Canolfan Ymchwil Canser Cymru
Wales Cancer Research Centre

Palliative and Supportive Care Research Development

What is the most effective treatment in achieving early haemostasis and preventing or delaying re-bleeding in cancer patients suffering from upper GI bleeds? A rapid review.

28/06/2023

Evidence Implications:

Clinical & Policy:

The role of Proton Pump Inhibitors (PPIs) remains unclear but given that the majority of patients are likely to have other risk factors for upper GI bleeding, ongoing use in this patient cohort is likely.

The role of endoscopic therapy remains unproven, and whilst haemostatic sprays may have a role in achieving haemostasis, more robust evidence on cost effectiveness and durability of response is required.

The ease of access and relatively low cost/side effect profile of palliative external beam radiotherapy regimens, combined with the evidence described above, suggest that it may be reasonable to undertake in select patients in order to maintain delayed haemostasis. However, no consensus in terms of number of fractions or length of treatment is available and likely to continue to vary significantly, dependent on local guidelines.

Glossary:

APC – Argon Plasma Coagulation
CI – Confidence Intervals
EBRT – External Beam Radiation Therapy
ET – Endoscopic Therapy
EWD – Endoscopic Wound Dressing
GI – Gastro Intestinal
GIST- Gastro Intestinal Stromal Tumour
Gy – Gray (Unit of Measurement)
Hb – Haemoglobin
OGD – Oesophago-Gastro-Duodenoscopy
PPI – Proton Pump Inhibitor/s
QoL – Quality of Life
RCT – Randomised Controlled Trial
RT – Radiotherapy
SEMS – Self-Expanding Metal Stents
TAE – Trans Arterial Embolisation
UGIB – Upper Gastrointestinal Bleed

Context

Acute upper gastrointestinal bleeding (UGIB) accounts for approximately 50,000–70,000 hospital admissions annually in the UK. Although most patients in the UK are managed in hospital, the mortality rate remains around 10%. This is highest in the elderly and those with significant co-morbidity (Dinesen and Benson, 2012).

Patients with upper GI malignancy represent an important subgroup with one of the lowest five-year survival rates – 22.2% (Nuffield Trust 2022). Patients with upper GI malignancy also have high rates of hospital admission (Linder et al. 2021). They are a group in whom the therapeutic target following an acute bleed may differ. Patients presenting are usually older and with limited prognosis in whom the goals of treatment more often relate to rapid symptom control and maintenance of haemostasis, with the aim of limiting time spent in hospital environments. Identifying a treatment algorithm which will allow rapid initial and subsequent maintenance of haemostasis is therefore likely to be of high impact in terms of patient quality of life and also in terms of resource use in the NHS.

The HALT-IT trial published in the Lancet in 2020 was an international randomised double-blind, placebo-controlled trial that looked at the effect of tranexamic Acid on death and thromboembolic events in patients with acute GI bleeding. This was an international trial over 6 years in 164 different centres across 15 countries with over 12000 patients. They found that tranexamic acid didn't reduce death from GI bleeds and on this basis, they recommend that tranexamic acid shouldn't be used for GI bleeding. However, there was only a very small proportion of patients with malignancy in the group (0.009%), so it is difficult to extrapolate this to our patient group. They did recommend further randomised trials targeted at specific pathophysiological processes which is likely to include a cancer group.

This review is an update of a review completed in 2016, as part of a MSc Dissertation by Dr Jessica Sui. Those results have not been published, except as part of the dissertation. The review at that time found that there was no high-quality evidence for proton pump inhibitors, tranexamic acid or Hemospray© in reducing tumour bleeding, but on-going trials may provide clearer understanding to for current practice. Within limitations, radiotherapy had some low-grade evidence to suggest an impact on haemostasis outside of the acute bleeding context. The role of Endoscopic Therapy remained unclear, due to lack of objective evidence, but may be confined to initial assessment of bleeding. Currently there is no standard of care for these patients and their management may differ across geographical areas. An updated understanding of the evidence base may allow development of guidance for Wales on achieving and maintaining haemostasis in this group. Lack of evidence would support the development of research into treatment options.

The aims of this updated rapid review were:

- To examine the evidence base for achieving immediate haemostasis in patients with upper GI malignant bleeding requiring hospitalization;
- To examine the evidence base for interventions, including radiotherapy, for maintaining homeostasis in these patients;
- To clarify the evidence for acute management of these patients which may lead to a consensus approach to guidance in Wales, and/or to identify gaps in the evidence base which would lead to a research proposal.

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Key Findings

Of 1,035 studies initially identified, 162 abstracts were screened, and 70 papers retrieved. Of those full text papers, 18 are included in this review. Ten studies from 11 publications are from the updated search, 8 studies are included from the previous review. Two of the papers had study centres in the UK, however, the majority were in healthcare systems not directly comparable to the UK.
Of the new studies, six focused on the use of radiotherapy to stop UGI tumour bleeds, three studies used a haemostatic spray and one focused on the use of a Proton Pump Inhibitor (PPI).

The studies which focused on radiotherapy showed mixed results. Of the studies identified, there was one multicentre, controlled RCT whose primary outcome was to assess the impact of palliative radiotherapy on dysphagia following oesophageal stent placement, but which prospectively captured pre-defined data on the impact of radiotherapy on future bleeding risk (Adamson et al. 2021); one prospective observational study of radiotherapy in patients following evidence of an upper GI tumour bleed (Saito et al. 2021) and five retrospective cohort studies of radiotherapy in the aftermath of a tumour related upper GI bleed (Lee et al. 2017, Lee et al. 2021, Sugita et al. 2021, Yu et. al 2021) and Asakura et al. 2011). Adamson et al. (2021) reported a median time to first bleed after palliative external beam radiotherapy of 65 weeks compared to usual care which had a median time to first bleed of 49 weeks. Saito et al. reported a haemostasis rate of 65% at 4 weeks in a prospective study of radiotherapy after onset of bleeding with re-bleeding rates and 30-day mortality of 32% and 11%, respectively. In the five retrospective studies, successful haemostasis ranged from 66.7 to 89%. However, the time period for measurement was variable and the dosing and fractionation schedules were very heterogeneous, precluding direct comparisons. Re-bleeding rates ranged from 21% to 60% with again varying time frames. Median time to re-bleed ranged from 6.4 weeks to 6 months. Overall survival rates also varied, with Lee et al. 2017 reporting overall survival of 12.6 weeks (from any cause) and Yu et al. (2021) stating median overall survival of 4.8 months. In two of the studies (Lee et al. 2017 and Sugita et al. 2021), overall survival was statistically significantly increased in those who had had radiotherapy and had not re-bled (Lee p=0.048 and Sugita p=0.0026).

In summary, the retrospective cohort evidence from the original and the updated review demonstrates a positive trend in achieving delayed haemostasis, but with high risk of bias and no evidence to support a specific dose or fractionation schedule. The positive findings in the two prospective studies by Adamson et al. 2021 and Saito et al. 2021 identified in this updated review give more robust evidence of a positive effect of radiotherapy in reducing bleeding risk at doses in the range of 20 Gray in 5 fractions but single fractionation schedules were not tested. Any consideration of radiotherapy in this context should take into account the potential burdens of travel and side effects versus benefits in this vulnerable population.

There were 3 new studies focusing on haemostatic powder sprays. Hussein et al. (2021) examined data from a prospective registry study in 17 international centres whereas Meng et al. (2019) and Shin et al. (2021) reported retrospective cohort studies with data from one centre. There was evidence of benefit in terms of immediate haemostasis (as visualized at the time of the index endoscopy) with immediate haemostasis rates in the three studies ranging from 88% to 100%, but the risks of selection and reporting bias was high. All reported either 28-day or 30-day re-bleeding rates with a range of 15 to 23%. Reporting of overall survival varied with Hussein et al. (2021) stating 20% all-cause mortality at 30 days, Meng et al. (2018) 48% at 30 days and Shin et al. (2021) reporting a 6-month cumulative survival rate of 73%. Combined with the studies from the previous review, this suggests potential for improvement in immediate haemostasis using endoscopic haemostatic powders, but high-grade evidence from appropriately designed randomised controlled trials remains lacking, and there has been no robust health economic evaluation.

In Kim et al. (2017), a prospective double-blind placebo controlled RCT, which looked at PPI to prevent bleeding in patients about to undergo first- or second-line chemotherapy for inoperable gastric cancer, there were bleeding events in 7.8% of those on the intervention compared to 9.5% in placebo – a non-significant difference. However, the study did not reach its target sample size and was prematurely stopped due to poor recruitment.

Overall limitations such as small sample sizes, recall bias, lack of information on missing data, and very heterogeneous study designs (participant populations, intervention type, outcomes and timing of outcome measurements) preclude more definitive recommendations. The studies did not give an indication of cost for their interventions or compared to other interventions, which is likely to be a factor when considering a treatment in our healthcare setting. None of the studies had length of hospital stay or readmission rate in their outcomes which again is another factor NHS commissioners may use when considering certain treatments. There were far fewer RCTs than cohort studies in this group which suggests RCTs are difficult to undertake in this palliative patient group with limited prognosis who are very under-represented in clinical trials. That the emergency nature of UGIB also creates challenges for recruitment and the small number of cancer patients included in the HALT-IT trial may attest to that. RCTs have been difficult in palliative patients due to factors including recruitment, attrition and randomisation and the ethical concerns this may raise. Better designed, prospective registry studies may provide improved evidence of clinical effectiveness of an intervention using a comparator group, and collect more robust evidence on cost-effectiveness and safety.

A. Reliability of evidence

In terms of study design in the review update, two were RCTs (Adamson et al. 2021, Kim et al 2017), one study was a case-control design (Sugita et al. 2021), one was a prospective observational design (Saito et al. 2021) with the remainder being retrospective cohort studies with the inherent biases involved in this design. Out of the eight studies included from the 2016 review, seven of the studies (Chaw et al. 2014, Kim et al. 2013, Sheibani et al. 2013, Tey et al. 2014, Asakura et al. 2011, Koh et al. 2013, Maluf-filho et al. 2013) were case series and one was a case control (Martins et al. 2016).

Sample sizes were largely small except in Adamson et al. (2021), which had 220 in total between radiotherapy and control arms which, given that it was a large multicentre trial over several years, reflects the challenges of recruitment in this patient cohort. Many of the retrospective studies were conducted over lengthy time periods with one study looking at radiotherapy as an intervention over 23 years (Lee et al. 2017). It is reasonable to expect treatments and care to change in this time and would be interesting to see the differences in outcomes in those reviewed at the start of the study compared to the end.

In some of the studies, the intervention which was stated was not the only intervention used such as in Shin where 44% of the patients had 'other therapies' as well as the haemostatic spray with an inability to detect which was the active intervention in preventing re-bleeding.

B. Consistency of evidence

It is difficult to compare all of these studies in terms of consistency as there were different study designs, outcome measures and interventions. Only two of the studies (Adamson et al. 2021 and Hussein et al. 2021) recruited UK patients, with the rest of the studies based in other healthcare systems. The radiotherapy studies differed in outcome measures, doses of radiotherapy and one study looked at radiotherapy to UGI stents particularly which the others did not specify.

C. Relevance of evidence

We sought to seek evidence for interventions which would give immediate haemostasis for UGI bleeds in UGI tumours and also to maintain haemostasis in the palliative patient group. The hope was to lead to a consensus approach and ultimately guidelines to aid management in Wales of this patient group.

Despite the PPI study (Kim et al. 2017) apparently showing little difference between PPI and placebo in terms of bleeding events, this finding is unlikely to stop PPI use in UGI cancer as it is useful in other symptoms that are associated with these cancer types.

Given the very limited options for this patient group, who are frequently frail and highly symptomatic, haemostatic sprays may have a role in achieving immediate haemostasis. However this involves an OGD which may not always be appropriate in palliative patient groups. Furthermore, patients would likely need to present to specialist centres to have these procedures which may not always be achievable.

External beam radiotherapy appears best placed to maintain haemostasis once initial haemostasis has been achieved and is widely accessible in the UK. A well designed RCT to define the dose, fractionation schedule and timing is needed but unlikely to be achievable in this vulnerable patient group due to challenges of recruitment already described and healthcare professional/patient perceptions of equipoise particularly given the relatively low side-effect profile of lower radiotherapy doses.

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Review Methods

Search Strategy: This rapid review is an update of a previous review which was part of a Master of Science (MSc) in Palliative Medicine thesis. All studies included in the previous review have been included in this one. An updated search was conducted across a wide-ranging set of databases: Ovid Medline, including In-Process & Other Non-Indexed Citations, Ovid Embase, Scopus and Cochrane Library. The preliminary search strategy was developed on Ovid Medline using both text words and Medical subject headings from January 2016 to date and restricted to English language humans. The search strategy was modified to capture indexing systems of the other databases. (Search strategies available upon request).

To identify additional papers, the following website was searched: http://hemospray.cookmedical.com.

Furthermore, electronic tables of content for the last two years were scanned for the Lancet, Journal of Clinical Oncology and GUT.

Reference lists of systematic reviews were checked for relevant studies. The searches generated 121 citations after removing duplicates and irrelevant records. Figure 1 represents the flow of information through the different phases of the review.

Inclusion: Adults ≥18 years of age with UGI cancer admitted with malignant, non-variceal bleeding. Patients undergoing: Pharmacological, endoscopic or radiation therapy.

Exclusion: Children <18 years of age. Patients with UGI bleeding due to haematological or hepatobiliary cancer or variceal bleeding secondary to portal hypertension. Patients undergoing curative treatments or radiological intervention. Case series studies consisting of less than 25 patients; non-English language studies, pilot studies and conference abstracts.

Study selection/Quality Assessment/Data Extraction: Study selection was based upon review of the abstract by two independent reviewers. The full text was then assessed independently using a pre-designed eligibility form according to inclusion criteria. Data extraction was carried out within a pre-agreed form, initially piloted with one article. Critical appraisal of studies was carried out using the relevant study design tool.

Any discrepancies between the two reviewers were resolved by consensus or by recourse to a third reviewer.

Flow Diagram:

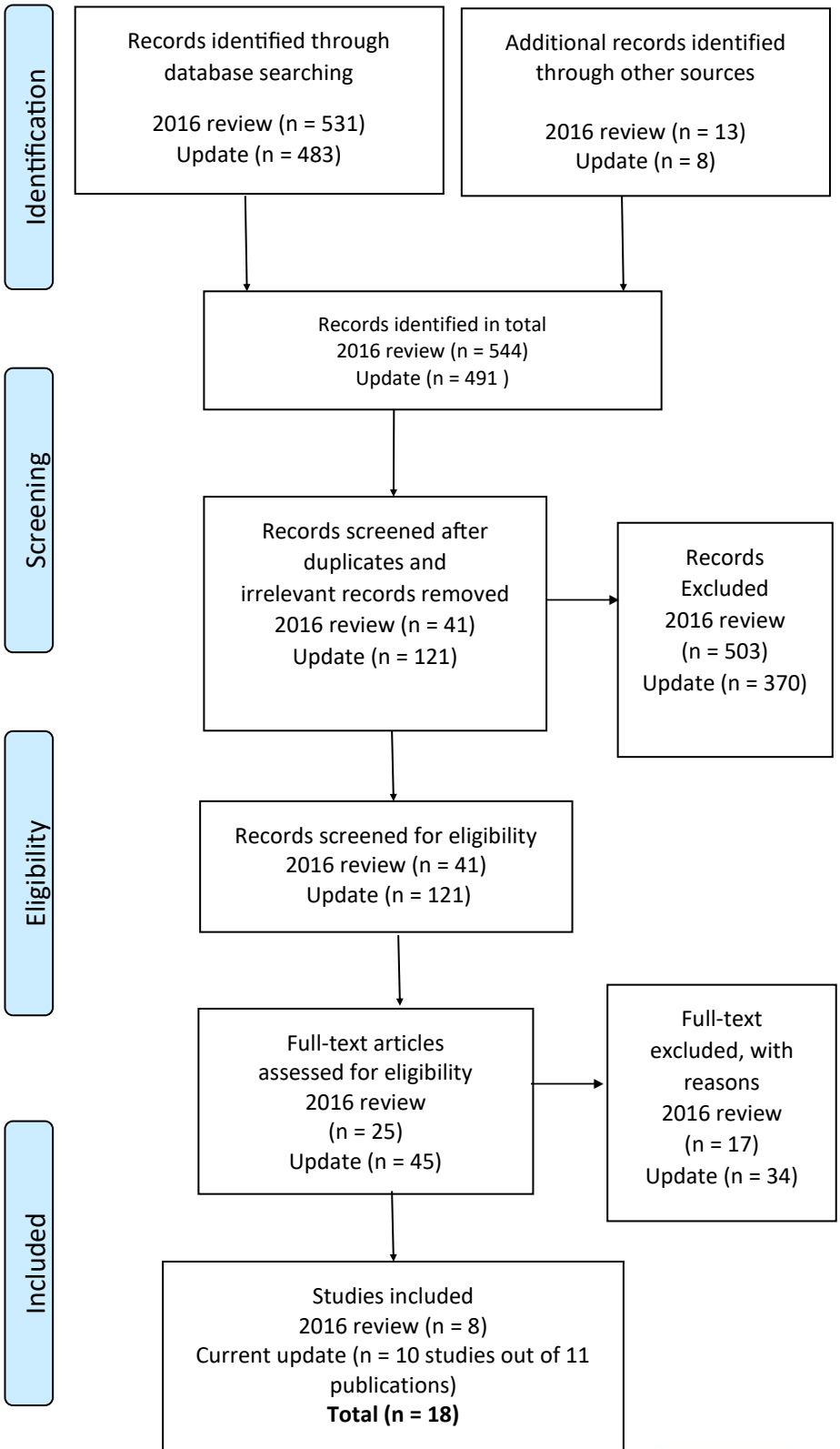

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Table 1: Characteristics of Included Studies (in alphabetical order)

Adamson et al. 2021a & Adamson et al. 2021b	**Study Setting & Design:** Randomised controlled trial in 23 cancer centres and acute care hospitals across Scotland, England and Wales.
Study Objective	To investigate the efficacy of adjuvant external beam radiotherapy (EBRT) in conjunction with self expanding metal stent (SEMS) placement compared with SEMS alone in reducing the risk of dysphagia deterioration and improving QoL and patterns of service use in patients with advanced oesophageal cancer. Prospective assessment of bleeding risk was a pre-defined secondary outcome.
Participants	220 patients with oesophageal carcinoma. Type of cancer: EBRT intervention - 63% adenocarcinoma; 35% squamous; 2% other Control - 67% adenocarcinoma; 32% squamous; 1% other
Interventions/ Comparators/ Methods	External Beam Radiotherapy (EBRT) intervention group: • 20 Gy in five fractions OR: • 30 Gy in 10 fractions
Proposed Outcomes	Bleeding events: 8% control group versus 2% EBRT group • Median time to first bleeding event: 49 weeks (CI = 33.3-not reached) in usual care group versus 65.9 weeks (CI = 52.7 - not reached) in EBRT group. • Median Overall Survival: 19·7 weeks (95% CI 14·4–27·7) in the usual care group versus 18·9 weeks (14·7–25·6) in the EBRT group
Summary of Results	It appears that there is a reduction of upper gastrointestinal bleeding observed in those randomised to EBRT group compared to control. Median time to first bleeding event is also increased in those randomised to EBRT compared to control. Median overall survival was similar for both groups.
Appraisal Summary	Overall methods well reported. Sample size was revised for the primary outcome in view of challenges with recruitment and the significant reduction in data completion after 12 weeks - reflective of the very unwell patient population (see median survival). As the sample size was calculated for dysphagia and not bleeding the ability to detect a difference may have been affected. Include: • Recruitment challenges as described above; however there was a pre-defined set of parameters captured including re-intervention rates for bleeding, transfusion requirements overtime and independent blind review of bleeding events and transfusions as to whether they were likely to relate to tumour bleeding. • The revised primary outcome might have affected the ability of the study to detect a true effect for EBRT.

Table 1: Characteristics of Included Studies (in alphabetical order)

Asakura et al. 2011	**Study Design and Setting:** Case Series, Cancer Centre, Japan.
Study Objective	To evaluate the effectiveness of short-course radiotherapy (RT) with 30 Gy in 10 fractions for bleeding from advanced gastric cancer.
Participants	30 gastric cancer patients
Interventions/ Comparators/ Methods	Radiotherapy at 30 Gy, 10 fractions - 27 pts, 27 Gy, 9 fractions - 2 pts or 21 Gy, 7 fractions - 1 pt
Outcomes	• Effective treatment rate 73% (22/30) • Re-bleeding rate 50% (11/22) • Mean haemoglobin pre transfusion 4.9g/dl with post transfusion level of 8.2g/dl (p<0.0001) • Reduction in blood transfusion requirement after radiotherapy from 2236ml to 273ml, p<0.0001 • Re-intervention rate 6.7% (2/30); 1 APC Expand? and 1 TAE Expand? • Median survival 3.6 months • For those receiving concurrent chemoradiotherapy, 50% (6/12) developed Grade 3 and 4 treatment toxicities • For those receiving radiotherapy alone, 33% (6/18) had only Grade 2 toxicities
Summary of Results	RT with 30 Gy in 10 fractions was effective and safe. 73% achieved hemostasis. Median time to re-bleeding of 3.3 months reflected that 30Gy 10 fractions regimen was adequate in controlling bleeding in patients with poor prognosis.
Appraisal Summary	A retrospective study with following limitations: • Single centre study • Small sample size • Selection bias due to the inclusion of patients in the study not enrolled from an entire target population.

Chaw et al. 2014	**Study Design and Setting:** Case Series, Cancer Centre, Ninewells Hospital & Medical School, Dundee, Scotland
Study Objective	To evaluate the outcomes of patients with gastric cancer bleeding who had been treated with palliative radiotherapy with haemostatic intent.
Participants	52 gastric cancer patients.
Interventions/ Comparators/ Methods	Radiotherapy • 8 Gy 1 fraction- 39 (75%) • 20 Gy, 5 fractions-13 (25%)
Outcomes	• Effective treatment rate in transfusion group 48% (12/29) vs. non-transfusion group 53% (8/15). • Mean haemoglobin pre transfusion was 9.53g/dl with post transfusion level of 10.2g/dl (p<0.01). • Median survival 160 days with 12-month survival of 15%.
Summary of Results	It is concluded that radiotherapy is a good option for patients with gastric bleeding, evidenced by median survival and Hb level pre/ post RT. 8Gy single fraction or 20Gy 5 fractions appear to provide similar response rates to those with higher doses.
Appraisal Summary	This study describes a series of patients who all appear to have benefitted from RT. Limitations: • Data collected from a single institution • Larger sample size would provide more evidence of the efficacy of this treatment • To evaluate the effectiveness a control group not receiving radiotherapy would provide useful evidence • Data regards to the effect of treatment on quality of life would have been valuable though such data are difficult to gather from frail patients.

Table 1: Characteristics of Included Studies (in alphabetical order)

Hussein et al. 2021	**Study Design and Setting** - Disease Registry observational study, 17 Gastroenterology Centres (United Kingdom, United States, France, Germany, and Spain).
Study Objective	To assess immediate haemostasis rates and re-bleeding rates following endoscopic treatment with the hemostatic powder Hemospray in patients with bleeding associated with an Upper GI malignancy.
Participants	105 patients with upper gastrointestinal bleeding. Type of cancer: 66% stomach 29% oesophageal 6% duodenum.
Interventions/ Comparators/ Methods	Hemospray monotherapy or Hemospray adjunct to other therapies. (Use of Hemospray was at physicians' discretion).
Outcomes	Immediate hemostasis defined as complete cessation of bleeding within 5 mins as observed at endoscopy. Re-bleeding: Defined as a drop in haemoglobin of > 2g/l or new melaena or haematemesis with haemodynamic instability or requirement for further blood products following index treatment with Hemospray. 30 day all cause mortality.
Summary of the Study Results	• Immediate hemostasis response rate: 97% (N=102/105) • Re-bleeding rate: 15% within 30 days • Thirty-days mortality: 20% (all-cause)
Appraisal Summary	A prospective longitudinal registry study with clearly reported outcomes. Limitations: • Study has high risk of selection bias as endoscopists had discretion over whether to apply Hemospray and data on why was not collected. • Lack of a control/comparator group. • Missing data on re-bleeding and mortality (which could have affected the overall results) and direct cause of mortality was not collected for patients. Conflict of interest also declared. The study is ongoing until 2026.

Table 1: Characteristics of Included Studies (in alphabetical order)

Kim et al. 2013	**Study Design and Setting:** Case Series, National Cancer Centre, Korea.
Study Objective	To evaluate the efficacy and clinical outcomes of endoscopic therapy (ET) for upper gastrointestinal bleeding (UGIB) from unresectable advanced gastric cancer
Participants	113 gastric cancer patients.
Interventions/ Comparators/ Methods	Endoscopic therapy: • Electrocoagulation - argon plasma coagulation • Clipping • Injection - epinephrine injection 1:10000, alcohol 99% • Haemostatic agent - thrombin, sodium alginate
Outcomes	• Immediate haemostasis rate 92.9% (105/113) • Early re-bleeding rate (<3 days after initial haemostasis) 44.2% (19/43) • Late re-bleeding rate (>3 days after initial haemostasis) 55.8% (24/43) • Re-intervention rate 53.5% (23/43); 18 had repeat ET, 4 had surgery and 1 had TAE • Mean in-patient stay was 9.7 days • 30 day mortality rate 15.9% • Median survival 3.2 months; early re-bleeding at 1 month vs. late re-bleeding at 3.1 months (p=0.004) • Red cell concentrate transfusion of >5 units was associated with early re-bleeding, p=0.04
Summary of Results	Endoscopic electrocoagulation should be considered as a primary treatment for UGIB from unresectable advanced gastric cancer (immediate haemostasis rate 93%).
Appraisal Summary	This study is a large-scale study to evaluate ET as a primary treatment for UGIB. Limitations: • It is a retrospective study. • Study was performed at a single cancer centre. • Efficacy comparisons between ET methods cannot be evaluated due to electrocoagulation use in most patients.

Kim et al. 2017	**Study Design and Setting:** Randomised Controlled Trial, 3 tertiary hospitals (National Cancer Center, Pusan National University Hospital, and Kosin University College of Medicine, Korea).
Study Objective	To investigate the effects of proton pump inhibitor (PPI) treatment (lansoprazole) for the prevention of gastric tumour bleeding.
Participants	130 gastric adenocarcinoma patients (64 placebo control; 66 PPI intervention).
Interventions/ Comparators/ Methods	Proton pump inhibitor oral lansoprazole (30mg) once daily from the time of randomization OR Placebo control.
Outcomes	Primary outcome: A tumour bleeding event in the intention-to-treat population: defined as a drop in haemoglobin of more than 2g/dl in one week with endoscopic evidence of tumour bleeding; a drop in haemoglobin of more than 3 g/dl in three weeks with endoscopic evidence of tumour bleeding; presentation with melaena or haematemesis confirmed by medical personal. Secondary outcomes: Transfusion requirement following randomization: defined as the proportion of patients in each group requiring a transfusion.
Summary of Results	There were no significant difference in tumour bleeding events between the intervention and control groups: 7.8% PPI group versus 9.5% in placebo group during a median follow up time of 6.4 months (p=0.515). During the follow up period there was no significant difference in proportions of patients requiring a blood transfusion.
Appraisal Summary	RCT design, double blind and placebo controlled. However, sufficient sample size wasn't reached to achieve the power target meaning that the true significance of any result could not be determined. Loss to follow up was large and there was a lack of description of rates of missing data, how missing data was handled and also on compliance with the intervention. Also, a higher % of control group received treatment with chemotherapy. Although not statistically significant, this could have had an effect on the outcome.

Table 1: Characteristics of Included Studies (in alphabetical order)

Koh et al. 2013	**Study Design and Setting:** Case Series, Chonbuk National Hospital Gastroenterology Department, Korea.
Study Objective	To evaluate predictive factors for endoscopic haemostasis failure and to differentiate which hemostasis procedure is more effective for advanced gastric cancer with bleeding.
Participants	45 gastric cancer patients.
Interventions/ Comparators/ Methods	a) Endoscopy therapy: • Epinephrine injection • Haemoclipping • Electrocoagulation - argon plasma coagulation b) Transarterial embolization
Outcomes	• Mean blood transfusion requirement 2.38 units • 30-day mortality 18.8%
Summary of Results	Small bleeding lesions of <2cm and exposed vessels in the bleeding site of gastric cancer indicated that endoscopic haemostasis would be an effective modality. Transarterial embolisation is recommended for larger bleeding lesions >2cm with non-exposed vessel in the bleeding site.
Appraisal Summary	Limitations: • This study was a retrospective analysis • Single centre study • Small sample size • Differences in the patients' conditions may have affected the survival rates

Lee et al. 2017	**Study Design and Setting:** Case Series, St. Mary's Hospital, Seoul, Korea.
Study Objective	To assess the outcomes and prognostic factors associated with palliative external beam radiotherapy (EBRT), administered to patients with advanced gastric cancer.
Participants	42 patients with advanced gastric cancer (78.6% adenocarcinoma; 21.4% others) over a 23-year period.
Interventions/ Comparators/ Methods	External Beam Radiotherapy ranging from 14 Gray to 50 Gray in differing fractionation schedules. 29 had targeted radiotherapy to part of the gastric bed; the remaining 13 had radiotherapy to the whole stomach.
Outcomes	Resolution of bleeding which was poorly defined but appeared to be a combination of resolution of symptoms such as haematemsis or melaena and the need for a further form of management to control bleeding.
Summary of Results	Overall response in terms of bleeding resolution was 69% (N = 29/42). Re-bleeding rate: 37% (N = 11). Median re-bleeding free survival: 14.9 weeks (95% CI = 11.87–17.93 weeks). Overall survival: median overall survival was 12.6 weeks (from any cause). Median radiotherapy dose: 40Gy in responders versus 21Gy in non-responders. The analysis suggested that a radiation dose of >36Gy was significantly associated with a bleeding cessation in patients with gastric cancer. Those who responded to EBRT had better overall survival than those who did not.
Appraisal Summary	Overall limitations include those of a single institution retrospective review, with no comparator group. The review period covered 23 years, with a small overall number of patients and significant variations in how radiotherapy was administered. Possibility that selection bias may have occurred for those with better performance (may have been given higher doses of radiation leading to better response). The definition of outcomes was poorly described and there was no information on the amount of missing data.

Table 1: Characteristics of Included Studies (in alphabetical order)

Lee et al. 2021	**Study Design and Setting:** Case Series, Yonsei Cancer Center, Korea
Study Objective	To investigate the efficacy of radiotherapy for palliation of gastric bleeding from gastric cancer and to identify an optimal radiotherapy strategy.
Participants	57 patients with gastric cancer (91.2% adenocarcinoma; 8.8% signet ring cell carcinoma) from a single institution over a 10 year period.
Interventions/ Comparators/ Methods	Palliative radiotherapy ranging in dose from 23.6-58.5 Gray in differing fractionation schedules. All but one patient received three dimensional conformal radiotherapy. No comparator group.
Outcomes	• Resolution of symptoms: defined as subjective reporting of melaena or haematemesis. • Cumulative re-bleeding rate: defined as time from radiotherapy completion to haemoglobin level dropping below 7g/dl or receipt of a blood transfusion. • Median time to re-bleeding: defined from the time of completion of radiotherapy, using the criteria described above.
Summary of Results	Resolution of symptoms: 75.4% showed subjective improvement in symptoms of bleeding at one month. Cumulative re-bleeding rate: 60.2% at 3 months. Median time to re-bleeding: 6.4weeks. Patients whose bleeding was controlled within 3 months after RT completion showed a significantly improved overall survival: 15.4 weeks in patients without re-bleeding versus 10.0 weeks in patients with re-bleeding (p=0.048).
Appraisal Summary	Nature of retrospective cohort study design could introduce selection bias. Prescription of radiotherapy was down to the individual physician and varied significantly between patients. Post-radiotherapy treatment with systemic chemotherapy (37 patients received chemotherapy either during or after radiotherapy) could also have affected the outcome and this was not appropriately analysed.

Maluf-Filho et al. 2013	**Study Design and Setting:** Case Series, Cancer Institute, University of Sao Paulo, Brazil.
Study Objective	To study the causes of bleeding in cancer patients and characterise outcomes after bleeding episodes. To describe the role of endoscopy in upper GI cancer bleeding.
Participants	41 upper gastrointestinal cancer patients.
Interventions/ Comparators/ Methods	For patients with tumour-related bleeds: • 7/41 had endoscopic treatment. • 34/41 did not receive it.
Outcomes	• Immediate haemostasis rate 85.7% (6.7). • Re-bleeding rate in endoscopic group 28.5% (2/7) vs. control 14.7%(5/34). • Mean length of in-patient stay 8 days. • 30-day mortality 43.9%. • Median survival 26 days.
Summary of Results	Well-described patient group with explicit grouping between those cancer patients whose upper GI bleed related to tumour or not. In those with upper GI cancers, the likelihood of a tumour related bleed was more than 90%. Re-bleeding, 30-day mortality and length of hospital stay rates did not differ between any of the groups. Re-bleeding and mortality rates in particular did not differ in the tumour bleeding groups between those who received or did not receive endoscopic treatment. Although the numbers are small this underlines the lack of evidence base for endoscopic management of this patient group, and suggests that at present the main role for endoscopy is to define the nature of the bleeding.
Appraisal Summary	Limitations: • Data collection from a single institution. • Lack of information on co-morbidities, transfusion rates and non-endoscopic management. • Consisted of a small numbers of tumour-related bleeds.

Table 1: Characteristics of Included Studies (in alphabetical order)

Martins et al 2016	**Study Design and Setting:** Case Series, Cancer Institute, University of Sao Paulo, Brazil.
Study Objective	To evaluate the efficacy of argon plasma coagulation (APC) for the treatment of upper gastrointestinal bleeding from malignant lesions.
Participants	52 upper gastrointestinal cancer patients.
Interventions/ Comparators/ Methods	Argon plasma coagulation - 25 pts
Outcomes	• Immediate haemostasis APC group 73.3% (11/15) • Re-bleeding rate in APC group 33.3% (8/24) vs. control 14.3% (4/28); note higher number of active bleeding in APC 62.5% (15/24) vs. control 14.3% (4/28). • Re-intervention rate in APC 37.5% (9/24) vs. control 28.6% (8/28). • 30-day mortality in APC 20.8% (5/24) vs. control 42.9% (12/28), p=0.091.
Summary of Results	Endoscopic haemostasis of UGI malignant bleeding with APC has no significant impact on re-bleeding rate or 30 days mortality date irrespective of patients' performance status.
Appraisal Summary	This study suggests similar re-bleeding and 30 day mortality rates for patients treated with APC compared to historical controls. It underlines the lack of an objective evidence base for its use. Limitations: • Bias in the historical control – lack of APC may have indicated less well patient group. • Much higher rate of active bleeding in the prospective APC group. • Lack of information on confounders such as comorbidities, cancer treatment and stage of disease. • Single institution study. • Small sample.

Meng et al. 2019	**Study Design and Setting: Retrospective multicentre cohort study at the University of Ottawa and Calgary.** .
Study Objective	Investigate the efficacy, safety and mortality associated with the use of the haemostatic powder Hemospray (TC-325) for the treatment of Metastatic Upper GI Bleeding.
Participants	25 patients with metastatic upper-gastrointestinal bleeding identified covering a 4 year period: 36% oesophageal cancer, 52% stomach cancer, 28% small bowel cancer.
Interventions/ Comparators/ Methods	TC-325 (Hemospray) administration at time of endoscopic intervention for upper GI bleeding.
Outcomes	Immediate haemostasis response rate and at 7 and 14 days. Haemostasis was defined as a lack of re-bleeding which would have resulted in clinical evidence of haematemesis or melaena, or hemodynamic instability and decrease in haemoglobin levels by 20 g/L after two consecutive stable haemoglobin values. 30 day mortality. Overall survival.
Summary of Results	• Immediate haemostasis response rate: 88% at 24 hours • Haemostasis retained: 50% of patients at 14 days • Re-bleeding rate: 16% within 30 days • 30-day mortality: 48% • Overall survival: 52% at 30 days No adverse effects were identified in association with use of TC-325 in the small cohort reviewed. Immediate haemostasis achieved at high levels within 24 hours and retained in 50% of patients after 2 weeks.
Appraisal Summary	This is a small retrospective review of 25 patients with significant risk of bias that this approach entails. Although the authors sought to identify patients through a variety of mechanisms, the completeness of the cohort is unclear, and the degree of missing data identified during the case note reviews is not discussed. Eight of the patients had other adjunctive endoscopic therapy at the time of Hemospray application so the effective intervention is unclear, and three patients also went on to have surgical intervention at a later date.

Table 1: Characteristics of Included Studies (in alphabetical order)

Saito et al. 2021	**Study Design and Setting: Prospective observational multicentre study.**
Study Objective	To investigate treatment response after palliative radiotherapy for bleeding gastric cancer and whether higher biologically effective dose is associated with survival, bleeding response or re-bleeding.
Participants	53 patients with gastric cancer (95% adenocarcinoma, 5% other cancer types) were recruited from 15 centres over 3 years.
Interventions/ Comparators/ Methods	Palliative radiotherapy in a median total dose of 20 Gray (8-45 Gray) within a median of 2 days from enrolment. Dosing schedule was at discretion of treating physician.
Proposed Outcomes	Primary endpoint: bleeding response rate at 4 weeks. Bleeding response rate was defined as haemoglobin level was ≥ 8.0 g/dL; 7 consecutive days without blood transfusion anytime between enrolment and blood sampling; no requirement for local salvage treatment for bleeding gastric cancer. Re-bleeding was defined as the need for a blood transfusion or local salvage treatment. Secondary outcomes included: • 30 day mortality. • Overall survival. • Proportion of patients completing treatment.
Summary of Results	53 patients received at least one fraction of radiotherapy and 50 completed the intended radiotherapy dose. The per protocol response rate at 4 weeks was 65% Re-bleeding rate: 32% 30-day mortality: 11% Median follow up was 12 months and median survival was 2.3 months. There was no dose-response relationship between either bleeding response or survival.
Appraisal Summary	This was a well protocolized prospective study with a pragmatic approach to recruitment and dosing schedule. The patient population had an advanced stage of disease with a short median survival. The majority of patients received the intended treatment regimen (50 of 53 who received any radiotherapy) but the study did not recruit to target (target sample size of 60). Evidence appears strong and largely reliable although there is no discussion of the degree of missing data or how that was handled. The ability to look at dose-response relationships is hampered by the small patient numbers as is the impact on survival.

Sheibani et al 2013	**Study Design and Setting:** Case Series, Los Angeles County and University of Southern California Medical Center, USA.
Study Objective	To determine the presentation, endoscopic findings, treatment and outcomes in patients with UGIB from malignant tumours and identify risk factors associated with re-bleeding.
Participants	106 upper gastrointestinal cancer patients.
Interventions/ Comparators/ Methods	Endoscopic therapy: • Ethanol injection - 5 pts (36%) • Epinephrine injection - 5 pts (36%) • Bipolar electrocoagulation - 1 pt (7%) • Argon photocoagulation - 1 pt (7%) • Epinephine + bipolar coagulation - 1 pt (7%) • Ethanol + clip - 1 pt (7%)
Outcomes	• Immediate haemostasis rate 86% (12/14) • Early re-bleeding rate (within 72 hours of index bleed) 7% (1/14) and delayed re-bleeding rate (^{3}72 hours after index bleed 49% (50/103). Supercript 3—Is this meant to say 372 hours? • Median time to re-bleeding 30 days. • Mean blood transfusion requirement 2 units with 75% requiring blood transfusion during delayed re-bleeding • Re-intervention rate 36% (18/50); 11 surgery, 2 radiotherapy, 4 TAE, 1 endoscopy.
Summary of Results	Patients with UGI malignant bleeding have substantial blood loss with three quarters requiring transfusion at presentation. Initial haemostasis occurs in almost all patients, with or without endoscopic therapy but re-bleeding requiring repeat hospitalisation occurs in approximately half the patients. Risk factors for re-bleeding include £ 60 years of age and haemodynamic instability. Was £ meant to be a different symbol: ≥/>?
Appraisal Summary	Limitations: • Due to the large proportion of racial/ethnic minorities and lower socioeconomic status patients, population may not be generalisable.

Table 1: Characteristics of Included Studies (in alphabetical order)

Shin et al. 2021	**Study Design and Setting:** Retrospective cohort study at a single institution in South Korea.
Study Objective	To evaluate the hemostatic effect of the application of the haemostatic powder UI-EWD for the treatment of Upper GI tumour bleeding
Participants	41 patients with upper-gastrointestinal tumour bleeding (80.5% adenocarcinoma, 4.9% squamous carcinoma, 12.2% GIST, 2.4% lymphoma) at a single institution.
Interventions/ Comparators/ Methods	UI-EWD hemostatic spray applied at the time of endoscopy for assessment of upper GI tumour bleeding
Proposed Outcomes	• Immediate haemostasis was defined as hemostasis achieved within 5 minutes and confirmed on visual inspection. Re-bleeding was defined as clinical evidence of bleeding such as melaena or haematemesis with an associated reduction of 2 g/dL within 30 days of endoscopy. • Time to re-bleeding was defined by time from endoscopy to re-bleed using the criteria above. • Six-month cumulative survival rate.
Summary of Results	• Immediate haemostasis response rate: 98% • Re-bleeding rate: 22.5% at 28 days • Time to re-bleeding: median of 10 days • Six-month cumulative survival rate: 73.2% • Overall, demonstrated a high immediate hemostasis response rate (98%) with a relatively low re-bleeding rate. No adverse effects recorded, demonstrating safety of use in patients.
Appraisal Summary	Small patient numbers, lack of a comparator group and the retrospective nature of the study imply the risk of potentially significant bias. Of the 41 patients, 23 had the hemostatic powder as a monotherapy and 18 had it as a salvage after other therapies. Those who had it as a mono therapy appear in the results to have a higher re-bleeding risk and appeared to re-bleed sooner.

Sugita et al. 2021	**Study Design and Setting: Retrospective Cohort study, Saitama Medical University Hospital,** Saitama **Japan**
Study Objective	To retrospectively assess the impact on hemostasis of radiotherapy for gastric cancer bleeding.
Participants	Thirty-three patients with gastric cancer who received radiotherapy as part of the management of upper GI tumour bleeding.
Interventions/ Comparators/ Methods	Radiotherapy: 25 patients received 30 Gray/10 fractions with the remaining eight receiving a variety of schedules ranging from 8Gray/one fraction to 20 Gray/10 fractions. Dosing schedule was at the discretion of the treating physician.
Proposed Outcomes	Hemostasis response rate was defined as >1 month following radiotherapy, patient was alive, and no evidence of further treatment needed). Re-bleeding rate which was defined by clinical evidence such as hematemesis or melaena, blood transfusion or receipt of another hemostatic intervention within the one month period. Overall survival.
Summary of Results	Hemostasis response rate: 73% (defined as >1 month following radiotherapy, patient was alive, and no evidence of further treatment needed). Re-bleeding rate: 21% of responders. Median re-bleeding survival: 149.5 days. High hemostasis response rate with moderate re-bleeding. Radiotherapy appears to have a positive effect on upper gastrointestinal bleeding in patients with gastric cancer.
Appraisal **Summary**	Overall, this study seems to show that RT may help with gastric cancer bleeding. However, the study did not clearly identify the design. Title states 'case-control' but data presented more as a retrospective cohort. Additionally, the authors did not identify any limitations within the study itself. There was also no consideration of potential bias and being retrospective in nature, there is the potential for selection bias.

Table 1: Characteristics of Included Studies (in alphabetical order)

Tey et al 2014	**Study Design and Setting:** Case Series, National Cancer Institute, Singapore.
Study Objective	The aim of this study was to report the outcome of palliative RT in patients with symptomatic locally advanced or recurrent gastric cancer managed with modern RT techniques.
Participants	115 gastric cancer patients.
Interventions/ Comparators/ Methods	Radiotherapy for 115 patients between 8-Gy single fraction to 40Gy/16 fractions.
Outcomes	• Effective treatment rate 80.6% (83/103) • Re-bleeding rate 30.1% (25/83) • Median time to re-bleeding 99 days • Median survival 85 days; responders to RT at 113.5 days vs. non-responders to RT at 47 days (p<0.001)
Summary of Results	It concluded that external beam radiation therapy, delivered using modern RT techniques, is an effective and well-tolerated modality in the local palliation of gastric cancer, with lasting palliation of local symptoms.
Appraisal Summary	Limitations: • A retrospective study. • Dose fractionation regimens were heterogeneous, including 8 different fractionation regimens. • Single institution study.

Yu et al. 2021	**Study Design and Setting:** Case Series, Asan Medical Centre, Korea.
Study Objective	To analyse the clinical outcomes of patients with unresectable advanced gastric cancer who received palliative radiotherapy for bleeding control.
Participants	61 patients with advanced gastric cancer (91.8% tubular adenocarcinoma, 8.2% signet ring cell carcinoma).
Interventions/ Comparators/ Methods	Palliative radiotherapy.
Proposed Outcomes	• Hemostasis rate: 88.5% of patients. • Median haemostasis time: 13 days (range 1-68 days). • Re-bleeding rate: 35%. • Median time to re-bleeding: 6 months. • Median overall survival: 4.8months [95% CI= 3.7-5.9 months].
Summary of Results	Overall, radiotherapy appeared to provide a high hemostasis rate for bleeding. However, high re-bleeding rate (in 1/3 of the population) showing potential short-term efficacy.
Appraisal Summary	Seems a reliable study largely. However, seems a long study period – 16 years, with low number of patients. Treatments may have changed in this time e.g. endoscopy treatment, RT, chemo therapies etc. Results of Hb appears to show it is rising but does not state if these patients had transfusions or chemotherapy. Those who had lower Hb may have died in this time.

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What is the most effective treatment in achieving early haemostasis and preventing or delaying re-bleeding in cancer patients suffering from upper GI bleeds? A rapid review.

Additional materials available upon request:

- Critical appraisal / data extraction forms
- Search strategies
- List of excluded studies

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Disclaimer: Palliative Care Evidence Review Service (PaCERS) is an information service for those involved in planning and providing palliative care in Wales. Rapid reviews are based on a limited literature search and are not comprehensive, systematic reviews. This review is current as of the date of the literature search specified in the Review Methods section. PaCERS makes no representation that the literature search captured every publication that was or could be applicable to the subject matter of the report. The aim is o provide an overview of the best available evidence on a specified topic using our documented methodological framework within the agreed timeframe.