from Asian countries and long-term

follow-up of Western randomised trials more generally D2 resection is recommended in medically fit patients at specialist high volume centres (29, 38), although this guidance is without specific consideration of older age. It is worth noting that none of these studies had pre-study criteria to establish differences in outcome with age and therefore unlikely to be powered adequately, however did carry out univariate or multivariate analyses to determine if age was an independent factor.

Certainly since the 1980s extended D2 gastric resection has been standard treatment in Japan (based on tumour location and lymph node drainage) due to significant improvements seen in survival with this technique, in the context of the high prevalence of gastric cancer in Asian countries and therefore increased surgical experience. However, with no significant survival benefit seen with extended gastrectomies specifically in the elderly, a more limited approach may be most appropriate (34, 37)[Table 1].

Most randomised studies have restricted eligibility to those under 80 or 85, and often studies evaluating outcomes from surgical resections in elderly patients with gastric cancer have used 70 years as a cut-off. However a number of retrospective observational studies have been carried out in Asian countries reviewing octogenarians, in whom incidence is high. A retrospective study of 115 Japanese patients undergoing gastrectomies over the age of 80 compared to 333 younger patients found a significant increase in the risk of respiratory complications (6% in the ≥80 years versus 2.1% <80, $p<0.05$) and in hospital death in those over 80 (4.3% versus 0.9%, $p<0.05$), as well as a reduced overall and cancer-specific survival (39). A high incidence of post-operative pneumonia was similarly demonstrated in a study comparing post-operative respiratory outcomes in patients over 85 with those aged 75-84 years, with the former found to have lower baseline vital capacity, and therefore perhaps an indication of lower reserve capacity with age (40), in keeping with other study results (41). However a study of 104 Japanese patients over the age of 80 who underwent curative intent gastrectomy found comparable risk of surgical complications (overall risk 29.9% versus 29.7%, $p=0.518$), compared to those under 80 years, although survival was found to be lower (42). Frequently the hesitation by surgeons to operate on the elderly is due to the perceived higher risk of complications, which with the exception of operative blood loss was found to be no different in this study. The same author group reviewed patients from multiple centres with a higher cut-off of age ≥85 and found gastrectomy with radical lymphadenectomy an effective and acceptable treatment in this cohort (43). However the average frequency of these patients over 85 years treated with surgery was deemed to be low, between 2.2-3.8% in the multiple centres included, therefore the number of cases in this study was small. Overall there has been significant variability in study outcomes and risk

of complications amongst the older age group, particularly in retrospective observational studies. Therefore the individual assessment of patient fitness and pre-operative morbidity is clearly most important prior to consideration of surgery. Most of these studies did not identify functional age as a measure of frailty, with varying cut-offs of chronological age used as a determinant of appropriateness for surgery, which as demonstrated, do not consistently indicate risks of complication or survival benefit in older patients with gastric cancer, even in those patients over 80 years old.

Survival outcomes in randomised data appear similar between laparoscopic versus open gastrectomy (44), however minimally invasive surgery is generally considered to have fewer postoperative complications and morbidity (45), and is a recommended option for certain patients with early stage cancer (29). Randomised data of laparoscopic surgery has predominantly been carried out in a younger age group, and therefore extrapolation of trial results for older patients is more difficult. However a number of smaller Asian observational studies have demonstrated an advantage of minimally invasive surgery with regards to improved recovery time and surgical complication rates (46-49). Therefore it may prove to be a more suitable technique for the older age group who may have a more limited functional reserve and at a higher risk of complications.

Perioperative Chemotherapy

Survival of patients with locally advanced gastric cancer treated with radical surgery remains poor due to a high rate of relapse. A number of randomised trials have evaluated the role of perioperative chemotherapy in addition to surgery in this setting, demonstrating a significant survival benefit (50-53). However concerns remain regarding treatment with chemotherapy in the elderly due to risks of perioperative morbidity from toxicity. To determine the feasibility of treating patients over the age of 65, a predefined exploratory subgroup analysis of patients within the randomised phase II FLOT 65+ trial compared patients treated with perioperative FLOT (5-fluorouracil (5-FU), oxaliplatin and docetaxel) or FLO (without docetaxel)(54). A high level of adherence was found, with 85% of patients receiving all 4 pre-operative cycles of FLOT, and no clinically significant increase in grade 3-4 toxicity postoperatively. Mortality and morbidity rates were comparable to that of the UK MRC Adjuvant Gastric Infusional Chemotherapy (MAGIC) and Fédération Francophone de Cancérologie Digestive (FFCD) trials, which were performed in patients of all ages, however only 75% of patients enrolled underwent surgical resection as planned (although of these only 2/11 (18%) were due to toxicity or death). Neoadjuvant FLO or FLOT chemotherapy is therefore a reasonable option in elderly patients with locally advanced resectable gastroesophageal cancer.

In addition to the effect of perioperative chemotherapy on toxicity, randomised trial evidence does not appear to show a detrimental effect on survival outcomes based on age. The MAGIC trial compared 3 cycles of pre and postoperative ECF (epirubicin, cisplatin, 5-FU) chemotherapy with surgery alone, with no heterogeneity in the hazard ratio (HR) for treatment effect by age, including in those over 70 (50). Similarly the phase III FLOT4 trial (comparing ECF with FLOT chemotherapy perioperatively) showed a consistent relative treatment effect with relation to age, favouring FLOT, with a HR of 0.77 in those under 60 versus HR 0.723 in those patients over 70 (p=0.9402) (53). Age related effects were not reported in the phase III randomised CROSS trial, comparing pre-operative chemoradiotherapy with surgery compared to surgery alone in oesophageal or oesophago-gastric junctional cancers, and eligibility was capped to an upper limit of 75 years of age (55).

Based on this evidence it would be reasonable to treat elderly patients with locally advanced gastric or oesophageal cancer with both perioperative chemotherapy and radical surgery. Although most trials had no upper age limit to eligibility, it is possible that older patients selected to participate were generally fit with a good baseline functional status, and therefore an individualised approach to selecting patients should be adopted to minimise the likelihood of toxicity.

A**djuvant Chemotherapy**

In patients with resected gastric cancer staged IB and above, who have not received preoperative chemotherapy, adjuvant treatment with chemotherapy or postoperative chemoradiotherapy is recommended (29). Regardless of age, morbidity is relatively high following radical surgery, and careful thought ought to be given to those deemed most appropriate for ongoing adjuvant treatment.

The CLASSIC trial, an Asian study of 6 months of adjuvant capecitabine plus oxaliplatin after D2 gastrectomy in 520 patients compared to surgery alone in 515 patients, was overall suggestive of a significant benefit of chemotherapy after surgery. Subgroup analysis by age showed a significant benefit from adjuvant chemotherapy in 5 year overall survival in those 766 patients aged under 65 years (HR 0.67, 95% CI 0.50-0.91), however significance was lost in those 269 patients over 65 years (HR 0.70, 95% CI 0.44-1.12) (56). Disease free survival was improved in both age groups. The feasibility or toxicity of treatment with adjuvant chemotherapy was not assessed in the older age group (57). The Japanese Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GS) similarly showed no advantage of S-1 (oral fluoropyrimidine) in overall or relapse-free survival in patients aged 70-80, although a clear benefit in those patients younger than 60 (58).

Although a meta-analysis of individual patient data from 17 randomised trials (including 3838 patients), comparing adjuvant chemotherapy with surgery alone, suggested an overall benefit in terms of survival (HR 0.82, 95% CI 0.76-0.9), the applicability of these results in Europe remains uncertain, as most studies in this setting were performed in Asia (59). Generally adjuvant chemotherapy is less well tolerated than neoadjuvant chemotherapy, and certainly in the older patient with resectable gastric cancer, perioperative chemotherapy may be a preferential option, or careful consideration given to those who have not received preoperative chemotherapy.

Adjuvant Chemoradiotherapy

In the US, adjuvant chemoradiotherapy after surgery is considered standard treatment, based on results of the South Western Oncology Group (SWOG)-Directed Intergroup Study 0116. This phase III trial of adjuvant chemoradiotherapy after surgery versus observation demonstrated a significant survival benefit, maintained after 10 years of follow-up, with age of included patients ranging from 23 – 87 (60). However no age specific subgroup analysis was performed to determine if benefit persisted in the older age group. Review of more than 8000 US gastric cancer patients has shown that although 61% of resections occur in patients over 65 years only a minority proceeded to adjuvant radiotherapy (61). In Europe adjuvant chemoradiotherapy hasn't yet been adopted due to concerns regarding late toxicity from radiotherapy and insufficiently extensive surgery carried out in a significant proportion of patients within the Intergroup 0116 trial (29). In a subset of higher risk patients, adjuvant chemoradiotherapy may prove beneficial, as demonstrated in the ARTIST trial of radiotherapy with or without cisplatin and capecitabine (62). Although recurrence rates were not reduced after curative resection with radiotherapy, a significant benefit was seen in those with lymph node metastases, however the higher rates of hand-foot syndrome and neutropenia may be relevant when considering treatment in the older age group. The more recent European CRITICS trial of chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer showed no additional benefit of postoperative chemoradiotherapy versus postoperative chemotherapy with regards to overall survival (hazard ratio from stratified analysis 1·01, 95% CI 0.84-1.22). Compliance was poor in both groups, and postoperative toxicity similar, with no clear evidence of heterogeneity of treatment effect by age (63), and results have been replicated in another retrospective study of patients over 65 years (64). It's likely that the predominant survival benefit comes from preoperative treatment, and perhaps should be prioritised over postoperative treatment in older patients, although more age specific prospective studies are required to better understand the adjuvant treatment requirements of the elderly [Table 1].

THE MANAGEMENT OF THE OLDER PATIENT WITH GASTRIC CANCER IN THE METASTATIC SETTING

Palliative chemotherapy

In fit patients with inoperable advanced or metastatic gastric cancer doublet or triplet platinum/fluoropyrimidine chemotherapy combinations are recommended first line (29, 65-70). There have been a few studies specifically evaluating the safety and efficacy of treatment of the elderly patient in this setting [Table 2]. Using data from 3 large randomised trials, one retrospective analysis of 1080 patients with gastro-oesophageal cancer compared those over the age of 70 years (*n*= 257) with younger patients on fluorouracil-based combination regimes (71). Response rates, overall survival and incidence of grade 3 or 4 toxicity were similar between the two age cohorts, suggesting patients over 70 gained a similar benefit to systemic chemotherapy to younger patients. However clinician bias in determining appropriate eligibility for trial candidates may explain these findings. No octogenarians were included in this study and patients over 70 received a lower dose intensity of chemotherapy, as such results suggesting an absence of increased toxicity with age should be interpreted with caution (71).

The FLOT65+ study of triple drug chemotherapy in 143 patients with a median age of 70 showed a lack of benefit of triplet (FLOT) chemotherapy over the doublet (FLO) combination with regards to response rate or progression-free survival (PFS) in patients with metastatic disease or in the subgroup over 70 years, unlike the 65-70 year age group or those with locally advanced disease (72). Despite a similar toxicity profile seen in the over and under 70 groups between both treatments, a significant deterioration in quality of life was demonstrated in patients on FLOT. The phase II miniDOX trial of reduced dose triplet regime, docetaxel, oxaliplatin and capecitabine, in advanced gastric cancer patients considered 'suboptimal' (defined as age ≥70, performance status 2 or weight loss of 10-25%) showed a comparable response rate to the equivalent phase II GATE study in good prognostic groups (73), however the toxicity profile was significant (74).

To determine the optimum number of agents for elderly patients, single agent capecitabine was compared to capecitabine and oxaliplatin (XELOX), in a Korean phase III trial of individuals over 70 with gastric cancer (75). The platinum-based doublet regime was associated with an overall and progression-free survival benefit, with an acceptable toxicity profile seen. The recent UK GO2 phase III trial evaluated the optimum dose of oxaliplatin and capecitabine in 514 frail, elderly patients, with a median age of 76 and deemed unsuitable for full dose triplet chemotherapy(76). They demonstrated that the lowest dose level (60% dose), versus 80% and standard dose, was non-inferior for PFS (lowest dose versus standard HR 1.10, 95% CI 0.90-1.33), with patients experiencing less toxicity and better

overall treatment utility (considered a composite of clinical benefit, tolerability, quality of life, and patient value). This study is the largest randomised trial to date in elderly patients with gastro-oesophageal cancer, demonstrating that a lower dose of treatment does not compromise on disease control or survival, together with better quality of life (77)

Other smaller phase II studies have also specifically looked at fluorouracil with reduced dose oxaliplatin (modified FOLFOX), reduced dose capecitabine with oxaliplatin (CAPOX) and single agent capecitabine versus S1 in elderly patients, suggesting single agent treatment, or modified dose double agent chemotherapy would be tolerable options for first line treatment (78-80).

Trastuzumab in combination with chemotherapy has been demonstrated in the Trastuzumab for Gastric Cancer (ToGA) trial to provide survival benefit in advanced HER2-positive gastro-oesophageal cancer (81). Median overall survival was 13.8 months (95% CI 12-16) in those individuals on trastuzmuab, versus 11.1 months (95% CI 10-13) in those on chemotherapy alone. Subgroup analysis of the effect of age showed an advantage in those on trastuzumab ≥60 years (HR 0.66, 95% CI 0.49-0.88) compared to ≤60 years (HR 0.84, 95% CI 0.62-1.14). However little other evidence is available directly assessing the effects of targeted treatment trastuzumab in the older cancer patient.

In patients over 70 with metastatic disease, it may be most appropriate to consider treatment with two-drug chemotherapy regimens, and to consider dose reduced therapy, in the context of an individual's functional age, for an optimum survival advantage equivalent to younger patients [Figure 1: Proposed treatment algorithm of gastric cancer in the older patient(29)].

Palliative surgery

Currently there is little evidence of a role for palliative resection in gastric cancer. The phase III REGATTA trial of 175 patients with incurable gastric cancer, randomised to palliative chemotherapy alone or gastrectomy with chemotherapy showed no survival advantage of surgery, with median OS 16.6 months (95% CI 13.7-19.8) with chemotherapy versus 14.3 months (95% CI 11.8-16.3) with surgery and chemotherapy (82). Patients included within the trial had an age range of 49-67, and therefore it did not adequately represent older adults. Regardless of this, palliative gastrectomy or metastatectomy should not be considered in patients with advanced gastric cancer, unless further evidence suggests a potential benefit (29)

CLINICAL TRIALS – ARE WE JUSTIFIED IN USING AGE RESTRICTIVE CRITERIA?

A number of studies have demonstrated that the proportion of older patients recruited into clinical trials has been significantly less than expected based on the high prevalence of older patients in the cancer population (83). Chronological age should not be an exclusive reason to underrepresent the elderly in clinical trials, which has been a significant issue in the past (83). It has become more evident that elderly patients may need a modified approach to treatment, based on their fitness and levels of frailty, however this requires evidence-based guidance. There has been an increasing focus on geriatric oncology in the last decade, particularly since the development of The International Society of Geriatric Oncology in 2000. A review of 1084 clinical trials from 2001-2014 demonstrated a tripling of subgroup analyses of elderly patients in phase III trials, but also a significant increase in phase I and II trials dedicated to elderly patients (84). One such study of 1004 patients treated in 30 phase I trials, which have strict inclusion criteria and often test agents which are first-in-man, demonstrated that the toxicity profile was independent of age, and comparable response and survival outcomes were seen in those patients over 65 years and those below (85). An increase in the inclusion of elderly patients within phase I trials is of course an important improvement, however the lack of sufficient representation in dedicated phase III trials limits the generalisability of these results to the general older population (84). Frequently clinical trials have restricted inclusion to an upper age limit of 75, and although this has been less common in more recent trials, concerns about increased risk of toxicity in the elderly continue to limit participation (86). The European Organisation for Research and Treatment of Cancer (EORTC)'s Elderly Task Force was established to improve access to research for older people with cancer, to provide the evidence base for management decisions in this cohort of patients (87). Guidelines have since been published requiring clinical trials to be without an upper age limit for inclusion and a more standardised approach to measuring frailty in clinical trials has been recommended (88). Low grade toxicity may have more clinical significance in older patients, with regards to treatment modification or discontinuation, and clinical trials should reflect this when reporting outcomes (89). More well designed randomised controlled trials, like the GO2 phase III trial, in the older population are required in the setting of gastric cancer to specifically address the age related changes in pharmacokinetics and pharmacodynamics, and variability in functional status, using low-toxicity interventions more relevant and acceptable to this cohort.

FUTURE DIRECTIONS AND CONCLUSION

Older patients continue to be underrepresented in clinical trials, and concerns remain amongst clinicians, particularly in gastric cancer where morbidity is high, regarding inclusion of patients in randomised clinical trials. Individuals currently entered into trials tend to be fitter, with fewer co-

morbidities, and perhaps better prognostic disease, and therefore may not accurately represent the older general population. As demonstrated by the evidence in this review, elderly patients have been shown to have the same advantages from radical treatment and palliative chemotherapy as younger patients, however an individualised approach to treatment decisions is required to improve outcomes in this cohort [Figure 1]. Use of a geriatric assessment is a feasible method of screening for frail patients, to optimise treatment decision based on functional age rather than chronological age.

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Table 1: Radical/ Localised Treatment Approaches in the Older Patient

Study / Year / Journal	Sample Size of Older Patients	Treatment	Outcome (95% CI)	Toxicity
Surgery				
MRC trial phase III Cuschieri et al. 1999 *Br J Cancer* (33)	*N*= 278; 60-69yrs *N*=324; ≥70yrs (*n*=198; <60yrs)	D1 vs D2 gastrectomy	Age HR 1.03 (1.01-1.04) No difference between D1 & D2 5yr survival	Higher postoperative morbidity/ mortality in D2 gastrectomy
Italian trial phase III Degiuli et al. 2014 *BJS* (34)	*N*=80; ≥70 yrs (*n*=187; ≤69)	D1 vs D2 gastrectomy	HR 1.03 (1.00-1.05) *p*=0.033 >70 (vs ≤69yrs) 5yr DSS benefit of D1 (≥70 (75% vs 51%, *p*=0.018)	No difference in morbidity/ mortality rates between D1/D2
Dutch trial phase III Bonenkamp et al. 1999 *NEJM &* Hartgrink 2004 *JCO &* Songun et al 2010 *Lancet* (35, 36, 38)	*N*= 365; >65 yrs (*n*=346; ≤65)	D1 vs D2 gastrectomy	5 yr survival 38-40% ≥65yrs vs 54-55% <65 HR 15yr survival D2 vs D1 >70yrs 0.88 (0.67-1.16)	High postoperative morbidity 43% vs 25% (*p*<0.001) and mortality 10 vs 4% (*p*=0.004) in D2, higher in >70 yrs
Italian retrospective study. Rausei et al. 2016 *EJSO* (37)	*N*=636; >70yrs (*n*=686; <70)	D1 vs D2 gastrectomy	5yr DSS benefit of D2 >70 (66.6% D2 vs 57.7% D1) No survival benefit of D2 in >70yrs	Postoperative morbidity high in >70 (*p*<0.001), particularly after D2
Fujiwara et al. 2017 *World J GI Oncol* (39)	*N*=115; > 80 yrs (*n*=333; <79)	Retrospective gastrectomies ≥80	5yr OS 36.8% >80 vs 68.8% <79 (*p*<0.05)	Postoperative morbidity higher >80 (*p*<0.05)
Yamada et al 2013 *IJS* (40)	*N*=24; ≥85 yrs *N*=152; 75-84	Retrospective gastrectomies	Not assessed	Post op pneumonia high in ≥85 years (*p*=0.0006)
Hsu et al. 2012 *J GI Surg* (41)	*N*=164; >80yrs (*n*=2258; <80yrs)	Retrospective gastrectomies	5yr survival 44.9% >80 vs 56.6% <80yr (*p*=0.001) No difference in cancer-specific death	Post op morbidity higher in >80yrs 18.3% vs <80yrs 12.6% (*p*=0.035)
Takeshita et al. 2013 *World J Surg* (42)	*N*=104; ≥80yrs) (*n*=1,089; <80)	Retrospective gastrectomies	OS lower ≥80yrs vs <80yrs *p*=0.0001	Operative mortality high in ≥80s 1.9% vs 0.7%
Perioperative Treatment				
Phase II FLOT65+ Lorenzen et al 2013 *BJC* (54)	*N*=43; ≥65 yrs	Perioperative FLOT vs FLO	PFS 21m FLOT vs 12m FLO (*p*=0.09) mOS not reached	More G3/4 AEs in FLOT 85.7% vs FLO 27.3%
Phase III MAGIC Trial Cunningham et al. 2006 *NEJM* (50)	*N*=105; ≥70yrs *N*=186; 60-69yrs (*N*=212; <60)	Perioperative ECF & surgery vs surgery alone	No heterogeneity in the HR for treatment effect by age *p*=0.43	No significant increase in G3/4 AE with postoperative chemo after surgery
Phase III FLOT4 Al-Batran et al. 2019 *Lancet* (53)	*N*=172; ≥70yrs *N*=229; 60-69yrs (*N*=315; <60)	Perioperative ECF vs FLOT	Favoured FLOT HR 0.723 >70 HR of 0.77 <70 (*p*=0.9402)	No difference in SAEs FLOT 27% vs 27%
Adjuvant Treatment				

Phase III CLASSIC trial Noh et al. 2014 *Lancet* (56)	*N*=269; ≥65yrs (*n*=766; <65yrs)	Adjuvant CAPOX vs surgery alone	No 5 yr survival benefit in ≥65yrs HR 0.70 (0.44-1.12) DSS benefit in ≥65 HR 0.51 (0.34-0.78)	G3/4 AE in chemo & surgery 56% vs 6% in surgery alone
Phase III ACTS-GS trial. Sakuramoto et al. 2007 *NEJM* (58)	*N*=257; 70-80yrs *N*=408; 60-69yrs (*n*=394; <60yrs)	Adjuvant S-1 vs surgery alone	No survival benefit >60	Most frequent G3/4 AE anorexia 6% with S-1 vs 2.1%
Phase III CRITICS trial Cats et al. 2018 *Lancet* (63)	*N*=172; ≥70yrs *N*=297; 60-69yrs (*n*=319; <60yrs)	Postoperative chemo vs CRT	No heterogeneity in the HR for treatment effect by age ≥70 HR 0.81 OS (0.48-1.35)	Postoperative SAEs 16% both groups

AE – adverse event; D1 – limited gastrectomy; D2 extended gastrectomy; FLOT – 5-fluorouracil, oxaliplatin, docetaxel; FLO – 5-fluorouracil and oxaliplatin; ECF – epirubicin, cisplatin, 5-fluorouracil; S-1 - oral fluoropyrimidine; CAPOX – capecitabine and oxaliplatin; CRT - chemoradiotherapy; OS – overall survival; HR – hazard ratio; DSS – disease specific survival;

Table 2: Summary of trials of the treatment of metastatic/advanced gastric cancer in older patients

Study / Year / Journal	Sample Size of Older Patients	Chemotherapy	Outcome (95% CI)	G3/4 Toxicity
GO2 (phase III) Hall et al. *JCO* (76, 77)	*N* = 514 Elderly +/- frail	Oxaliplatin & Capecitabine Standard dose (A): 80% (B): 60% (C)	Non-inferiority of PFS HR 1.10 (0.90-1.33) of C vs A mOS 7.5m(A) : 6.7m(B) :7.6m(C)	Abstract only
Meta-analysis REAL-2 & ML17032 Okines et al. 2009 *Annals of Onc* (66)	*N* =731; ≥60 years (*N*=582; <60 years)	Capecitabine combination vs 5-FU combination	OS HR 0.83 (0.73-0.94) benefit in ≥60 years	Not reported
Trumper et al. 2006 pooled analysis 3 trials *EJC* (71)	*N*= 257; ≥70 *N*= 823; <70	ECF vs PVI 5-FU vs FAMTX	Effect of age on OS HR 1.068 (0.97-1.271); 1 year OS 35% (both cohorts)	No significant difference ≥70 vs <70
Hwang et al. 2017 (Phase III) *J Geriatr Oncol* (75)	*N*=50; ≥70	Capecitabine vs XELOX	mOS 11.1m XELOX vs 6.3m Capecitabine HR 0.58 (0.30-1.12)	Most frequent G3/4 toxicity fatigue <13%
ToGA (phase III) Bang et al. 2010 *The Lancet (*81)	*N*=305 ≥60 years (*n*=279 <60)	Cisplatin + 5FU or Cape +/- Trastuzumab	<60 yrs HR for OS 0.84 (0.62-1.14) ≥60 yrs HR 0.66 (0.49-0.88)	201 (68%) Trastuzumab 198 (68%) Chemo
FLOT65+ (phase II) Al-Batran et al. 2013 *EJC* (72)	*N* = 143 ≥65 years	FLOT vs FLO	No benefit ORR in metastatic (FLOT 44%, FLO 32.7%, *p*=0.303) & ≥70s (FLOT 32.4%, FLO 31.7%, *p*=1.0)	81.9% FLOT 38.6% FLO
miniDOX (phase II) 2015 Rivera et al. *Cancer Chemother Pharmacol (*74)	*N*=43 ≥70 years PS ECOG = 2 Weight loss 10-25%	Reduced dose DOX	mOS 13.3months 1 year OS 52%	*N*=32 (76.2%)
Catalano et al. (phase II) 2013 *Gastric Cancer* (80)	*N*=43 ≥70 years	Modified FOLFOX	ORR 34.9% (20.6-49.1) mOS 10.5m mPFS 6.8m	*N*=13 (30.2%)
Xiang et al. 2012 (Phase II) *Chemotherapy (79)*	*N*=46 ≥70	Capecitabine & Oxaliplatin	ORR 48.9% mOS 10.0m (8.6-11.4) mTTP 6.0m (3.9-8.1)	Most frequent toxicity leukocytopenia 5 (10.8%)
Lee et al 2008 (phase II) *BJC (78)*	*N*=96 ≥65 years	Capecitabine vs S-1	ORR 26.1% vs 28.9%; mOS 9.5 vs 8.2months; 1year OS 30.2% vs 27.3%; mTTP 4.7m vs 4.2m	Most frequent G3/4 toxicity anaemia (11.4% vs 14.3%)

PVI 5FU - protracted venous infusion of 5-fluorouracil +/- mitomycin C; FAMTX - 5-fluorouracil, doxorubicin + methotrexate; DOX - docetaxel oxaliplatin capecitabine; FLOT - 5-fluorouracil oxaliplatin docetaxel; FLO - 5-fluorouracil oxaliplatin; XELOX - capecitabine and oxaliplatin; FOLFOX – 5-fluorouracil and oxaliplatin; OS – overall survival; PFS – progression free survival; TTP – time to progression; RR – relative risk

Figure 1: Proposed Treatment Algorithm of Gastric Cancer in the Older Patient Based on Current Guidelines (29)