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Factors Affecting Treatment Resilience in Patients With Oesophago-gastric Cancers Undergoing Palliative Chemotherapy: A Rapid Review

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Abstract

Aims: Oesophago-gastric cancers are the fifth most common in the UK. Most patients present with advanced disease and are unsuitable for curative surgery, instead receiving palliative treatment to improve prognosis and symptom burden. Treatment resilience refers to the ability of patients to tolerate their anticancer treatment. Palliative chemotherapy can result in significant toxicity; almost 40% of patients are unable to complete their chemotherapy regimen, with this proportion rising significantly in older and frailer patients. Despite most cases occurring in patients over 70, older and frailer patients are often excluded from clinical trials, resulting in limited evidence to guide which patients are most likely to benefit from palliative chemotherapy. This review therefore aimed to appraise evidence regarding treatment resilience to guide clinicians in identifying the most suitable candidates for palliative chemotherapy.
Materials and Methods: This study was conducted using modified systematic methods. Search results were limited to articles from the last 10 years. Pre-treatment characteristics influencing treatment resilience were assessed, as measured by completion rates, dose reductions and toxicities.
Results: Of the 931 papers returned, 14 reports of 13 studies were included in this review. Factors assessed included age, performance status, frailty, lymphopenia and sarcopenia. Frailty and body composition appear potentially reliable indicators of chemotherapy toxicity. Poor performance status may be a possible indicator of treatment non-completion. There was no clear relationship between treatment resilience and age or lymphopenia.
Conclusion: Although this review was unable to specify patient characteristics to reliably predict patient tolerance of palliative chemotherapy, potential factors were identified. Future research should focus on prospective investigation of these factors to support a precision medicine algorithmic approach by multidisciplinary teams in assessing treatment resilience. Age should not necessarily be a barrier to receiving chemotherapy. Decisions regarding palliative treatment may be guided by these factors as well as patient preference.

Key words: Frailty; oesophago-gastric cancer; palliative chemotherapy; toxicity

Introduction

Oesophago-gastric cancer is the fifth most common in the UK [1]. Approximately a third of patients are diagnosed with stage 4 disease [2] yet 5-year survival for patients with any stage of disease is roughly 25% [3]. Hence, many patients are unsuitable for curative surgery and instead receive palliative treatments, including systemic anticancer therapies (SACT) to improve prognosis and symptom burden. However, palliative chemotherapy can cause serious adverse effects, including vomiting, diarrhoea and infection, with many patients unable to complete their chemotherapy regimen as a result [4].

There is limited research exploring which patient characteristics may influence an individual's ability to tolerate palliative chemotherapy, here referred to as treatment resilience. A more nuanced understanding of treatment resilience would allow clinicians to better identify those patients who are more likely to experience adverse events, require treatment delays or are unable to complete their planned chemotherapy regimen. This would allow more nuanced consideration of available treatment options and promote more personalised treatment decisions.

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OG cancers overwhelmingly affect older people, with almost 50% of new cases occurring in individuals over 75 years. Many patients will experience varying states of frailty which significantly affect their resilience to palliative treatment [5]. Although strongly associated with age, frailty is not exclusive to older people. Frailty is a state of reduced physiological reserve, leading to decreased resilience and increased vulnerability to stressors [6]. Frailty has significant implications in oncology, from predicting prognosis [7] to influencing how well patients can tolerate their treatment [8].

An audit in the UK found only 61.1% of patients with OG cancer who were unsuitable for non-curative surgery and treated with palliative chemotherapy were able to complete their treatment regimen [9]. The most common reason for treatment discontinuation is toxicity.

With the use of advanced techniques like radiomics and genomics, in addition to standard clinical data, multidisciplinary teams (MDTs) face overwhelming amounts of data to incorporate when making treatment decisions. The use of decision support systems (DSSs) has been proposed to aid MDTs, using artificial intelligence to develop predictive models which can support precision treatment choice [10]. However, DSSs are often heavily disease-focused, neglecting information about how well patients can tolerate treatment, substantially limiting their use in frail populations [11,12].

Some scoring systems, like the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH), can offer broad predictions of how likely a patient is to suffer toxicity but were not developed specifically for palliative chemotherapy nor are tumour-specific [13]. Older and frail patients are also a diverse, heterogeneous group, which currently cannot accurately be reflected in traditional scoring algorithms. The current limitations are further exacerbated by the frequent exclusion of older and frailer patients from clinical trials, despite most cases occurring in this population [14–16].

A reliable measure of treatment resilience could align person-centred information with tumour-focused data to support a precision medicine approach to the treatment of these complex patients. Furthermore, an accurate and reproducible method for reliably determining treatment resilience ensures its applicability, even as treatments evolve and DSSs become increasingly complex.

This review aims to identify pretreatment characteristics as markers of treatment resilience which can predict an individual's ability to tolerate palliative chemotherapy. The findings from this review can be used to identify those patients most suitable for palliative chemotherapy and possibly contribute to the construction of a more accurate and reliable treatment resilience assessment tool for this population.

Methods

This rapid review used an adapted methodology developed by the Palliative Care Evidence Review Service (PaCERS), a knowledge transfer partnership that quickly synthesises evidence to inform rapid changes to clinical practice and policy (Table 1) [17]. This service enables clinicians or decision-makers to request reviews to be undertaken to realign research evidence directly with clinical practice and policy needs, aiming to balance efficient knowledge transfer with methodological rigour.

Employing modified systematic review methods, a literature search was conducted across MEDLINE, EMBASE and the Cochrane Library databases. The search strategy was developed by four researchers. Keywords included: oesophageal, gastric, and palliative chemotherapy (see Supplementary Material for full search criteria). The search included articles published between January 2014 and May 2024; to focus on recent chemotherapy regimens and treatment practices.

Eligibility criteria included:

1. Articles available in English and published within 10 years.
2. Participants with oesophageal, gastric or gastro-oesophageal junction cancer.
3. Participants treated with palliative chemotherapy.
4. Data available comparing patients' pretreatment characteristics (physiological, biochemical, clinical etc.) and treatment resilience measures (e.g. toxicity, dose reduction, etc.)

Excluded articles included those that did not compare treatment resilience markers against patients' pretreatment characteristics. Reviews, qualitative studies, grey literature and studies not available in English were also excluded.

Two researchers conducted the initial screening process of titles and abstracts using the Rayyan web-based systematic review management tool [18]. Forward citation searching using Google Scholar was also performed. Full-text screening was performed by one researcher and checked by a second. Reasons for each article excluded were recorded in a spreadsheet.

Details of study design were extracted, including study type, setting, population, chemotherapy regimen, patient characteristics and treatment resilience measures. Tolerability was assessed using three domains: completion rates, dose reductions and toxicities. Data were analysed and quality assessment was performed using CASP checklists before data synthesis and preparing the final report [19,20].

Table 1
PaCERS methodology process

Stage 1	Engaging with requesters and identifying the need for evidence
Stage 2	Defining the review process and refining scope of research aim
Stage 3	Literature search and evidence retrieval
Stage 4	Screening process and study selection
Stage 5	Data extraction
Stage 6	Data analysis and appraisal
Stage 7	Evidence summary and communication

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Results

The literature search returned 931 articles. No additional articles were identified by forward citation searching. Some 462 duplicates were excluded and a further 439 were excluded after screening of titles and abstracts, as outlined in the PRISMA diagram (Figure 1) [21]. Of the 30 full manuscripts evaluated, 14 articles from 13 studies were eligible for analysis.

Twelve articles reported the results of retrospective cohort studies; there was one prospective cohort study and one randomised controlled trial, summarised in Table 2. Seven studies were conducted in Western Europe and the others across East and Southeast Asia. Factors that were assessed against treatment resilience were: age, performance status, frailty, lymphopenia, metastatic site and body composition. No patient factor was identified that was associated with all three domains of treatment resilience.

Quality Assessment

A quality assessment of all 14 articles was conducted reliablity, consistency and relevance were considered in all articles, as guided by the PaCERS format. Full results of the appraisal outcomes are shown in Tables 3–5.

Reliability – 12 studies were retrospective and observational, leading to the usual limitations in determining causality and addressing confounders. Five had poorly representative participants with average or median participant ages below 65. Nonetheless, numerous factors affecting treatment resilience were identified that can be further investigated in future larger-scale prospective trials.

Consistency – Two articles used measures of treatment resilience as the primary endpoint. The remainder used mortality measures as the primary outcome. A wide variety of chemotherapy regimens were studied. No studies consistently and robustly supported the use of a particular patient characteristic in estimating treatment resilience.

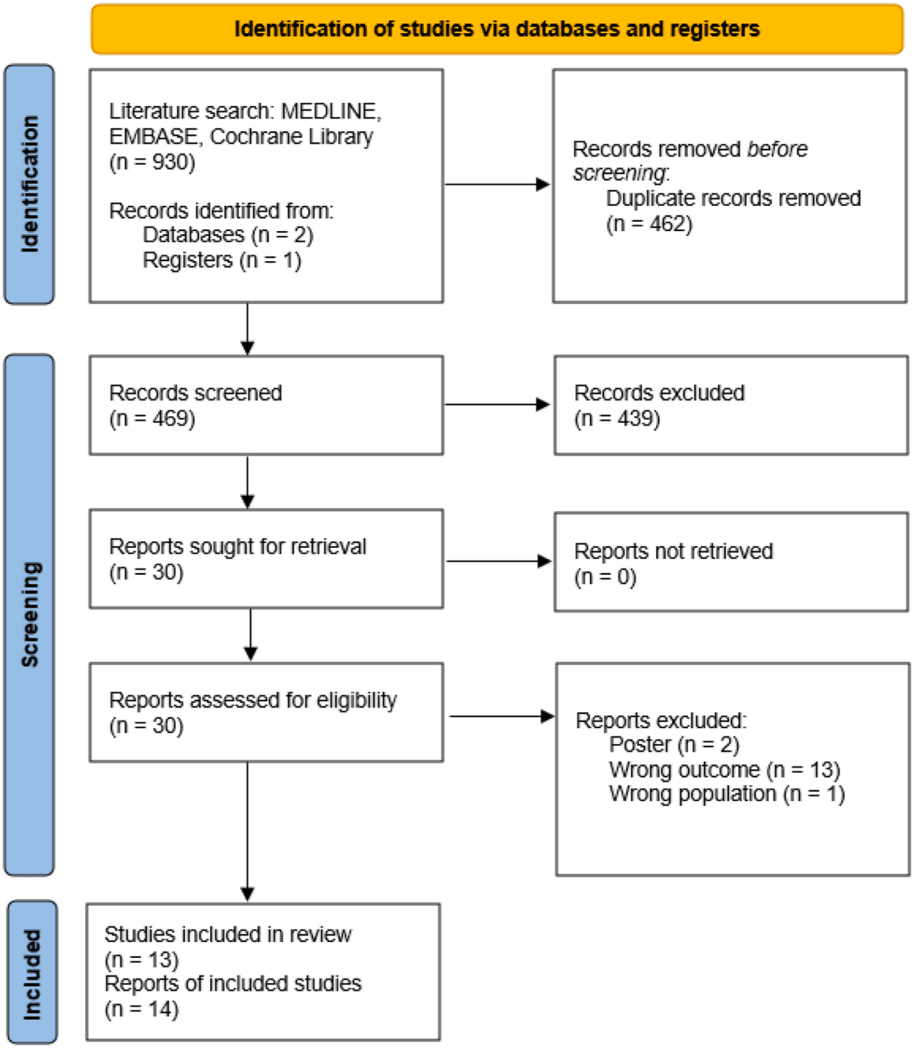

Fig 1. PRISMA flowchart of included studies.

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Table 2
Studies included in this review

Authors	Year	Design	Setting	Sample size	Median age	Cancer type	Regimen	Measure of resilience	Factor affecting treatment resilience
Berger *et al.* [22]	2015	Retrospective cohort	Germany	55	76	OG	Majority doublet oxaliplatin-based	Toxicity leading to treatment modification (grade ≥3), duration of first-line therapy, treatment completion	Age, performance status
Catanese *et al.* [23]	2021	Retrospective cohort	Italy	67	78	Gastro-oesophageal junction and gastric	First-line majority doublet oxaliplatin-based	Toxicity (grade 3–4), treatment completion	Sarcopenia
Dijksterhuis *et al.* [24]	2019	Retrospective cohort	Netherlands	88	63	OG	Oxaliplatin and capecitabine	Toxicity (any grade 3–4, grade 2–4 PSN)	Sarcopenia, body composition
Groene *et al.* [25]	2015	Prospective cohort	England	2313	Not stated	OG	Not recorded	Treatment completion	Age, performance status
Hall *et al.* [26]	2021	RCT	England	514	76	OG	Oxaliplatin and capecitabine	Toxicity (as part of OTU)	Frailty, NLR
Kou *et al.* [27]	2016	Retrospective cohort	China	215	58	Metastatic oesophageal SCC	First-line majority paclitaxel-based	Toxicity (haematologic and non-haematologic, grade 3–4)	Lymphopenia
Liao *et al.* [28]	2022	Retrospective cohort	Taiwan	428	64	Gastro-oesophageal junction and gastric	First-line	Toxicity (haematologic grade 0–4), treatment completion	Age
Matsunaga *et al.* (A) [29]	2021	Retrospective cohort	Japan	67	67.6[a]	Gastric	First-line fluoropyrimidine-, taxane- or irinotecan-based regimes	Toxicity observed during cycles 1–2; haematologic toxicity, FN and GI toxicity	Sarcopenia
Matsunaga *et al.* (B) [30]	2021	Retrospective cohort	Japan	83	65.4[a]	Gastric	5-FU-based	Toxicity (haematologic, febrile neutropenia, gastrointestinal)	Sarcopenia
Matsunaga *et al.* [31]	2023	Retrospective cohort	Japan	63	66.2[a]	Gastric	Second-line, majority paclitaxel-based	Toxicity during first three cycles	Sarcopenia
Matsunaga *et al.* [32]	2024	Retrospective cohort	Japan	102	65.9[a]	Gastric	First-line, 5-FU-based	Toxicity during first three cycles	Sarcopenia
Mohring *et al.* [33]	2022	Retrospective cohort	Germany	57	58	OG	FLOT	Toxicity (haematologic and non-haematologic, grade 3–5), dose reduction, treatment completion	Age
Pearce *et al.* [34]	2022	Retrospective cohort	England	514	76	OG	Oxaliplatin and capecitabine	Toxicity (as part of OTU)	Frailty, performance status
Tan *et al.* [35]	2018	Retrospective cohort	Singapore	470 (but only 274 received PC)	62.5[a]	Gastric	First-line, majority doublet of platinum and nucleoside analogue	Toxicity and chemotherapy-related hospitalisation	Metastatic site

[a] Denotes average age. 5-FU – 5-fluorouracil, FLOT – 5-fluorouracil, leucovorin, oxaliplatin, docetaxel, FN – febrile neutropenia, GI – gastrointestinal, NLR – neutrophil-lymphocyte ratio, OG – oesophago-gastric, OTU – Overall Treatment Utility, PC – palliative chemotherapy, PSN – peripheral sensory neuropathy, RCT – randomised control trial, RT – radiotherapy, SCC – squamous cell carcinoma.

Table 3
Appraisal summary

Authors	Methods	Findings	Strengths and limitations
Berger *et al.* [21]	Retrospectively identified patients aged ≥70 receiving PC for GC. Identified clinical data from EMR.	No differences in toxicity requiring discontinuation between patients ≥75 or ECOG PS ≥ 2	Limited data on toxicity, no comorbidity data collected. High median age reflects 'real-world' patients.
Catanese *et al.* [22]	Identified patients with GOJ and GC who received PC. Body composition calculated using CT and compared against clinicopathological data.	Chemotherapy administration not affected by sarcopenia or fat distribution. Sarcopenia associated with grade 3–4 neutropenia. No correlation between VFA/SFA ratio and toxicity.	Small, heterogeneous sample size. Unclear whether chemotherapy administration refers to treatment delays or discontinuation.
Dijksterhuis *et al.* [23]	Identified patients with OGC who received PC. Calculated SMI and SMD using CT and compared against clinicopathological data.	Lower pretreatment SMD associated with toxicity grade 3–4. Pretreatment sarcopenic obesity associated with PSN grade ≥2.	Sample skewed towards younger, male patients. Not able to assess significance of change in body composition pre- and post-treatment.
Groene *et al.* [24]	Collected data as part of a national multicentre audit on chemotherapy completion and reasons for discontinuation.	53% of patients completed treatment, but <35% completed who were either aged ≥55 or had PS ≤2. Comorbidities, site, pretreatment stage had no effect.	Large sample size but no information on chemotherapy regimen. Large amounts of missing data.
Hall *et al.* [25]	Multicentre, open-label RCT. Participants randomised to 3 groups with varying treatment intensity or BSC.	Baseline frailty, QOL and NLR associated with better OTU.	Robustly conducted multi-centre RCT. No difference in OTU between each treatment arm.
Kou *et al.* [26]	Obtained pretreatment patient characteristics from EMR and compared against haematological and non-haematological toxicity.	Pretreatment lymphopenia is associated with higher rate of grade 3–4 haematological toxicity but not non-haematological toxicity.	Sample skewed towards younger, male participants. 58.1% also received palliative radiotherapy.
Liao *et al.* [27]	Participants split into groups ≤70 and >70. Resilience data compared between age groups.	Incidence of severe haematologic toxicity and discontinuation rates similar between groups.	Groups not weighted equally (e.g. comorbidities, worse PNI etc.) which could be confounding.
Matsunaga *et al.* (A) [28]	Patients with recurrence following curative gastrectomy were split into low and high SMI groups.	The SMI^{Low} group had greater incidences of toxicity.	Only focused on ADRs during first and second treatment cycles. Small sample. No accepted cut-off value for SMI.
Matsunaga *et al.* (B) [29]	Analysed participants specifically who received first-line 5-FU. Split participants into low and high SMI groups.	Incidence of all grade 3–4 toxicities was higher in the SMI^{Low} group. High NLR associated with SMI^{Low}.	Multiple chemotherapy regimens, despite all having 5-FU in common. Includes both patients with unresectable and recurrent GC.
Matsunaga *et al.* [30]	Participants with UGC who received at least 2nd line chemotherapy. Analysed effect of a second SMI ($2^{nd}SMI$) measured before second-line chemotherapy.	Incidence of all grade 3–4 toxicities was higher in the second $2^{nd}SMI^{Low}$ group.	$2^{nd}SMI^{Low}$ group also had initially lower $1^{st}SMI$. No accepted cut-off value for SMI.
Matsunaga *et al.* [31]	Participants with GC treated with first-line 5-FU chemotherapy stratified into CXI^{Low} and CXI^{High}.	Rates of grade 3–4 toxicity higher in CXI^{High} group.	Patients in the CXI^{High} group were more likely to have better PS, greater SMI, lower NLR and greater serum albumin.
Mohring *et al.* [32]	Participants split into groups <65 and ≥65. Differences in toxicity compared against each group.	No difference in toxicity, dose reduction or treatment non-completion between age groups.	Small sample size, retrospective design.

(*continued on next page*)

Table 3 (*continued*)

Authors	Methods	Findings	Strengths and limitations
Pearce *et al.* [33]	Retrospective analysis of GO2 cohort. Analysed correlation between various frailty measures and OTU.	Worse GO2FS, mCFS and G8 scores were associated with poor OTU. Worse PS and CARG were not associated with poor OTU.	Scoring systems were used outside of their validated age group. mCFS was derived retrospectively using an algorithm.
Tan *et al.* [34]	Stratified patients with metastatic gastric cancer into 3 metastatic groups: only peritoneal (P), only distant metastases (D) or both (PD).	Groups P and PD had higher proportions experiencing chemotherapy disruption due to unplanned hospitalisation. Frequency and severity of toxicity were similar across groups.	Groups not weighted equally, especially regarding gender, smoking status and Lauren classification.

5-FU - 5-fluorouracil; BSC - best supportive care; EMR - electronic medical records; G8 - Geriatric-8 score; GC - gastric cancer; GO2FS - GO2 frailty score; GOJ - gastro-oesophageal junction; mCFS - modified clinical frailty score; NLR - neutrophil-lymphocyte ratio; OTU - overall treatment utility; PC - palliative chemotherapy; PNI - prognostic nutrition index; PS - ECOG performance status; PSN - peripheral sensory neuropathy; QOL - quality of life; RCT - randomised controlled trial; SMD - skeletal muscle density; SMI - skeletal muscle index; UGC - unresectable gastric cancer; VFA/SFA - ratio of visceral fat area to subcutaneous fat a.

Relevance – Where recorded, most studies used similar chemotherapy regimens to those used in UK settings, demonstrating a good degree of applicability.

Factors Affecting Treatment Resilience

Age and Performance Status [22,25,28,33]

Three studies examined age in relation to chemotherapy toxicity. Liao *et al.* [28] and Mohring *et al.* [33] stratified participants into two groups using 70 and 65 years, respectively, as a cut-off to define the older group. Berger *et al.* included only participants over 70 [22].

None of these articles observed significant associations between age and toxicity. Dose reductions were also comparable between the <65 and ≥ 65 groups reported by Mohring *et al.*

Age therefore appears to be a poor predictor for the risk of increased chemotherapy toxicity. However, both Berger *et al.* and Mohring *et al.* followed small samples. Liao *et al.* had a considerably larger sample but there were numerous statistically significant differences in the baseline characteristics between groups: though younger participants generally had better performance status and fewer comorbidities, they were more likely to receive combination chemotherapy, putting them at higher risk of toxicities.

Findings by Groene *et al.* differ—they used prospective data collected as part of a national audit, analysing factors associated with chemotherapy completion [25]. While this study had large amounts of missing data, they found that significantly fewer patients over 75 completed chemotherapy compared to those under 55, though the reason for discontinuation was not provided.

While Berger *et al.* found no association between performance status and chemotherapy completion, Groene *et al.* observed that patients with a performance status of ≥ 2 were almost 70% less likely to complete their regimen, though this information was missing in almost a third of participants. Performance status was not recorded by Liao *et al.* or Mohring *et al.* but given that Groene *et al.* collected data on a much larger sample than Berger *et al.* as part of a multicentre national audit, it appears that good performance status may be a more reliable predictor of chemotherapy completion.

These studies demonstrate that there is limited evidence for the utility of age as a predictor of chemotherapy toxicity and the need for dose reduction. As regards to treatment non-completion, poor performance status appears to be a more reliable marker than age, however further evidence is required to verify the reliability of these factors.

Frailty [26,34]

Hall *et al.* conducted a non-inferiority randomised controlled trial looking at the efficacy and tolerability of reduced-intensity chemotherapy in a population rarely eligible to participate in clinical trials (GO2 trial): "older frail, older non-frail and younger frail" patients [26]. They evaluated the efficacy of reduced-intensity chemotherapy using three different doses of an oxaliplatin/capecitabine

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Table 4
Results of CASP appraisal for cohort studies

Authors	Q1	Q2	Q3	Q4	Q5a	Q5b	Q6a	Q6b	Q7	Q8	Q9	Q10	Q11	Q12
Berger *et al.* [23]	Y	Y	Y	CT	N	N	Y	Y	Y	N	Y	Y	Y	CT
Catanese *et al.* [24]	Y	Y	Y	Y	CT	N	Y	Y	Y	Y	Y	CT	Y	CT
Dijksterhuis *et al.* [25]	Y	Y	CT	Y	CT	N	Y	Y	Y	Y	Y	CT	Y	CT
Groene *et al.* [26]	Y	Y	CT	CT	Y	Y	CT	Y	CT	CT	Y	Y	CT	CT
Kou *et al.* [28]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	CT	CT	Y	CT
Liao *et al.* [29]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	CT	Y	CT
Matsunaga *et al.* (A) [30]	Y	Y	Y	Y	CT	N	Y	Y	CT	Y	Y	CT	Y	CT
Matsunaga *et al.* (B) [31]	Y	Y	Y	Y	CT	N	Y	Y	CT	Y	Y	CT	Y	CT
Matsunaga *et al.* [32]	Y	Y	Y	Y	CT	N	Y	Y	CT	Y	Y	CT	Y	CT
Matsunaga *et al.* [33]	Y	Y	Y	Y	CT	N	Y	Y	CT	Y	Y	CT	Y	CT
Mohring *et al.* [34]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	CT
Pearce *et al.* [35]	Y	Y	CT	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CT
Tan *et al.* [36]	Y	Y	Y	Y	CT	N	Y	Y	Y	Y	CT	CT	CT	CT

Key: Y - Yes, N - No, CT - Can't tell.
Q1. Did the study address a clearly focused issue?.
Q2. Was the cohort recruited in an acceptable way?.
Q3. Was the exposure accurately measured to minimise bias?.
Q4. Was the outcome accurately measured to minimise bias?.
Q5a. Have the authors identified all important confounding factors?.
Q5b. Have they taken this into account during design and analysis?.
Q6a. Was the follow up of participants complete enough?.
Q6b. Was the follow up of subjects long enough?.
Q7. What are the results of the study?.
Q8. How precise are the results?.
Q9. Do you believe the results?.
Q10. Can the results be applied to the local population?.
Q11. Do the results of this study fit with other available evidence?.
Q12. What are the implications of this study for practice?.

regimen. Any patient with OG cancer was eligible – regardless of age or performance status – if deemed unsuitable for the full-dose standard palliative regimen (epirubicin/oxaliplatin/capecitabine). They used a previously developed novel endpoint: Overall Treatment Utility (OTU), a composite score using CT imaging and clinical assessment of progression status, toxicity, quality of life and patient acceptability of treatment [36]. They observed that a higher dose did not improve progression-free survival and that no group (e.g. participants with better performance status) benefited from higher-dose treatment. They found several predictors for OTU: baseline frailty, the EQ-5D Visual Analogue Scale and neutrophil-lymphocyte ratio (NLR). Frailty was assessed using various geriatric assessment (GA) screening tools and incorporated into the GO2 frailty score (GO2FS).

Table 5
Results of CASP appraisal for randomised controlled studies

Authors	Q1	Q2	Q3	Q4a	Q4b	Q4c	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Hall [27]	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y

Key: Y - Yes, N - No, CT - Can't tell.
Q1. Did the study address a clearly formulated research question?.
Q2. Was the assignment of participants to interventions randomised?.
Q3. Were all participants who entered the study accounted for at its conclusion?.
Q4a. Were the participants blinded?.
Q4b. Were the investigators blinded?.
Q4c.Were the people analysing outcomes blinded?.
Q5. Were the groups similar at the start of the study?.
Q6. Apart from the experimental intervention, did each study receive the same level of care?.
Q7. Were the effects of intervention reported comprehensively?.
Q8. Was the precision of the estimate of the intervention or treatment effect reported?.
Q9. Do the benefits of the experimental intervention outweigh the harms and costs?.
Q10. Can the results be applied to your local population/in your context?.
Q11. Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?.

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Pearce *et al.* conducted a retrospective analysis of the GO2 cohort and compared the correlation between various frailty scores and OTU [34]. Frailty measures assessed included ECOG performance status, GO2FS, modified Clinical Frailty Scale (mCFS), Geriatric-8 (G8) and the Cancer and Aging Research Group (CARG) toxicity score. Worse GO2FS, mCFS and G8 scores were all significantly associated with a poor OTU compared to a good or intermediate outcome. However, performance status and CARG were not significantly associated with poor OTU, progression or death. These findings demonstrate some of the uncertainty surrounding the reliability of performance status: despite some studies in this review noting its ability as a measure of treatment resilience, it has been criticised for poor sensitivity and being a subjective measure [37]. Importantly, much of the data used by Pearce *et al.* were derived retrospectively, especially for the mCFS which was calculated using an algorithm and data from patient questionnaires, limiting its reliability.

de la Fouchardiere *et al.* outlined important concerns in the use of OTU as an outcome measure, demonstrating significant differences in OTU between the different dose groups, indicating minimal sensitivity [5]. Furthermore, the GA performed in the GO2 trial was strictly observational, yet GA-led interventions have been shown to substantially reduce the risk of chemotherapy toxicity [38].

The GO2 trial represents a landmark shift in the way clinical trials are conducted, with impressively broad inclusion criteria. They also attempted to assess the treatment value and acceptability to participants as part of OTU, a crucial step in moving towards value-based healthcare, which aims to minimise unnecessary or harmful healthcare interventions [39]. Above all, it showed the considerable utility of using geriatric screening tools in predicting treatment resilience and that their use should not be limited exclusively to older patients. They demonstrated that frailty is a key confounder to treatment outcomes in oncology and made a compelling argument for the routine inclusion of GA not only in clinical trials but also in wider clinical practice.

Metastatic Site [35]

Tan *et al.* analysed the effect of metastatic site on treatment resilience. Their sample was divided into three groups depending on the site of metastasis at initial presentation: solely peritoneal metastasis (P), solely distant metastasis (D) or both peritoneal and distant metastases (PD) [35]. There was no significant difference in chemotherapy toxicity of any grade across each group. Likewise, the average number of unplanned hospital admissions secondary to chemotherapy toxicity was broadly similar.

Other studies have generally focused on the number rather than the site of metastasis, and this may be a promising indicator of chemotherapy resilience [40]. However, this article does not provide convincing evidence that the site of metastasis is a reliable indicator in this population.

Lymphopenia [27]

Kou *et al.* investigated pretreatment lymphopenia as a marker of chemotherapy tolerance [27]. They divided the sample into two groups depending on the presence or absence of pretreatment lymphopenia (lymphocyte count $<1 \times 10^9$/L), investigating its relationship with chemotherapy efficacy and toxicity. They found pretreatment lymphopenia was significantly associated with grade 3–4 haematological toxicity, but not non-haematological toxicity.

However, pretreatment lymphopenia was associated with liver and bone metastases, leukopenia, neutropenia and raised NLR which are potential confounders. Their cohort was also poorly representative, being skewed heavily towards younger, male participants. Inflammatory markers show promise as measures of treatment resilience as shown here, by Hall *et al.* [26] and further supported by the fact that they are routinely collected and easily interpreted but require further validation.

Body Composition, Sarcopenia and Cachexia [23,24,29–32]

Six articles evaluated the association between body composition and treatment resilience. Sarcopenia is primarily a geriatric syndrome and is a broad term, encompassing age-related muscle mass but also functional consequences, e.g. gait speed [41]. Cachexia, a principally metabolic and inflammatory syndrome, is also characterised by loss of muscle mass but due to an underlying disease process, e.g. malignancy or chronic illness [42].

Each of the studies obtained pretreatment CT scans enabling them to determine different body composition measurements at the level of the third lumbar vertebra, including skeletal muscle density (SMD) and skeletal muscle mass index (SMI).

Dijksterhuis *et al.* [25] found that both pretreatment SMD and sarcopenic obesity – the presence of reduced muscle mass in the context of obesity – were associated with chemotherapy toxicity. Low SMD was associated with a higher incidence of toxicity grade 3–4, while sarcopenic obesity was significantly associated with peripheral sensory neuropathy grade $\geq$2.

Catanese *et al.* investigated the impact of sarcopenia and fat distribution on toxicity during first-line palliative chemotherapy [23]. They found sarcopenia was associated with the development of grade 3–4 neutropenia.

Three articles by Matsunaga *et al.* examined the impact of skeletal muscle mass on the development of chemotherapy toxicity in gastric cancer [29–31]. These analysed skeletal muscle mass index (SMI) by stratifying participants into two groups: SMI^{Low} and SMI^{High}. In each of these, the SMI^{Low} group showed greater incidences of all chemotherapy toxicities. There was no consensus between specific toxicities being more likely to occur in this group across the different studies.

Studies used different methods to calculate cut-off values for SMI. Dijksterhuis *et al.* and Catanese *et al.* used values obtained from another study, while Matsunaga *et al.* calculated specific values for each sample. While the external value has not been validated in specific OG cancer populations, the different values calculated by Matsunaga *et al.* were also not validated and are different between each article, limiting their comparison.

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A fourth article by Matsunaga *et al.* evaluated the cachexia index (CXI), a composite score using the skeletal muscle index, serum albumin level and neutrophil-lymphocyte ratio [32]. They again divided the sample into CXI^{High} and CXI^{Low} groups (where CXI^{High} had better scores and less cachexia). While the groups were generally well balanced, the CXI^{High} were more likely to have a PS of 0, recurrence and receive three or more lines of chemotherapy. The CXI^{Low} group had a higher total rate of grade 3–4 side effects. The only specific toxicity that was more common in this group was febrile neutropenia.

This dataset demonstrates that sarcopenia may be a promising indicator of chemotherapy toxicity but a validated cut-off value for SMI is required. Inflammatory markers may also be a confounding factor as one article by Matsunaga *et al.* found that a raised NLR was associated with low SMI [30]. As such, the cachexia index may be a more reliable indicator of treatment resilience, incorporating both inflammatory markers and the SMI.

Discussion

This review identified frailty and body composition as potentially reliable indicators of treatment resilience, but age and metastatic site appear less reliable. Performance status and lymphopenia may also be associated with treatment resilience but require further validation in larger, more representative cohorts.

While the relationship between age and treatment resilience appears inconclusive, this review has highlighted the utility of GA as a generally more objective and representative measure than performance status. It underscores the need for frailty assessment across age groups to ensure its applicability for younger patients.

Existing chemotherapy toxicity prediction tools – e.g. CRASH [13] and CARG scores [8] – also support the utility of GA but are not specific to OG cancers. These have been validated across multiple cohorts and incorporate the toxicity attributed to the chemotherapy regimen. However, these have not been validated in participant groups treated solely with palliative chemotherapy. Both were also developed in specifically older populations, restricting their validity in younger patients with late-stage cancer who may also have cumulative multisystem deficits that result in a cancer frailty syndrome that is not age-dependent.

This review has also underlined the importance of pragmatic clinical trials. Traditional RCTs are highly controlled environments which fail to reflect the diversity and heterogeneity of patient populations in real-world practice. Pragmatic trials are beginning to reflect the limited utility of age [43], instead opting for functional assessments in determining patient eligibility for clinical trials [44].

Importantly, none of the studies included participants treated with immune checkpoint inhibitors (ICIs), which are increasingly used as a stand-alone treatment or in combination with chemotherapy for OG cancers, especially in the palliative context [45,46]. While ICIs are associated with a lower incidence of toxicities compared to chemotherapy, and can offer more favourable outcomes, their safety profiles are broadly similar [47–49]. However, their combination can lead to synergistic toxicities and novel immune-related adverse events [50].

More data are required to better understand how frailty and functional status affects treatment tolerance for patients treated with ICIs compared to traditional chemotherapy, and as combined therapies. Nonetheless, the risk of significant ADRs with ICI therapy in certain patient subgroups echoes findings in this article, which proposes a cumulative multi-deficit model or cancer frailty in assessing physiological resilience across the range of treatments. It is possible that many of the patient factors discussed here will be similarly relevant for patients treated with ICIs and future novel therapies.

Additionally, we recognise the challenges posed by the lack of consensus on the optimal number of cycles of palliative chemotherapy in this population. Standardization is hampered by individual patient contexts and emergent treatment options. Clear clinical documentation *a priori* of the proposed number of cycles would benefit assessment of treatment tolerance in both clinical and research settings.

Future research should focus on the development and validation of a similar aggregate scoring tool specifically for patients undergoing palliative SACT constructed using similar pretreatment characteristics identified here and integrating specific data on the toxicity of individual and combination chemotherapy regimens. While incorporating both disease-specific aspects of cancer pathophysiology and factors affecting treatment resilience, it could also promote a more nuanced shared decision-making process. Patients who are older and frailer should be actively enrolled in future clinical trials to improve evidence around the safety, efficacy and tolerability of palliative chemotherapy and ensure this is applicable to typical oesophago-gastric cancer patients.

Limitations

A limitation in this review was the heterogeneity of evidence. While some studies reported the specific chemotherapy regimen used, these were often not consistent or not even recorded, compounded by the fact that some studies included participants also treated with palliative radiotherapy and/or surgery. This was also a rapid review, adopting a modified systematic review method; hence, some relevant articles may have been excluded.

Conclusion

This review has identified that performance status, frailty, inflammatory markers and sarcopenia are all factors that might predict the ability of patients with oesophago-

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gastric cancer to tolerate palliative chemotherapy. Age as a factor requires further investigation and thus should not necessarily be a barrier to receiving chemotherapy; physiological frailty should be considered across all age groups.

While no single factor identified here appeared definitive, future trials should focus on their investigation and validation in larger prospective cohorts. Results from these can guide the development of a treatment resilience score for patients receiving palliative chemotherapy which can be incorporated into routine clinical assessments and promote more personalised decision-making.

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Author Contribution

1. guarantor of integrity of the entire study: A. Byrne
2. study concepts and design; manuscript editing: K. Datta, D. Holland-Hart, A. Byrne
3. literature research: K. Datta
4. clinical studies; statistical analysis: N/A
5. experimental studies/data analysis: K. Datta
6. manuscript preparation: K. Datta, D. Holland-Hart

All authors agreed to the final draft of the article.

Conflict of interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Daniella Holland-Hart reports financial support was provided by Marie Curie. Daniella Holland-Hart reports financial support was provided by Wales Cancer Research Centre. Anthony Byrne reports financial support was provided by Marie Curie. Daniella Holland-Hart reports a relationship with Marie Curie that includes: funding grants. Anthony Byrne reports a relationship with Marie Curie that includes: funding grants. Daniella Holland-Hart reports a relationship with Wales Cancer Research Centre that includes: funding grants. There are no relationships or activities to declare. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2025.103963.

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