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Reconsidering the role of radiotherapy for inoperable gastric cancer - A systematic review of gastric radiotherapy given with definitive and palliative intent

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	There is a body of mainly non-randomised, observational evidence showing high-dose RT is efficacious, safe and may maintain QOL for patients with IGC. A change in practice will require a prospective randomised controlled trial, which should explore the role of prophylactic, high-BED RT combined with optimal systemic therapy using modern IMRT techniques and RT quality assurance.

Essential Title Page

Reconsidering the role of radiotherapy for inoperable gastric cancer - A systematic review of gastric radiotherapy given with definitive and palliative intent

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Declaration of Interest Statement

The authors declare no conflict of interest

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HIGHLIGHTS

- Patients with inoperable gastric cancer have limited treatment options
- Low dose radiotherapy (RT) is used reactively to manage symptoms such as bleeding
- This review shows higher doses of RT are effective and safe with low toxicity rates
- High-dose RT, along with chemotherapy, may improve survival and quality of life
- Randomised trials evaluating high-dose RT for inoperable gastric cancer are needed

Reconsidering the role of radiotherapy for inoperable gastric cancer - A systematic review of gastric radiotherapy given with definitive and palliative intent

ABSTRACT

Introduction: The role of radiotherapy (RT) for inoperable gastric cancer (IGC) is commonly low-dose, given reactively for symptoms (e.g. bleeding), in contrast to the oesophagus, where high quality evidence exists for higher doses of RT. This systematic review aims to evaluate the use of, and evidence for, definitive and high-dose palliative RT for IGC and whether a change in practice is warranted.

Materials/Methods: Following registration with PROSPERO (CRD42022297080), MEDLINE, EMBASE and The Cochrane Library were searched in accordance with PRISMA standards for studies evaluating definitive (non-metastatic disease, BED10 >45Gy) or high-dose palliative RT (for symptom/local control, minimum BED10 >30Gy). A manual search of meeting proceedings and clinical trial registries was also performed.

Results: 31 studies were selected for analysis. 10 definitive studies totalling n=354 patients receiving RT with 45-50.4Gy/25-28#, showed median overall survival ranging between 11-26.4 months, clinical complete response range 12-45%, G3 gastrointestinal toxicity 0-31% (range) and RT completion rates ranging from 81-100%. 21 high-dose palliative studies (n=955) mostly evaluated haemostatic control and reported 38 different RT regimens (most commonly 30Gy/10#). Bleeding response rate (RR) was 59.6-90%, pain RR 45.5-100%, obstruction RR 52.9-100%, G3 gastrointestinal toxicity <5% and RT completion 68-100%. An additional American National Cancer Database review >4700 non metastatic IGC patients which combined both definitive and palliative doses found significant benefit to RT in addition to chemotherapy. Evidence regarding a dose-response relationship is conflicting, limited by retrospective data. Two studies report high quality of life (QOL) scores following gastric RT.

Conclusion: There is a body of mainly non-randomised, observational evidence showing high-dose RT is efficacious, safe and may maintain QOL for patients with IGC. A change in practice will require a prospective randomised controlled trial, which should explore the role of prophylactic, high-BED RT combined with optimal systemic therapy using modern IMRT techniques and RT quality assurance.

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INTRODUCTION

Gastric cancer (GC) is the 5th most common malignancy worldwide. In the UK, it accounts for 6,500 new cases and 4,200 deaths annually, with adenocarcinoma comprising 95% [1]. Surgery is the only curative treatment. For patients with stage Ib-IVa operable disease suitable for surgery, multi-modal therapy is recommended, consisting of peri-operative chemotherapy (CT) and radical gastrectomy with modified D2 lymphadenectomy [2].

However, in the UK only 65.8%, 56.6% and 52.1% of patients with stage I, II and III disease respectively will undergo surgery, often due to co-morbidity, locally advanced disease, or patient choice [3]. For those deemed inoperable, there are no alternative curative treatments. The current standard of care (SOC) is palliative intent systemic anti-cancer therapy (SACT) and prognosis is poor - around 11 months [4]. Additionally, patients face potentially distressing symptoms from the primary tumour including nausea and vomiting, bleeding, or obstructive symptoms, markedly impairing quality of life (QOL), highlighting the urgent need to develop new treatment strategies.

Current role of Radiotherapy for gastric cancer in the UK

A recent survey of UK oesophago-gastric clinical oncologists' use of gastric radiotherapy (RT) showed 93% had prescribed palliative intent RT (dose <40Gy) over the preceding 3 years, compared to only 16.7% definitive (≥40Gy). The main reasons for this difference were; rarely indicated within standard UK practice (88.4%), lack of UK protocol (53.5%), and toxicity concerns (44.2%) [5].

Other indications for RT include post-operatively, where following a number of phase III studies, chemoradiotherapy (CRT) is offered to selected high-risk patients [6-9]. Pre-operatively, whilst the recently published phase III TOPGEAR trial did not demonstrate a progression free (PFS) or overall survival (OS) benefit of pre-operative CRT compared to peri-operative CT alone, it did find that CRT doubled the pathological complete response (pCR) rate (17% CRT vs 8% CT) and increased major pathological response (50% CRT vs 29% CT), with acceptable rates of G3 toxicity, demonstrating the safety and efficacy of gastric RT [10]. However, at present, peri-operative CT remains standard of care (SOC) in the UK for resectable patients [11-15].

In the palliative setting, RT is most often a single fraction (#) of 6-8Gy, or 20Gy/5#, usually offered reactively for symptoms such as bleeding [16]. In contrast, higher doses are used in the distal oesophagus or gastro-oesophageal junction (GOJ) where CRT is established in the neo-adjuvant and definitive settings [17-20].

In light of the growing evidence supporting the safety and efficacy of gastric RT, this systematic review (SR) aimed to address whether it is time to reconsider the role of RT for IGC. We present the current evidence for the efficacy, tolerability and impact on QOL of gastric RT in the definitive and high-dose palliative settings, as well as review RT technique, dose/fractionation, and dose/response relationship.

MATERIAL AND METHODS

The review was registered with PROSPERO (CRD42022297080, registered 15.2.2022) and performed in accordance with PRISMA standards (Preferred Reporting Items for Systematic Reviews and MetaAnalyses)[21].

Search Strategy

Electronic databases MEDLINE (Ovid), EMBASE (OVID) and The Cochrane Library were searched using a combination of text terms and relevant controlled vocabulary described in Supplementary Materials, Appendix A (initial search date 10.3.2022, updated 27.3.2023). Duplicate results were identified using

EndNote and manually excluded. Forward citation tracking for a sample of included studies was conducted with Web of Science (Clarivate). Meeting proceedings from ASCO, ASTRO and ESTRO for the 2 years preceding the search date were manually searched. A search of clinical trial registries was also performed (clinicaltrials.gov, the WHO International Clinical Trials Registry Platform and the ISRCTN registry).

Eligibility Criteria

Clinical studies published in English, after 1.1.1998, of any design, reporting relevant outcomes following external beam RT to the primary tumour in patients with gastric or Siewert III GOJ adenocarcinoma were included. Definitive studies were defined as those delivering ≥45Gy BED10 (BED10 = biologically effective dose, $\alpha/\beta=10$) to non-metastatic disease, and high-dose palliative those with primary aim of local/symptom control, including studies ≥30Gy BED10. Palliative papers solely including doses <30Gy BED10 were not included as they have been analysed by previous SRs. Following pilot screening of 3000 titles, inclusion/exclusion criteria were further refined (see original and final eligibility criteria, Appendix B).

Selection process

Citations were uploaded to Covidence SR online software, all titles and abstracts screened by the principal reviewer (AC), and any meeting eligibility criteria were retained for full text review. Any of uncertain eligibility, plus a random sample of 10% of both included and excluded titles, underwent independent second review (SG), and any discrepancy discussed between reviewers to reach a conclusion. Risk of bias assessment was performed (AC) using the most appropriate Joanna Briggs Institute checklist for the study type (Appendix C)[22, 23].

Data collection

Basic data extracted included demographics, study design and patient characteristics. RT data included dose/fractionation, median BED10, modality (e.g. 3D-CRT, IMRT), definition of gross, clinical and planning target volumes (GTV, CTV and PTV) and any image guidance (IGRT). Survival, toxicity and QOL data were also collected (Appendix D). Data were collated in an Excel spreadsheet independently by two reviewers (AC,FW).

RESULTS

The PRISMA flow diagram (Figure 1) summarises the screening process [24]. 12,436 records were screened, 2509 assessed for eligibility, following which 11 definitive studies and 21 high-dose palliative studies were selected for final analysis.

No previously published SRs of definitive CRT for IGC were identified during our search. In the palliative setting, this review encompasses an additional 10 papers to those evaluated by Viani *et al*. in their 2020 meta-analysis [25].

Definitive setting (i.e. ≥45Gy BED10, non-metastatic disease)

Ten studies were included representing 549 patients, 354 undergoing RT (Table 1)[26-35]. Nine are non-randomised. In addition, a retrospective review of RT for non-metastatic, stage I-III IGC of the American National Cancer Database (NCDB) database was included, but results not analysed with the other definitive studies due to inclusion of both definitive and palliative dose fractionations [36].

Dose/fractionation was similar across studies, with 9/10 delivering between 45Gy-50.4Gy in 25-28# (BED10 = 52.1-59.4Gy). Two studies reported a boost of 5.4Gy/3# to a GTV boost volume (after 45Gy/25# to PTV)[26, 28]. Definition of RT volumes, where available, varied across the 7 studies, with 5 incorporating an elective lymph node volume (ELNI) (Appendix E). For planning, 6 used 3D-CRT and 4 used IMRT. Only one study reported IGRT technique, stipulating deep inspiration breath hold and stomach filling protocol, with twice weekly CBCT [26]. SACT regimens varied, but all included 5FU, taxane or platinum (single agent or combination). RT completion rates ranged from 81-100%.

Median OS (mOS) ranged from 11-26.4 months (Table 2). Clinical complete response (cCR) rate ranged between 12-45%, with six studies reporting cCR>20%, and overall response rate (RR) between 37.5 – 83%.

A significant relationship between CR and OS was reported by four studies. Liu *et al.* reported a longer OS for patients achieving cCR than those who did not (median not reached vs 17.7 months p=0.004)[26]. Similarly, Suzuki *et al*. reported mOS of 30.7 months following cCR vs 10.6 months if <cCR, with cCR the only statistically significant variable on multivariate analysis, also reported by two further studies [27, 33, 35].

Two studies compared CT alone to CRT. Dong *et al*. reported 1 yr OS of 21.4% and median survival time of 7.5 months following CT alone vs 32.3% and 11 months for CRT (p=0.038)[32]. Mizrak Kaya *et al*. also compared CT alone to CRT – mOS was 2.2 years for CRT and 1.6 years for those who did not receive RT (HR 0.62), with multivariate analysis confirming that inclusion of RT improved OS (p=0.05)[33].

Most common G3/4 toxicities were nausea/vomiting (2.7-31%), neutropenia (0-14.3%), and lymphopenia (24.5% - 92.3%). Two papers reported late toxicity; Liu *et al.* n=2 (n=1 duodenal ulcer, n=1 gastric ulcer) and Leong *et al.* n=1 (G3 enteritis)[26, 31]. A total of 3 deaths during CRT were recorded across all studies (0.5% of 549 patients) though none were directly attributed to treatment [27, 35].

Quality of life (QOL) was reported by only one study (n=16 patients), which reported high global scores post treatment (median 91.7), measured using the validated EORTC QLQ-C30 questionnaire [26].

The NCDB review of n=4,795 stage I-III, un-resected, non-metastatic GC patients who did not undergo surgery, compared CT alone (n=3,316, 69.2%) vs CRT (n=1,479 30.8%), median dose 45Gy [36]. They reported mOS of 11.3 months and 2yr OS 21.5% with CT alone vs 12.3 months and 28.3% for CRT (p<0.001). mOS for those who received <45Gy was 9 months vs 14.3 months >45Gy (p<0.001). CRT was a significant predictor for improved OS on multivariate analysis. Notably, the inclusion of a wide range of RT regimens, including palliative doses, may have diluted the true benefit of RT in this series.

<u>High-dose Palliative setting</u> (i.e. primary aim of local/symptom control, ≥30Gy BED10)

Twenty-one studies (n=955) are summarised in Table 3 [37-57]. All are non-randomised - 18 are retrospective reviews, 17 are single-centre, and only two evaluate RT in a Western population. Study populations represented a high proportion of metastatic disease (18 studies report >50% M1 disease) and highly symptomatic population at baseline. Bleeding was an index symptom for 100% of patients in >70% of studies, with median baseline Hb 5.1-9.0 g/dL.

Haemostasis was the primary outcome measure in 16/21 studies, though definition of bleeding control varied widely (Appendix F). Survival outcomes and toxicity were frequently reported secondary outcomes, but local control (LC) rates were not commonly measured.

38 different dose/fractionations were reported, most commonly 30Gy/10# (n=12), 20Gy/5# (n=8), or 8Gy/1# (n=4), with >80% studies describing least 3 different dose/fractionation regimens. Most studies reported median dose BED10 ≥39Gy (87.5% of n=14/16 studies providing this data).

There was large variation in RT volumes, with 2 studies treating whole stomach, 5 partial stomach, and 8 allowing either approach (Appendix G). Only two treated regional lymph nodes. Anterior-posterior opposing fields (APPA, n=8) or 3DCRT (n=8) were most commonly used, with only one study allowing IMRT.

Assessment of respiratory motion during RT planning is becoming increasingly common; reported by n=3/11 (27%) pre-2020, compared to n=5/10 (50%) post.

RT completion rates were high, ranging from 68-100%, though 9/10 studies report completion rates >80%.

Symptom response rates are summarised in Table 4. Overall bleeding response rates (RR) ranged from 59.6 – 95%, with 11/16 studies reporting RR >70%. Re-bleeding rates ranged from 11-60%. Several studies (n=8) report statistically significant reductions in BT requirement post RT [40, 42-45, 47, 54, 55]. Five papers reported increase in Hb post-RT (range 1.8 – 3.4 g/dl)[43-46, 55] .

mOS from date of RT ranged from 2.7 – 5.2 months (excluding the Mizrak Kaya study, which quoted mOS from diagnosis of 41.5 months[51]). Median re-bleeding free survival ranged from 1.5 -11.9 months. Improvement in other symptoms, such as pain or obstruction ranged from 45.5-100% and 52.9-100% respectively [37, 38, 49, 52, 57].

Several studies reported improved outcomes when RT was combined with CT. Asakura *et al*. reported a 3-month cumulative incidence of re-bleeding of 60% with RT alone vs 17.5% with CRT [54]. Three studies found the addition of CT to RT a statistically significant prognostic factor on multivariate analysis, of which Yagi *et al*. report mOS of 6.5 months for RT + CT vs 1.6 months for RT alone [41, 43, 45]. Kim *et al.* reported a trend in improvement in mOS with addition of SACT to RT, 6.7 months CRT vs 2.4 months RT alone, with CT not increasing toxicity significantly (G3 = 15% RT alone vs 21% CRT)[57].

Five studies reported significant association between bleeding control and survival, of which Tey *et al*. reported the mOS of RT responders was significantly longer than non-responders (47 vs 113.5 days, $p<0.001$), also seen by Lee *et al*. (mOS for RT responders 16.6 weeks vs 5.1 weeks non-responders)[37, 43, 46, 50, 52].

There was variation across studies regarding a RT dose-response relationship, summarised in Appendix H. Six studies [39, 42, 43, 46, 47, 49] found no association between RT dose and symptom response/haemostatic effect, compared to 5 that did [40, 45, 50, 56, 57]. The latter all delivered a higher median BED of ≥39Gy. The largest, Takeda *et al.*, (n=117), reported haemostatic control rate of 71.1% for those who received BED10 ≥39Gy vs 32.4% <39Gy [40]. Similarly, Yu et al, report statistically significant improvement in time to re-bleeding for doses >39Gy BED10 (19.3 vs 2.6 months). Lee *et al*. report BED10 ≥36Gy was significantly associated with bleeding control [45, 50]. A higher dose of BED10 ≥ 50Gy was found to be correlated with treatment success by Hashimoto et al [56]. Though Tey *et al*. found no evidence of symptom response using a cut off median BED of 39Gy, they reported a trend for poorer LC with BED ≤39Gy [52]. Kim *et al*. reported inferior LC in patients treated with BED <41Gy, they did not find an association with OS. Conversely, Mizrak Kaya *et al*. reported longer OS for patients receiving <50.4Gy [51, 57].

Overall, toxicity rates were low, with 9 studies reporting no ≥G3 toxicity, and ≤5% G3 gastro-intestinal in the others. Only 3 deaths were reported (0.3% of 955 patients); n=1 GI perforation, n=1 pneumonia, n=1 haemorrhage)[38, 44, 47].

Only one study reported QOL data. Tey *et al.* demonstrated improvement in global health status following RT in 44% of patients (n=36), with 63%, 31% and 50% of patients experiencing improvement in fatigue, nausea/vomiting and pain subscales 1 months post-RT (n=16)[37].

DISCUSSION

Is RT an effective treatment for inoperable GC?

We have shown the benefit of RT in managing symptoms associated with advanced IGC, in particular bleeding, with high haemostatic response rate. However, the data relates to a largely metastatic, heavily pre-treated, symptomatic population, where RT was used reactively in response to symptoms. Though it is

currently unknown whether there is a role for pre-emptive RT in GC (i.e. with intention to reduce or delay the onset of symptoms), the phase III ROCS study, demonstrated that upfront palliative oesophageal RT almost halved upper GI bleeding events from 28% to 16% and increased median time to GI bleeding from 49 to 65.9 weeks, raising the possibility that pre-emptive RT may also prove beneficial in IGC [58].

In the definitive setting, encouraging cCR rates of up to 45% shown here clearly signal the potential efficacy of high-dose CRT regimens (BED10>53Gy). Whilst as previously discussed, TOPGEAR did not demonstrate a PFS or OS benefit of pre-operative CRT for resectable GC, the pCR rate of 17%, major pathological response rate (i.e. <10% residual tumour) of 50% and greater tumour downstaging (32% vs 25%), demonstrates the efficacy of gastric RT [10]. This, along with further phase II evidence from the pre-operative setting, where pCR rates are up to 30%, demonstrates the potential value of high-BED RT for IGC [13-15].

Optimal dose of RT for inoperable GC.

Data exploring a dose-response relationship was limited to the palliative setting and largely related to haemostasis. In their review of seven studies (n=291 patients), Tey *et al*. reported no difference in bleeding response between high-BED (≥39Gy) vs low-BED (<39Gy) regimens [59]. In contrast, the later Viani *et al*. review (11 studies, n=409 patients) reported a significant relationship between BED10 and bleeding response (p=0.001), with a significantly worse response in studies with BED10 <30Gy [25]. Data relating to dose and LC/survival was both lacking and conflicting, though NCDB data of >1400 patients undergoing CRT reported shorter mOS for patients who received <45Gy vs >45Gy (9 vs 14.3 months respectively, p<0.001). We observed that the five studies that reported a dose-response relationship all had a median BED of ≥39Gy.

Given the high haemostasis rate of low-BED regimens, short, lower dose-fractionation schedules remain appropriate for those with high disease burden, poor performance status and limited life expectancy. However, we have presented a large body of retrospective data demonstrating the safety and efficacy of high-BED regimens in both the palliative and definitive setting, several >50Gy BED10, leading many study authors to conclude that high-BED schedules should be considered for those with lower disease burden/ better performance status. At present, due to conflicting, non-randomised, observational data, the optimal RT dose and fractionation schedule remains unclear, with insufficient evidence to recommend a change in practice.

Does addition of RT improve survival for inoperable GC?

As haemostatic control was associated with improved survival, in addition to managing distressing symptoms, there is the possibility that RT given pre-emptively, and/or at higher doses, may by reducing bleeding also prolong survival.

In the definitive setting there are data to suggest upfront RT, particularly for non-metastatic disease, may improve OS compared to SACT alone (11-26.4 months), further extended for those achieving cCR (up to 30.7 months). Induction SACT followed by RT resulted in an impressive 41.5 month mOS in the gastric cohort by Mizrak Kaya *et al.*, superior to the 22.8 months achieved in the oesophageal group [51]. Nevertheless, these data are largely observational and have not changed practice, further highlighting the need for a RCT.

Is gastric RT well tolerated?

Rates of toxicity were low, with ≥G3 gastrointestinal toxicity of <5% following high-dose palliative regimens (BED10 28-50.8Gy), even with older RT techniques. In the post-operative setting, the adoption of modern RT techniques has seen reduction in ≥G3 toxicity (from 33% in INT0116 to 0-17%) in later phase 3 studies [8, 9].

Higher rates of GI toxicity were seen in the definitive studies (≥G3 up to 31%), likely partly due to more intensive concurrent SACT, with highest rates following triplet regimens, although in the palliative setting, addition of SACT to RT was not shown to increase toxicity.

Treatment completion rates were high (>80%), even in the definitive setting where high doses (BED10 up to 59.47Gy) were delivered to large volumes including ELNI. This is echoed in the pre-operative setting, where TOPGEAR reported that 92% of patients completed the planned 45Gy/25# (BED10 = 53Gy)[10]. Together this demonstrates the feasibility of delivering high-BED10 regimens to volumes including entire stomach, with acceptable rates of ≥G3 toxicity.

QOL data were limited, but the high global scores reported by Liu *et al*., suggest that QOL may be maintained following RT to the primary tumour, supporting the hypothesis that a pre-emptive, rather than reactive approach may prolong good QOL - an important avenue of future research [26].

Optimal combination of RT with SACT

Whilst RT offers excellent LC, with local relapse rates as low as 9.5%, rates of distant recurrence are high (up to 70%), demonstrating the importance of optimal SACT in combination with local treatment [26, 51]. Additionally, several studies reported here show improved outcomes when RT is combined with SACT, though the optimal regimen is unknown.

For patients with advanced, HER2-negative GC, whose tumours express PD-L1 (CPD ≥1%), the addition of PD-L1 inhibition, is now SOC in the UK [60]. Sasaki *et al.* measured RT response in 18 metastatic GC patients who had previously been exposed to anti-PDL1 compared to 18 who had not, reporting 70% reduction in tumour volume on CT scan in 28% of the anti-PDL1 group vs 0% in the anti-PDL1 naïve group, and 63% vs 0% endoscopic response [48]. Evidence supporting immunotherapy-RT combination is also building in the pre-operative setting, including two phase II studies - Neo-PLANET report pCR of 33.3% following CRT + camrelizumab, and SHARED reported pCR of 42.1% after CRT + sintilimab [61, 62].

The optimal timing of SACT with RT remains unclear. The role of consolidation RT following induction SACT has been explored in the metastatic setting. Hingorani *et al*. reported on 97 patients (n=30 gastric); 53 underwent consolidation RT following 3 months of induction SACT, and 44 underwent SACT alone, with a marked mOS benefit with addition of RT, 23.3 months (RT group) vs 14 months (SACT alone), and increased time to local progression of 17.4 vs 8.3 months respectively [63]. Mizrak Kaya *et al*. report significantly longer OS (32.5 months vs 21.8 months) for those who had >3 month induction SACT followed by RT, with shorter survival to those who did not receive any SACT (12 months), further supporting the addition of SACT to RT [51]. Both concluded that randomised studies were needed to explore these findings further.

Further work is needed to establish the optimal timing of RT in conjunction with SACT, immunotherapy and other targeted treatments (e.g. anti-HER). Whether any molecular subtype responds more favourably to RT remains unknown and should be investigated by future studies.

Future directions

Of 30 active clinical trials investigating RT for GC (Appendix I and J), 21 are pre-operative, including 3 phase III RCTs. We note an increase in the number combining checkpoint inhibition with RT, which is being explored by 19 studies. Four are evaluating the role of stereotactic RT for oligometastatic disease. Interest is growing regarding the role of hypofractionation, the subject of six studies. However, to our knowledge, there are no currently active trials investigating definitive or high-dose palliative radiotherapy for IGC.

CONCLUSION

We have presented a significant body of largely non-randomised, observational data showing the feasibility, safety and tolerability of high-BED gastric RT, which can improve LC and survival, and may even result in complete response in the non-metastatic setting. The UK is out-of-step with other countries with regards to the almost exclusive use of reactive, low-BED regimens. Although effective at providing symptom control, we postulate that pre-emptive, higher-BED regimens may provide superior LC, reduce symptomatic burden, and improve survival and QOL for patients with IGC. A change in UK (and wider global) practice will require a prospective RCT, which should explore the role of prophylactic high-BED RT, combined with optimal SACT, using modern IMRT, IGRT and RT quality assurance. We believe such a study is urgently needed to improve outcomes for this under-studied group of patients.

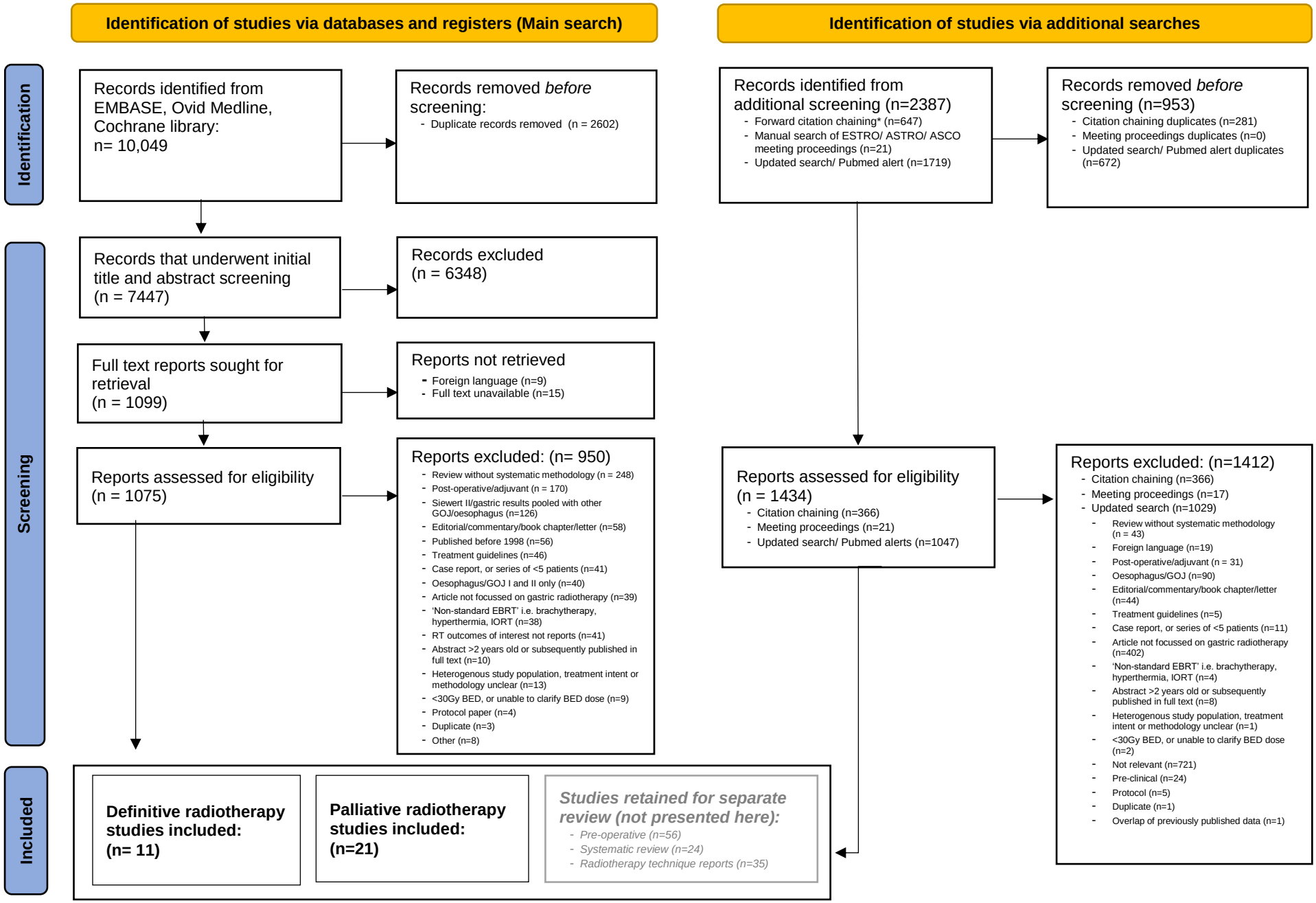

Figure 1. PRISMA 2020 flow diagram showing screening process for initial and additional searches, the latter including citation chaining, manual searches of meeting proceedings and updated search results. To appraise the current status of published literature relating to gastric RT, systematic reviews (SR) (reporting recognised methodology) were retained for separate evaluation, though their results were not collated with that of the selected original studies presented in this review. Pre-operative studies and reports describing RT technique retained by the overarching search will not be discussed further here, but are shown on the PRISMA diagram for completeness. *Forward citation chaining was conducted on all selected definitive and neoadjuvant titles.

Table 1. Study characteristics of selected definitive radiotherapy studies

Study details		Patient population				Treatment details			
First Author/ Year of publication	**Study type**	**Total no. of patients (no. planned for RT)**	**% Gastric /GOJ**	**Patient Characteristics**	**M Stage**	**Radiotherapy**	**% completing planned RT**	**Chemotherapy**	**% completing chemotherapy**
Liu *et al.* 2017 [26]	Phase 2, multicentre, single arm	36	100% gastric	n= 21 co-morbid unsuitable for surgery n =8 unresectable disease n = 7 refused surgery	M0	45Gy/25# + 5.4Gy/3# boost	86%	Induction mDCF x2 cycles Concurrent weekly docetaxel 20mg/m^2 x6 Adjuvant mDCF x 2cycles	97% induction (n=35/36) 86% concurrent (n=30/35) 75% adjuvant (n=27/30 who underwent CRT)
Wydmanski *et al.* 2014 [27]	Phase 2, single centre, single arm	13	100% gastric	n= 6 (46.2%) refused surgery n= 7 (53.8%) CI to anaesthesia	M0	45Gy/25# over 5 weeks	92.3%	Concurrent 5FU (bolus infusions 325mg/m^2 D1-5, 29-33)	38% (of n=5 having chemotherapy 100% completed)
Safran *et al.* 2000* [28]	Phase 2, multicentre, single arm	27	100% gastric	Unresectable or borderline resectable n=6 tumours >10cm length n= 6 medical CI to surgery n=1 T4 disease n = 6 coeliac LNs n= 7 retroperitoneal LNs	M1 (n=7) RPLN, portal or mesenteric LN permitted	45Gy/25# + /- 5.4Gy/3# boost (if inoperable, n=12)	99%	Concurrent Paclitaxel (50mg/m^2, weekly for up to 6 weeks)	89%
Chen *et al.* 2022 [29]	Prospective, randomised trial (Phase NS), single centre	74	100% gastric	Stage II-IIIC, must have refused or have contra-indications to surgery	M0	45Gy/25# over 5 weeks	NS	All patients: concurrent oxaliplatin (130mg/m^2 q21) and tegafur (40mg/m^2 BD 14 days, q21) + For Group B (n=34): Propranolol 10-60mg BD	NS
Ling *et al.* 2012 [30]	Phase 1 (investigating MTD docetaxel), multicentre	21	100% gastric	Unsuitable for resection due to advanced T/N stage or medically CI. n=10 T4 severe adjacent invasion n = 6 Bulky nodal metastases n= 5 Both T4 and bulky N	NS	50.4Gy/28#	NS	Concurrent Cisplatin (20mg/m^2 weekly) Docetaxel (5mg/m^2 – 15mg/m^2 in increments of 2.5mg/m^2 per dose level)	NS
Leong *et al.* 2003* [31]	Prospective data collection as part of a pilot toxicity/feasibility study, single centre	26 (n=8 CRT)	62% Gastric#, 38% GOJ/cardia#	2 cohorts: Group 1 (n=18) = Post-operative RT following R0 resection. Group 2 (n=8) = Locally advanced, not suitable for surgical resection due to tumour size/invasion of adjacent structures/ advanced locoregional LN involvement/ medically unsuitable for surgery	M0	45Gy/25# over 5 weeks	81%#	Induction ECF x1 cycle Concurrent 5FU continuous infusion (225mg/m2/day 7 days per week throughout entire period of RT) Adjuvant ECF x2 cycles~	n=1 failed to completed concurrent 5FU/adjuvant ECF n=2 failed to complete adjuvant chemotherapy
Dong *et al.* 2018 [32]	Prospective case series, non-randomised, single centre	194 (n=31 CRT)	91.2% gastric# 8.8% gastric cardia and GOJ#	n=59 locally advanced, MO, could not undergo radical resection, or residual disease/local recurrence after radical resection, of which 31 had CRT n= 94 organ mets n= 41= distant LN mets	M0 = 30%# M1 = 70%#	45-50.4Gy/25-28# over 5-6 weeks	NS	For CRT both sequential chemo or concurrent CRT were permitted (regimens NS)	NS
Mizrak Kaya *et al.* 2018^ [33]	Retrospective case series, single centre	71 (n=57 CRT)	60.6% gastric, 39.4% GOJ III	Technically operable patients who did not have surgery due to: n=34 (47.9%), medical co-morbidity# n= 14 (19.7%) poor performance status# n=23 (32.4%) patient choice. #	M0	Median dose 45Gy (range 36-50.4)	NS	Induction (46.5%) or concurrent (33.8%) FU +/- platinum. 19.7% had chemo alone#	NS
Saki *et al.* 2017 [34]	Retrospective case series, single centre	21	100% gastric	n=14 unresectable local recurrence n=2 unresectable primary locally advanced	M0	50Gy/25# over 5 weeks	100%	Concurrent TS-1 (80mg/m2) daily 4 weeks, q42, n=15 OR 5FU 250mg/m2 + cisplatin	n=1 radiotherapy alone Chemotherapy

				n=5 inoperable primary due to poor general condition				5mg/m2 d1-5, 8-12, 15-19, 22-26 n=5	discontinued due to leucopenia n=9
Suzuki *et al.* 2012^ [35]	Retrospective case series, single centre	66	45.5% gastric, 54.4% GOJ III	Reasons for no surgery: n=20 (30.3%) Stage IV before CRT, 8 positive peritoneal cytology, 6 with T4 disease, 6 local RPLN) n=17 (25.8%) co-morbidities, n= 5 (7.6%) patient choice, n= 22 (33%) too frail and or tumours too bulky for surgery, who developed predominantly peritoneal mets **after** CRT (and n=2 died during CRT)	M0= 77.3% (n=51) M1 = 22.7% (n=15)[§]	45Gy/25# over 5 weeks or 50.4Gy/28#	NS	Induction (62.1%, regimen NS) Concurrent (100%) FU +/- taxane or platinum	NS
Studies combining definitive and palliative doses[¤]									
Qi *et al.* 2018[¤] [36]	Retrospective NCDB review	4795 (n=1479 CRT)	100% gastric	Non-metastatic, inoperable stage I-III disease	M0	Median dose 45Gy (IQR 43.2-50.4Gy)	NS	n= 947 concurrent n= 524 sequential (regimens not stated)	NS

CI = Contra-indication, LN = lymph nodes, NS= not stated, NA = not applicable, RPLN = retroperitoneal lymph node. mDCF = Docetaxel 37.5mg/m2 d1 and 8, cisplatin 25mg/m2 d1-3, and 5FU 750mg/m2/24h d1-d5 q3 weeks. ECF = epirubicin 50mg/m^2 d1, cisplatin 60mg/m2 d1, 5FU 200mg/m2/day infusion continuously. *Permitted patients to proceed to surgical exploration. [#]data quoted relates to whole study population (not just CRT cohort) ~A small number of patients had 5FU 425mg/m2/day and leucovorin 20mg/m2/day for 5 days in place of ECF pre and post radiation n=2/8. ^Potential overlap between case-series. Suzuki et al have previously reported on a subset of the patients reported by Mizrak Kaya (both studies from MD Anderson) [§] Patients with positive peritoneal washings but no gross peritoneal disease permitted.

[¤] Displayed with 'definitive' studies as reports on patients with non-metastatic, inoperable disease, treating up to 50.4Gy. However, palliative intent dose regimens also included in study, and results pooled. Therefore considered separately from other "definitive" studies in this review.

Table 2. Outcome data for the selected definitive papers

Study details			Response			Survival			Toxicity (CTCAE criteria)		
First Author/ Year of publication	**No. of patients**	**BED10Gy range**	**cCR (%)**	**cPR (%)**	**SD (%)**	**mOS**	**1 year OS**	**3 year OS**	**G3/4 Gastrointestinal**	**G3/4 Haematological**	**Mortality/ cause**
Liu *et al.* 2017 [26]	36	53.1 – 59.5	n=13/36 (36%)	n=17/36 (47%)	n=4/36 (11%)	25.8 months	NS	42%	G3/4 nausea = 31% (n= 11)* G3/4 vomiting =26 % (n=9)* G3/4 anorexia = 17% (n=6)* G3/4 diarrhoea = 3% (n=1)*	G3/4 neutropenia = 14% (n=5)* G3/4 lymphopenia = 40% (n=14)* G3/4 thrombocytopenia = 6% (n=2)* G3/4 febrile neutropenia = 6% (n=2)*	Nil
Wydmanski *et al.* 2014 [27]	13	53.1	n=5/12 (41.7%)	n=1/12 (8.3%)	n=2 (16.7%)	17.1 months	59%	48%	G3 nausea/vomiting = 7.7% (n=1) G4 GI toxicity = 0	G3/4 lymphocytopenia = 92.3% (n=12)	n=1 (7.7%) cause uncertain
Safran *et al.* 2000 [28]	27	53.1 – 59.5	n=3 (12%)#	n=12 (44%)#	n=7 (26%)#	11 months#	52%	NS	G3 esophagitis/gastritis = 15% (n=4)~ G4 = 11% (n=3)~ G3 nausea/vomiting 19% (n=5)~ G4 = 0~ G4 anorexia = 4% (n=1)~ G3 diarrhoea 4% (n=1)	G3 neutropenia = 4% (n=1)~ G3 thrombocytopenia = 8% (n=2)~ G4 haematological = 0	Nil
Chen *et al.* 2022 [29]	74	53.1	n=12 (16%)#	n=29 (39%)#	n=24 (32%)#	NS	NS	NS	G3/G4 gastrointestinal = 2.7%#	G3/G4 bone marrow suppression =0#	NS
Xing *et al* 2012 [30]	21	59.5	n=6 (28.6%)	n=8 (38.1%)	n=4 (19%)	NS	NS	NS	G3 nausea/vomiting = 4.8% (n=1) G4 GI toxicity = 0	G3 neutropenia =14.3% (n=3) G4 neutropenia= 4.8% (n=1)	Nil
Leong *et al.* 2003 [31]	26 (n=8 CRT)	53.1	n=1 (12.5%)	n=2 (25%)	NS	NS	NS	NS	G3 GI toxicity = 25% (n=2)	G3/4 haematological = 25% (n=2)	Nil
Dong *et al.* 2018 [32]	194 (n=31 CRT)	53.1 – 59.5	NS	NS	NS	11.1 months^	32.3%^	NS	G3/4 gastrointestinal = 20.6%#	G3/4 leukopenia = 24.5%# G3/4 granulocytopenia = 31.4%# G3/4 thrombocytopenia = 2.9%#	Nil#
Mizrak Kaya *et al*. 2018 [33]	71 (n=57 CRT)	NS (Median dose 45Gy)	n= 32 (45%)	NS	NS	26.4 months^	NS	NS	NS	NS	NS
Taki *et al.* 2017 [34]	21	60	n=5 (23.8%)	n=9 (42.8%)	n=3 (14.2%)	19.8 months	NS	NS	NS	NS	NS
Suzuki *et al.* 2012$ [35]	66	53.1 – 59.5	n=23 (34.8%)	NS	NS	14.5 months *(MO)* 16.8 months *(M1)*	NS	22.6%#	NS	NS	n=1 myocardial infarction n=1 septic shock
Studies combining definitive and palliative intent/doses¤											
Li *et al.* 2018¤ [36]	4795 (n=1479 CRT)	NS (Median dose 45Gy)	NS	NS	NS	12.3 months *(CRT)* 11.3 months *(chemo)*	NS	NS	NS	NS	NS

cCR= Clinical complete response (includes pathological response when stated), cPR= clinical partial response, SD = stable disease, mOS= median overall survival, G3/NS= not stated. LAGC CRT = locally advanced gastric cancer, chemoradiotherapy.# result refers to all patients in study across all groups (For Safran et al. also includes those who underwent surgery subsequently.) $ Studies that included an M1 population.
* toxicity to concurrent chemoradiotherapy section of treatment stated. ~ CALGB criteria used to grade toxicity. ^results refers to the cohort with local advanced GC who underwent CRT

Table 3. Study characteristics of selected palliative studies

Study details			Patient population					Primary outcome measure	Treatment delivered		
First Author/ Year of publication	Study type	Site	Total no. of patients	% Gastric /GOJ	M Stage	Performance status (PS)	Patient characteristics		Radiotherapy dose/fractionation (or median dose if not stated)	Median dose $BEDGy_{10}$ (range)	Concurrent Chemotherapy % (regimen)
Prospective clinical trials											
Tey *et al.* (2019) [37]	Phase II, single arm	Singapore	50	Gastric 100%	74% M1	PS 1-2 = 90%, PS 3-4 = 10%	100% had bleeding as index symptom, n=2 pain, n=1 obstruction	Haemostasis	36Gy/12#	48.6Gy	Not permitted
Yoshikawa *et al.* (2009) [38]	Phase I	Japan	9	Gastric 100%	22% M1	PS 0-1 = 100%	100% had symptoms of pain or obstruction	Tolerability of concurrent chemotherapy	Up to 45Gy/25#	NS	100% (paclitaxel and cisplatin)
Observational studies											
Sato *et al.* (2023) [39]	Multicentre prospective observational study	Japan (15 centres)	55	Gastric 100%	76% M1	PS 0-2 = 75% PS 3 = 25% (PS 4 excluded)	100% bleeding, with Hb <8. Median baseline Hb 6.2	Haemostasis	8Gy/1# (21%) 20Gy/5# (32%) 30Gy/10# (38%)	28Gy	NS
Takeda *et al.* (2022) [40]	Retrospective review, multicentre	Japan (4 centres)	117	Gastric 97.5%	75.8% M1	NS	Evaluated patients who had RT for bleeding Median baseline Hb 8.2	Haemostasis	30Gy/10# (64.2%) 20Gy/5# (19.2%)	39Gy (7.8-60Gy)	11.7% (NS)
Yagi *et al.* (2023) [41]	Retrospective cohort study, single centre	Japan	48 (n=25 RT cohort)~	Gastric 100%	NS	PS 0-1= 56%, PS 2-3 = 44%	100% had either endoscopically confirmed bleeding, symptoms of bleeding or need for BT. Median baseline Hb 9.4	Haemostasis	39Gy/13# (52%) 30Gy/10# (24%) 36Gy/10# (8%) 50Gy/25% (4%) 24Gy/8# (4%) 15Gy/5# (4%)	NS	NS
Kataoka *et al.* (2023) [42]	Retrospective cohort study, single centre	Japan	23	Gastric 100%	87% stage IV	PS 0-2 = 100%	100% had symptoms such as bleeding or obstruction. Median baseline Hb 9	Haemostasis	30Gy/10# (52%) 20Gy/5# (43%) 8Gy/1# (4%)	39Gy^{+}	13% (SOX or FOLFOX)
Sunita *et al.* (2022) [43]	Retrospective review, single centre	Japan	33	Gastric 100%	85% stage IVB	PS 0-2 = 85% PS 3-4 = 15%	100% endoscopically confirmed bleeding. Median baseline Hb 6.3	Haemostasis	30Gy/10# (76%) 20Gy/5# (12%) 20Gy/10# (3%) 18Gy/6# (3%) 8Gy/1# (3%) 6Gy/2# (3%)	39Gy^{+}	NS
Kabasawa *et al.* (2022) [44]	Retrospective review, single centre	Japan	20	Gastric 100%	45% M1	PS 2 = 30% PS 3-4 = 70%	100% endoscopically confirmed bleeding. Median baseline Hb 6.2	Haemostasis	30/10# (80%) 10.5Gy/3# (5%) 15Gy/5# (5%) 20Gy/5# (5%)	39.9Gy (14.1-39.9Gy)	0
Yu *et al.* (2021) [45]	Retrospective review, single centre	Korea	61	Gastric 100%	67.2% M1	PS 0-2 =31.1% PS 3-4 =68.9%	100% endoscopically confirmed bleeding. Median baseline Hb 7.1	Haemostasis	Median dose = 30Gy (range 12.5-50Gy)	39Gy (16-60Gy)	0
Lee *et al.* (2019) [46]	Retrospective review, single centre	Korea	57	Gastric 100%	87.7% M1	PS 1-2 =82.4% PS 3-4 =17.5%	100% endoscopically confirmed bleeding. Median baseline Hb 6.6	Haemostasis	25Gy/5# (29.8%) 20Gy/5# (24.6%) 30Gy/10 # (22.8%) 45Gy/25# (5%)$^{¥}$	37.5Gy (23.6-58.5Gy)	17.5% (NS)
Mitsuhashi *et al.* (2021) [47]	Retrospective review, single centre	Japan	28	Gastric 100%	53% stage IV	PS 0-2 = 57%, PS 3-4 = 43%	Evaluated patients who had RT for bleeding.	Haemostasis	30Gy/10# (60%) 40Gy/20# (21%)	NS	10.7% (S-1 and CPT-11)

									20Gy/5# (4%) [§]		
Sasaki *et al.* (2020) [48]	Retrospective cohort study, single centre	Japan	36	Gastric 100%	100% M1	Ps 0-2 = 100%	100% had bleeding, pain or obstruction. N=18 had received prior anti-PDL1 therapy before RT	Response of primary tumour to RT, after prior anti-PD1 therapy	30Gy/10#	39Gy[+]	NS
Hiramoto *et al.* (2018) [49]	Retrospective review, single centre	Japan	23	Gastric 100%	91.3% M1	PS 0-2 =95.7% PS 3-4 =4.3%	All exhibited bleeding (n=18) and/or obstruction (n=10)	Haemostasis, Response of RT for obstruction	Median 42Gy/20# (range 30-60Gy/ 10-30#)	50.8Gy[+]	43.5% (cisplatin + 5FU n=8, 5FU+ methotrexate n=1, S-1 n=1)
Lee, Y *et al.* (2019) [50]	Retrospective review, single centre	Korea	42	Gastric 100%	83.3% M1	PS 1-2= 81%, PS 3-4 = 19%	All had evidence of bleeding	Haemostasis	Median = 39.6Gy (range 14-50.4Gy) Median # = 20 (7-28)	46.9Gy (16.8-60Gy)	16.7% (5FU+ leucovorin)
Mirek Kaya *et al.** (2017) [51]	Retrospective cohort study, single centre	USA	101	Gastric/ GOJ III = 29.7%	100% M1	NS	All had metastatic disease. 25.7% subsequently underwent surgery after CRT	OS	Median = 50.4Gy (range 45-65Gy)	NS	100% (5FU + platinum OR taxane)
Tey *et al.* (2014) [52]	Retrospective review, single centre	Singapore	115	Gastric 100%	67.8% M1	PS 0-2 =90.4% PS 3-4 = 9.6%	All required at least 1 symptom such as bleeding (n=103), pain (n=11) or obstruction (n=17)	Symptom response (bleeding, pain, obstruction)	30Gy/10# (40%) 36Gy/12# (33%) 20Gy/5# (16.5%) 40Gy/16# (4%) 8Gy/1# (2.6%)^	39Gy	0
Choi *et al.* (2013) [53]	Retrospective review, single centre	Hong Kong	28	Gastric 100%	64.3% M1	PS 1-2=75%, PS 3-4= 25%	All had evidence of low grade GI bleeding, and all except n=2 required BT prior to RT. Median baseline Hb 6.9	Haemostasis	30Gy/10# (82.6%) 22.5Gy/5# (28.6%) 32.5Gy/13# (4.3%) 40Gy/20# (4.3%)	39Gy[+]	0
Asakura *et al.* (2011) [54]	Retrospective review, single centre	Japan	30	Gastric 100%	96% M1	PS 0-2 = 60%, PS 3-4 = 40%	All required BT, 87% symptomatic of melaena or haematemesis. Median baseline Hb 5.1	Haemostasis	30Gy/10# (90%) 27Gy/9# (7%)** 21Gy/7# (3%)**	NS	40% (S1+cisplatin n=6, S-1 n= 1, methotrexate + 5FU n= 2, 5FU n= 2, paclitaxel n=1)
Lee, J *et al.* (2009) [55]	Retrospective review, single centre	Korea	23	Gastric 100%	87% M1	PS 1-2= 74%, PS 3-4= 26%	100% endoscopically confirmed bleeding	Haemostasis	Median 30Gy/10# (range 30-44Gy/ 10-22#)	39Gy[+]	NS
Hashimoto *et al.* (2009) [56]	Retrospective review, single centre	Japan	19	Gastric 100%	100% Stage IV	PS 1-2 = 79%, PS 3-4 = 21%	Median baseline Hb 5.4	Haemostasis	40Gy/16# (53%) 20Gy/10# (10%) 50Gy/25# (5%) 40Gy/20# (5%) 35Gy/14# (5%)[¤]	50Gy	21% (5FU+cisplatin n=1), S-1 n=1, paclitaxel n=1, 5FU + methotrexate n=1)
Kim *et al.** (2008) [57]	Retrospective review, single centre	USA	37	Gastric 100%	73% M1	NS	54% bleeding, 43% dysphagia, 19% pain	Symptom control	Median 35Gy/14# (range 20-36Gy)	41Gy (25-41Gy)	65% (most commonly fluoropyrimidine)

BT = Blood transfusion, OS = overall survival, QOL = quality of life, NS= not stated. CPT-11 = camptothecin-11. Hb stated in g/dL.

‡ cohort comparing surgery to radiotherapy, n=25 of 48 patients underwent RT, n=23 had palliative surgery. **+** not directly stated but median BED10 calculated from stated median total dose/#. ***** Potential overlap between patient populations recruited from same centre with cross over of dates of inclusion/recruitment to study. **¥** 10 other dose/# regimens listed in publication, each n=1, not listed here. **¤** 4 other dose/# not listed in table: 27Gy/9# (5%), 18Gy/9# (5%), 7.2Gy/4# (5%), 26Gy/1# (5%) **§** 4 other dose/# regimens not listed in table, of patients whom could not complete the schedules 24 Gy/12# (4%), 34/17 (4%), 36/18 (7%). **^** 3 other dose regimens not listed in table 37.5Gy/15# (1.7%), 30 Gy/12# (0.8%), 35Gy/14# (0.8%). ****** represent patients who could not complete planned 30Gy/10#

Table 4. Outcomes of palliative papers

Study details			Symptom response rates (as defined by each paper, see supplementary materials, appendix 6)				Radiological/ pathological response	Survival (months)		Toxicity		
First Author/ Year of publication	No. of patients	Median BED10Gy (range)	Bleeding	Re-bleeding	Other bleeding endpoints	Other symptom endpoints		mOS	Median bleeding free survival*	G3-4 Gastrointestinal	G3-4 Haematological	Mortality (cause)
Prospective clinical trials												
Tey *et al.* (2019) [37]	50	48.6	80%	NS	Median duration of response = 3.4 months (in responders)	100% pain response. 100% obstruction response	NS	2.7	NS	Overall G3 toxicity =5% (n=1 gastritis, n=1 anorexia)	0	0
Yoshikawa *et al.* (2009) [38]	9	NS	NS	NS	NS	100% pain response 89% obstruction response	NS	NS	NS	G3 anorexia n=1, G3 nausea n=1, G3 vomiting n=1, G3 esophagitis n=1,	G3 neutropenia n=1, G3 anaemia n=1, G4 thrombocytopenia n=1	n=1 (Pneum-onia and DIC)
Observational studies												
Saito *et al.* (2022) [39]	55	28	69% (PP = 90% at 8 weeks)	32%	Mean duration of response = 2.3 months.	NS	NS	3.8	NS	G3 anorexia = 2%#	0	0
Takeda *et al.* (2022) [40]	117	39 (7.8-60)	59.6% (77.8% in those followed up >4wks)	NS	Mean volume of BT before RT= 716ml, after RT = 230ml (p0.0001)	NS	NS	3.7	NS	Overall ≥G3 = 5%. G3 anorexia n=5. G4 GI perforation n=1	NS	0
Tsai *et al.* (2023) [41]	48 (n=25 RT cohort)~	NS	88%	40%	NS	NS	NS	4.9~	NS	0~	0~	0~
Katano *et al.* (2022) [42]	23	39+	NS	NS	83% had reduced BT requirement after RT. Mean units transfused decreased from 4.2 to 1.7. No difference in mean Hb before vs after RT.	70% pain and obstruction symptom response	NS	3.9	NS	0	0	0
Sugita *et al.* (2022) [43]	33	39+	73%	21%	Mean Hb 6.3 pre-RT vs 9.7 post-RT (p=0.0001). 91% required BT pre-RT vs 24% post-RT.	NS	NS	3.7	4.9	0	0	0
Kawabata *et al.* (2022) [44]	20	39.9 (14.1-39.9)	95%	11%	Mean Hb 8.0 pre-RT vs 9.8 post-RT. Mean units transfused decreased from 6.8 pre-RT to 0.6 post-RT	NS	NS	NS	11.9	G3 anorexia n=1	NS	n=1 (GI perforat-ion)
Yi *et al.* (2021) [45]	61	39 (16-60)	88.5%	35.2%	Hb at 1, 2, 3 months post-RT higher than pre-RT (p<0.001). Average daily BT requirement decreased post-RT from 217ml pre-RT to 4ml post-RT (p<0.001)	NS	NS	4.8	6	G3 Nausea = 1.6%	0	0
Lee, J *et al.* (2021) [46]	57	37.5 (23.6-58.5)	75.4%	60% (at 3 months)	Mean Hb 6.6 pre-RT vs 9.7, 10.3 and 9.7 immediately, 1 and 2 months post-RT (p<0.001)	75.4% subjective symptom improvement in melaena/ haematemesis.	PR = 24.3% SD = 64.9%	NS	1.5	0	0	0

Mitsuhashi *et al.* (2021) [47]	28	NS	NS	NS	No significant decrease in Hb 4 weeks post-RT. No patients required BT within 4 weeks of RT. One year BT free survival = 69%	NS	NS	NS	NS	0	0	n= 1 (Haemor-rage)
Sasaki *et al.* (2020) [48]	36	39[+]	NS	NS	NS	"Palliation of symptoms" =77.8% anti-PDL1 exposed, 66.7% anti-PDL1 naïve (p=0.71)	PR = 28% anti-PDL1 exposed vs 0% anti-PDL1 naïve (on CT)	NS	NS	0	0	0
Hiramoto *et al.* (2018) [49]	23	50.8[+]	88.8%	NS	NS	80% obstruction response	NS	3.9	3.4	0	0	0
Lee, Y *et al.* (2017) [50]	42	46.9 (16.8-60)	69%	37%	Median time to palliation of bleeding = 15 days	NS	NS	2.9	3.4	0	0	0
Mirak Kaya *et al.** (2017) [51]	101	NS	NS	NS	NS	NS	NS	41.5 (gastric cohort)	NS	NS	NS	NS
Tey *et al.* (2014) [52]	115	39	80.6%	NS	Mean net % relief of bleeding = 92%[¥]	52.9% partial response of obstruction (net % relief 85.6%[¥]) 45.5% partial response of pain (net % relief 91.3%[¥])	NS	2.8	3.2	Overall = 3% (G3 N+V n=1, G3 gastritis n=1, G3 anorexia n=1)	0	0
Choi *et al.* (2012) [53]	28	39[+]	65.2%	NS	NS	NS	NS	2.2	2.0	0	0	0
Asakura *et al.* (2011) [54]	30	NS	73%	50%	77% had improvement in melaena/ haematemesis. Mean BT volume 1 month pre-RT 2236ml vs 273ml post-RT (p<0.0001)	NS	NS	3.6	2.6	G3 bleeding (late) n=1	G3 leucopenia n=3 G4 leucopenia n=1 G4 thrombocytopenia n=1	0
Lee, J *et al.* (2009) [55]	23	39[+]	91%	NS	Mean Hb 9.1 before RT vs 10.6 after RT (p<0.001). Mean BT units 1 month pre-RT 9.5 vs 2.8 post-RT (p<0.001)	NS	NS	4.0	NS	0	0	0
Hashimoto *et al.* (2009) [56]	19	50	68%	NS	NS	50% response rate in improving dysphagia and oral intake	NS	3.4	1.5	G3 nausea n=1 G3 anorexia n=3	G3 anaemia n=9[^] G3 leucopenia N=2 G4 anaemia n=6	0
Fu *et al.** (2008) [57]	37	41	70%	NS	70% had bleeding controlled without need for additional intervention	81% dysphagia response 86% pain response Median duration of control of pain/dysphagia 6.2 months	NS	5.2	11.4	*RT alone:* G3 nausea n=2 *CRT:* G3 nausea n=2 G3 dehydration n=1	*CRT:* G3 neutropenia n=2	0

N/V = nausea and vomiting, NR = not recorded, PP = per protocol, BT = Blood transfusion

[*] Cohort comparing surgery to radiotherapy, n=25 of 48 patients underwent RT, n=23 had palliative surgery. The results stated in the table relate to the radiotherapy cohort only. [+] Not directly stated but median BED10 extrapolated from stated median total dose/#. [¤] Phase I, therefore primarily focussed on toxicity data rather than efficacy. [#] Radiation related adverse events quoted. [*]Bleed free survival relates to those who had initial haemostatic response to RT. Therefore this figure will be longer than the mOS, the latter also including those who did not have a response to RT. [¥] 'Percent net symptom relief 'was defined as the ratio between duration of symptom relief and duration of survival multiplied by 100'.

[^] 10 patients had G3 anaemia at start of RT

References

1. CRUK. *Cancer Research UK Stomach Cancer Incidence Statistics*. 2022 [cited 2022 15/12/2022]; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer/incidence#ref-5
2. Lordick, F., et al., *Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up.* Annals of Oncology, 2022. **33(10)**: p. 1005-1020.
3. Park MH, W.M., Maynard N, Crosby T, Thomas B, Trudgill N, Geisler J, Napper R. Cromwell D., *National Oesophago-Gastric Cancer Audit. 2022 Annual Report*. 2023, The Royal College of Surgeons of England: London.
4. Macdonald, J.S., et al., *Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction.* N Engl J Med, 2001. **345**(10): p. 725-30.
5. Case, A.N., et al., *Gastric Radiotherapy in the UK - Current Practice and Opinion on Future Directions.* International journal of radiation oncology, biology, physics, 2023. **117 2S**: p. e286.
6. Macdonald, J.S., et al., *Chemoradiotherapy after Surgery Compared with Surgery Alone for Adenocarcinoma of the Stomach or Gastroesophageal Junction.* New England Journal of Medicine, 2001. **345**(10): p. 725-730.
7. Park, S.H., et al., *Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses.* J Clin Oncol, 2015. **33**(28): p. 3130-6.
8. Cats, A., et al., *Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial.* The Lancet Oncology, 2018. **19**(5): p. 616-628.
9. Park, S.H., et al., *A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial(☆).* Ann Oncol, 2021. **32**(3): p. 368-374.
10. Leong, T., et al., *Preoperative Chemoradiotherapy for Resectable Gastric Cancer.* N Engl J Med, 2024.
11. Leong, T., et al., *TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG.* Ann Surg Oncol, 2017. **24**(8): p. 2252-2258.
12. Slagter, A.E., et al., *CRITICS-II: a multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer.* BMC Cancer, 2018. **18**(1): p. 877.
13. Ajani, J.A., et al., *Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma.* J Clin Oncol, 2004. **22**(14): p. 2774-80.
14. Ajani, J.A., et al., *Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome.* J Clin Oncol, 2005. **23**(6): p. 1237-44.
15. Ajani, J.A., et al., *Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response.* J Clin Oncol, 2006. **24**(24): p. 3953-8.
16. *Radiotherapy dose fractionation Fourth edition*. 2024 [cited 2024 10/01/2024]; 4th:[Available from: https://www.rcr.ac.uk/our-services/all-our-publications/clinical-oncology-publications/radiotherapy-dose-fractionation-fourth-edition/
17. Stahl, M., et al., *Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial.* Eur J Cancer, 2017. **81**: p. 183-190.
18. Shapiro, J., et al., *Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial.* Lancet Oncol, 2015. **16**(9): p. 1090-1098.
19. Mukherjee, S., et al., *Oxaliplatin/capecitabine or carboplatin/paclitaxel-based preoperative chemoradiation for resectable oesophageal adenocarcinoma (NeoSCOPE): Long-term results of a randomised controlled trial.* Eur J Cancer, 2021. **153**: p. 153-161.
20. Gwynne, S., et al., *Definitive chemoradiation for oesophageal cancer--a standard of care in patients with non-metastatic oesophageal cancer.* Clin Oncol (R Coll Radiol), 2011. **23**(3): p. 182-8.
21. Moher, D., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Systematic Reviews, 2015. **4**(1): p. 1.
22. Munn, Z., et al., *Methodological quality of case series studies: an introduction to the JBI critical appraisal tool.* JBI Evid Synth, 2020. **18**(10): p. 2127-2133.
23. Quigley, J.M., et al., *Critical appraisal of nonrandomized studies-A review of recommended and commonly used tools.* J Eval Clin Pract, 2019. **25**(1): p. 44-52.

24. Page, M.J., et al., *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews.* Bmj, 2021. **372**: p. n71.
25. Viani, G.A., et al., *Palliative radiotherapy for gastric cancer: Is there a dose relationship between bleeding response and radiotherapy?* Clinics (Sao Paulo), 2020. **75**: p. e1644.
26. Liu, Y., et al., *Multicenter Phase 2 Study of Peri-Irradiation Chemotherapy Plus Intensity Modulated Radiation Therapy With Concurrent Weekly Docetaxel for Inoperable or Medically Unresectable Nonmetastatic Gastric Cancer.* International Journal of Radiation Oncology Biology Physics, 2017. **98**(5): p. 1096-1105.
27. Wydmanski, J., et al., *Radiotherapy and chemoradiotherapy as a novel option for the treatment of locally advanced inoperable gastric adenocarcinoma: A phase II study.* Mol Clin Oncol, 2014. **2**(6): p. 1150-1154.
28. Safran, H., et al., *Paclitaxel and concurrent radiation for gastric cancer.* Int J Radiat Oncol Biol Phys, 2000. **46**(4): p. 889-94.
29. Chen, Y., et al., *Clinical value of propranolol combined with oxaliplatin and tigio in concurrent chemoradiotherapy for locally advanced gastric cancer.* Pakistan Journal of Medical Sciences, 2022. **38**(5): p. 1316-1320.
30. Xing, L., et al., *Phase I study of docetaxel, cisplatin and concurrent radiotherapy for locally advanced gastric adenocarcinoma.* Neoplasma, 2012. **59**(4): p. 370-375.
31. Leong, T., et al., *Adjuvant and neoadjuvant therapy for gastric cancer using epirubicin/cisplatin/5-fluorouracil (ECF) and alternative regimens before and after chemoradiation.* Br J Cancer, 2003. **89**(8): p. 1433-8.
32. Dong, H.M., et al., *A clinical analysis of systemic chemotherapy combined with radiotherapy for advanced gastric cancer.* Medicine (Baltimore), 2018. **97**(23): p. e10786.
33. Mizrak Kaya, D., et al., *Potentially curable gastric adenocarcinoma treated without surgery.* Eur J Cancer, 2018. **98**: p. 23-29.
34. Taki, T., et al., *Usefulness of chemoradiotherapy for inoperable gastric cancer.* Ann R Coll Surg Engl, 2017. **99**(4): p. 332-336.
35. Suzuki, A., et al., *Localized gastric cancer treated with chemoradation without surgery: UTMD Anderson Cancer Center experience.* Oncology, 2012. **82**(6): p. 347-51.
36. Li, R., et al., *Chemoradiation Improves Survival Compared With Chemotherapy Alone in Unresected Nonmetastatic Gastric Cancer.* J Natl Compr Canc Netw, 2018. **16**(8): p. 950-958.
37. Tey, J., et al., *Palliative radiotherapy in symptomatic locally advanced gastric cancer: A phase II trial.* Cancer Med, 2019. **8**(4): p. 1447-1458.
38. Yoshikawa, T., et al., *A phase I study of palliative chemoradiation therapy with paclitaxel and cisplatin for local symptoms due to an unresectable primary advanced or locally recurrent gastric adenocarcinoma.* Cancer Chemotherapy and Pharmacology, 2009. **64**(6): p. 1071-1077.
39. Saito, T., et al., *Treatment response after palliative radiotherapy for bleeding gastric cancer: a multicenter prospective observational study (JROSG 17-3).* Gastric Cancer, 2022. **25**(2): p. 411-421.
40. Takeda, K., et al., *Palliative radiotherapy for gastric cancer bleeding: a multi-institutional retrospective study.* BMC Palliative Care, 2022. **21(1) (no pagination)**.
41. Yagi, S., et al., *Clinical outcomes of palliative treatment for gastric bleeding from incurable gastric cancer.* Surgery Today, 2023. **53**(3): p. 360-368.
42. Katano, A. and H. Yamashita, *The Impact of Palliative Radiation Therapy on Patients With Advanced Gastric Cancer: Results of a Retrospective Cohort Study.* Cureus, 2022. **14**(12): p. e32971.
43. Sugita, H., et al., *Verification of the Utility of Palliative Radiotherapy for Hemostasis of Gastric Cancer Bleeding: a Case Control Study.* Journal of Gastrointestinal Cancer, 2022. **53**(2): p. 420-426.
44. Kawabata, H., et al., *Palliative Radiotherapy for Bleeding from Unresectable Gastric Cancer Using Three-Dimensional Conformal Technique.* Biomedicines, 2022. **10**(6): p. 13.
45. Yu, J., et al., *Role of palliative radiotherapy in bleeding control in patients with unresectable advanced gastric cancer.* BMC Cancer, 2021. **21**(1): p. 413.
46. Lee, J., et al., *Efficacy of radiotherapy for gastric bleeding associated with advanced gastric cancer.* Radiat Oncol, 2021. **16**(1): p. 161.
47. Mitsuhashi, N., et al., *Hemostatic Effect of Palliative Radiation Therapy in Preventing Blood Transfusions from Bleeding Occurring within Advanced Gastric Cancer.* Palliat Med Rep, 2021. **2**(1): p. 355-364.
48. Sasaki, A., et al., *Enhanced tumor response to radiotherapy after PD-1 blockade in metastatic gastric cancer.* Gastric Cancer, 2020. **23**(5): p. 893-903.
49. Hiramoto, S., et al., *Efficacy of palliative radiotherapy and chemo-radiotherapy for unresectable gastric cancer demonstrating bleeding and obstruction.* Int J Clin Oncol, 2018. **23**(6): p. 1090-1094.
50. Lee, Y.H., J.W. Lee, and H.S. Jang, *Palliative external beam radiotherapy for the treatment of tumor bleeding in inoperable advanced gastric cancer.* BMC Cancer, 2017. **17**(1): p. 541.

51. Mizrak Kaya, D., et al., *101 Long-Term Survivors Who Had Metastatic Gastroesophageal Cancer and Received Local Consolidative Therapy.* Oncology, 2017. **93**(4): p. 243-248.
52. Tey, J., et al., *Clinical outcome of palliative radiotherapy for locally advanced symptomatic gastric cancer in the modern era.* Medicine (Baltimore), 2014. **93**(22): p. e118.
53. Choi, C.Y., *Palliative haemostatic radiotherapy for advanced cancer of the stomach.* Journal of Pain Management, 2012. **5**: p. 53-62.
54. Asakura, H., et al., *Palliative radiotherapy for bleeding from advanced gastric cancer: is a schedule of 30 Gy in 10 fractions adequate?* J Cancer Res Clin Oncol, 2011. **137**(1): p. 125-30.
55. Lee, J.A., et al., *Radiation therapy for gastric cancer bleeding.* Tumori, 2009. **95**(6): p. 726-30.
56. Hashimoto, K., et al., *Palliative radiation therapy for hemorrhage of unresectable gastric cancer: a single institute experience.* J Cancer Res Clin Oncol, 2009. **135**(8): p. 1117-23.
57. Kim, M.M., et al., *Clinical benefit of palliative radiation therapy in advanced gastric cancer.* Acta Oncol, 2008. **47**(3): p. 421-7.
58. Adamson, D., et al., *Palliative radiotherapy after oesophageal cancer stenting (ROCS): a multicentre, open-label, phase 3 randomised controlled trial.* Lancet Gastroenterol Hepatol, 2021. **6**(4): p. 292-303.
59. Tey, J., et al., *Palliative radiotherapy for gastric cancer: a systematic review and meta-analysis.* Oncotarget, 2017. **8**(15): p. 25797-25805.
60. Rha, S.Y., et al., *Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial.* Lancet Oncol, 2023. **24**(11): p. 1181-1195.
61. Tang, Z., et al., *The Neo-PLANET phase II trial of neoadjuvant camrelizumab plus concurrent chemoradiotherapy in locally advanced adenocarcinoma of stomach or gastroesophageal junction.* Nature communications, 2022. **13**(1): p. 6807.
62. Wei, J., et al., *SHARED: Efficacy and safety of sintilimab in combination with concurrent chemoradiotherapy (cCRT) in patients with locally advanced gastric (G) or gastroesophageal junction (GEJ) adenocarcinoma.* Journal of Clinical Oncology, 2021. **39**(15_suppl): p. 4040-4040.
63. Hingorani, M., et al., *Palliative Radiotherapy in the Presence of Well-Controlled Metastatic Disease after Initial Chemotherapy May Prolong Survival in Patients with Metastatic Esophageal and Gastric Cancer.* Cancer Res Treat, 2015. **47**(4): p. 706-17.

Reconsidering the role of radiotherapy for inoperable gastric cancer - A systematic review of gastric radiotherapy given with definitive and palliative intent

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Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: