Haemostatic radiotherapy for bleeding cancers of the upper gastrointestinal tract

ABSTRACT

Bleeding can cause significant morbidity in patients with upper gastrointestinal malignancies. Palliative radiotherapy can palliate bleeding effectively across numerous cancer sites such as the lung and rectum. The data available regarding the role in bleeding from upper gastrointestinal cancers are limited to a single meta-analysis, a phase 2 trial, eleven retrospective cohorts and two case reports, with the majority focusing on gastric cancer. From the data available radiotherapy appears to be a well-tolerated, effective haemostatic agent that should be considered in all patients with bleeding from an upper gastrointestinal malignancy. Questions remain regarding the radiobiology of haemostasis and the optimum fractionation schedule. There is no convincing evidence that protracted higher dose regimens provide additional benefit. Commonly used fractionation schedules use 1, 5 or 10 fractions. Short fractionation schedules have been used in patients with deteriorating performance status.

Upper gastrointestinal malignancies are a common cause of morbidity and mortality globally. There are on average 9101 and 6697 new diagnoses of oesophageal and gastric cancer every year (the cancers with the 14th and 17th highest incidence) in England. They are aggressive and present late – 34% of gastric and 30% of oesophageal cancers present with stage 4 (metastatic) disease and the overall 5-year survival is 18.9% (gastric) and 15.5% (oesophageal) (Cancer Research UK, 2019). Advanced disease can cause local symptoms such as dysphagia, pain and bleeding that can become debilitating and pose significant challenges in supportive care.

As tumours grow they disrupt the normal organ mucosal surface. Angiogenesis and invasion are hallmarks of cancer, which result in highly vascular lesions with large numbers of chaotic and friable vessels that are prone to bleeding (Hanahan and Weinberg, 2000). This can present with no observable symptoms other than progressive lethargy, anaemia or with more distressing symptoms such as melena and haematemesis (especially if the tumour invades larger blood vessels). Traditionally a haemoglobin level of 70 g/litre is used as the threshold for transfusion (in the absence of symptoms or ischaemic heart disease). Lower levels than this can cause fatigue or breathlessness, precipitate angina and in certain circumstances be life threatening. Correcting this with blood product support can provide temporary relief. However, symptoms are likely to reoccur and because of the risk (allergic reactions, overload) and cost associated with repeated transfusions definitive management is preferred. It is important to note that in patients with large volume active bleeding or who are exhibiting signs of shock (stage 1 shock can be as simple as a resting tachycardia) there is no role for immediate radiotherapy as haemostasis is not immediate and the associated toxicity could increase morbidity. These patients need to be stabilized with resuscitation, blood product support and input from radiology and endoscopy teams before referral to oncology teams.

Treatment options

Decisions regarding the treatment of a patient who presents with bleeding from an oesophageal or gastric cancer depend on the histological subtype, whether the disease is operable, patient preference, performance status and overall fitness.

Many patients are not suitable for treatment strategies with curative intent as a result of the disease stage at presentation or coexisting medical problems (the risk factors for upper gastrointestinal cancer include age, obesity, alcohol consumption and smoking). This review focuses on the evidence for palliative (non-curative) radiotherapy to an upper gastrointestinal malignancy to control bleeding.

Palliative radiotherapy to the upper gastrointestinal tract is delivered using a parallel pair of radiotherapy fields (anterior and posterior) (*Figure 1*). A radiotherapy beam is delivered using a linear accelerator. Initially patients require a radiotherapy planning computed tomography scan; using this scan clinical oncologists create a treatment field encompassing the gross tumour volume with a margin to account for microscopic tumour spread, internal organ motion (i.e. during breathing) and variation in day-to-day patient positioning called planned treatment volume.

Radiotherapy as a haemostatic agent

There is a wealth of evidence across different cancer sites that radiotherapy is an effective haemostatic agent. Evidence going back as far as 70 years in the form of a case series from the MD Anderson Hospital, Texas, published in 1979, showed effectiveness of palliative radiotherapy to control the symptoms of advanced pelvic malignancies (Boulware et al, 1979). There is high quality meta-analysis evidence that bleeding secondary to non-small cell lung

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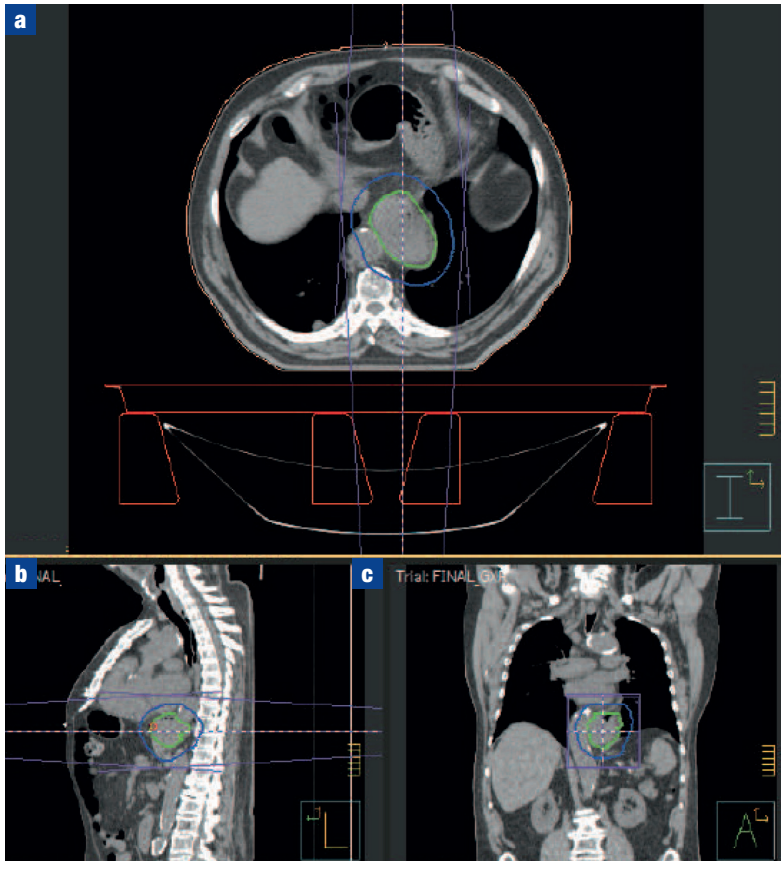

Figure 1. Patient receiving palliative radiotherapy to the gastro-oesophageal junction for a gastrointestinal stromal tumour with 20 Gy delivered in five fractions. **a.** Radiotherapy planning computed tomography scan transverse beam arrangement of a parallel opposed pair with the bleeding tumour visible as the gross tumour volume in green and the planned treatment volume in blue. **b.** Coronal and **(c)** sagittal view of the beam arrangement, gross tumour volume and planned treatment volume.

Table 1. Retrospective studies showing effectiveness of palliative radiotherapy to control bleeding

Study	Response to palliative radiotherapy % (no)	Reduced need for further transfusion	Increase in haemoglobin level
Walls et al (2017)	58% (15/26)	Yes	Not reported
Hashimoto et al (2009)	68% (13/19)	Not reported	Not reported
Lee et al (2017)	69% (29/42)	Not reported	Not reported
Kim et al (2008)	70% (14/20)	Not reported	Not reported
Kondoh et al (2015)	73% (11/17)	Yes	Yes
Asakura et al (2011)	73% (22/30)	Yes	Not reported
Chaw et al (2014)	75% (22/44)	Yes	Yes
Kawabata et al (2017)	75% (figures not given)	Yes	Yes
Navalpotro et al (2014)	85% (17/20)	Yes	Yes
Hiramoto et al (2018)	88% (figures not given)	Not reported	Not reported
Tey et al (2014)	81% (83/103)	Yes	Not reported

cancer (Fairchild et al, 2008; Stevens et al, 2015) and locally advanced rectal cancer (Cameron et al, 2016) can be well managed with palliative radiotherapy.

How does radiotherapy stop bleeding in cancer?

Radiotherapy uses high energy (mega voltage) X-rays in the order of 6–10 MV (standard diagnostic X-ray energy is 125 KV). X-rays are a form of ionizing radiation. The target for radiotherapy is the cellular DNA of the cancer cells. DNA damage is caused by ionizing radiation either directly to the DNA or indirectly (the majority) through the production of hydroxyl radicals by ionization of water. In cancer cells with poorly functioning DNA repair systems this damage disrupts DNA and chromosome structure which proves fatal to the cell as it divides.

The radiobiological process of haemostasis by ionizing radiation is poorly explained in the literature. The principle of DNA damage, cell death, scarring and reduction of the tumour bulk can in part explain the effect of radiotherapy on bleeding. Ionizing radiation is also felt to induce a prothrombotic state (Goldin-Lang et al, 2007). The mechanism by which it does this could include secretion of prothrombotic factors such as tissue factor (Goldin-Lang et al, 2007) and von Willebrand factor (Jahroudi et al, 1996). Capillaries appear to be the most radiosensitive part of the vascular system because they contain endothelial cells. A review of the pathological assessment of post-radiation tissue has shown inflammation of the capillary bed, thrombosis, detachment of endothelial cells from plasma membrane and loss of large portions of capillary segments (Fajardo, 2005). Extrapolating from this, these changes could explain ischaemia in normal tissues (contributing to long-term side effects), and haemostasis in tumour tissue.

Upper gastrointestinal malignancies

A literature search undertaken using the key words oesophagus, gastric, gastro oesophageal junction, palliative, radiotherapy and bleeding identified 139 articles. Irrelevant, duplicate and non-English language (one) papers were excluded. There was one relevant non-comparative prospective phase 2 trial, 11 retrospective cohorts, two case reports and one meta-analysis. Based on the Oxford classification of evidence there is no level 1 or 2 evidence available (Howick et al, 2011).

There is a lack of robust controlled trial evidence for the role of palliative radiotherapy in upper gastrointestinal malignancies (*Table 1*). The majority of the evidence available is from single institution retrospective observational case series and related to gastric malignancies. The only phase 2 trial found in this literature search was performed by Tey et al (2019) who performed a single arm trial of 50 patients with proven gastric adenocarcinomas using 35 Gy in 12 fractions. The management of bleeding was a primary outcome – 80% (40/50) of patients with problematic bleeding had

a measurable and durable response (median duration 102 days) to radiotherapy. A response to radiotherapy was defined as no further requirement for blood transfusion and no further symptoms (e.g. melena).

Tey et al (2014), Walls et al (2017), Kawabata et al (2017), Kondoh et al (2015), Hiramoto et al (2018), Lee et al (2017), Hashimoto et al (2009), Kim et al (2008), Navalpotro et al (2014) Asakura et al (2011) and Chaw et al (2014) all performed small (between 17 and 39 patients) single centre retrospective cohorts looking specifically at gastric cancer. All patients had inoperable gastric malignancies and all treatment was with palliative intent. The majority of patients received palliative radiotherapy alone although some studies included patients who had received concurrent (Kim et al, 2008; Kondoh et al, 2015; Hiramoto et al, 2018) chemotherapy and radiation with various regimens including 5-flourouracil alone (Kim et al, 2008), weekly paclitaxel, weekly paclitaxel and trastuzumab, methotrexate and 5-fluorouracil (5-FU), low-dose cisplatin and 5-FU, and FOLFOX (oxaliplatin, folinic acid and 5-FU)(Kondoh et al, 2015). These patients were in the minority.

The majority of studies primarily assessed response to bleeding. Tey et al (2014) and Kim et al (2008) were looking at palliative radiotherapy more generally but reported specific response rates to bleeding. All studies demonstrated a benefit (*Table 1*). Although it was the largest study of palliative radiotherapy for gastric cancer, Walterbos et al (2019) had low numbers of patients with haemorrhage and did not report the specific response in this group.

The only meta-analysis was performed by Tey et al (2017). The pooled meta-analysis estimated a response rate of 74% to bleeding and did not find a difference between radiotherapy dosing schedules (high dose *vs* low dose). This included seven of the retrospective trials previously mentioned. Papers by Kawabata et al (2017), Walls et al (2017) and Hiramoto et al (2018) were published after publication of this meta-analysis. The only publication missing from the meta-analysis was by Navalpotro et al (2014) which was a small study (20 patients) where all patients received 30 Gy in 10 fractions. Results were in keeping with other studies with efficacy assessed using an increase in median haemoglobin levels 1 month and 3 months after radiotherapy.

Subtypes of oesophageal and gastric carcinoma

The two most common pathological subtypes of oesophageal cancer are squamous cell carcinoma and adenocarcinoma. Globally the proportion of cases that are squamous cell carcinomas is decreasing, but these remain the most common subtype. Gastric cancers are most commonly adenocarcinomas. Tey et al's (2014) phase 2 trial required patients to have biopsy-proven adenocarcinoma, and other retrospective trials did not specify a histological subtype. There is little trial evidence regarding other histological subtypes of upper gastrointestinal malignancies.

> **“Tissues with rapid turnover ... are more vulnerable to the acute effects of radiotherapy whereas tissues such as blood vessels and nerves are more vulnerable to the long-term side effects”**

Radiotherapy is listed as an option in the palliative management of bleeding from gastrointestinal stromal tumours in the British sarcoma group guidelines (Judson et al, 2017). A retrospective cohort (Cuaron et al, 2013) supports the use of radiotherapy in symptomatic primary and metastatic gastrointestinal stromal tumours but does not state the effect in bleeding. Other histological subtypes are confined to isolated case reports such as a single case of gastric melanoma being treated with radiation alone to successfully manage bleeding (Slater et al, 2014).

Toxicity and consent

Toxicity following radiotherapy should be assessed using a validated scale such as the RTOG (Radiation Therapy Oncology Group) scale. In the phase 2 trial by Tey et al (2019) the most commonly reported side effects were grade 1–2 (controlled by outpatient supportive medication) nausea and fatigue, with two cases of grade 3 (requiring inpatient admission) gastritis and anorexia. Toxicity is difficult to report using retrospective data. The majority of trials reported very low levels of toxicity. Kondoh et al (2015) reported one case of grade 3 nausea and 3 cases of grade 3 anorexia. In the retrospective review by Walterbos et al (2019) toxicity was low with 3.4% of patients having a grade 3 toxicity (oesophageal stenosis ($n=4$), fatigue ($n=3$), oesophagitis ($n=1$) or melena ($n=1$)). The only grade 4 toxicities (life threatening) reported were in Kondoh et al (2015) and Asakura et al (2011) and were related to concurrent chemoradiotherapy. An outlier was Kim et al (2008) who reported 15% grade 3 toxicity.

The only studies to report performance status were Tey et al (2014) and Kondoh et al (2015) where 11/115 (9.6%) and 7/15 (67%) respectively had a performance status of three or lower. With such low numbers it is difficult to assess safety in this patient group, but these studies did not report excess toxicity.

Optimum fractionation schedule

There is a balance in radiotherapy between efficacy and toxicity. Toxicity is caused by the effect of radiation on the normal tissues. Different tissues have different tolerance to radiation. Tissues with rapid turnover (e.g. oesophagus, mouth and skin) are more vulnerable to the acute effects of radiotherapy whereas tissues such as blood vessels and nerves are more vulnerable to the long-term side effects which can affect future organ function (heart, spinal cord and oesophagus). Treatment schedule can influence the side effects that patients experience. Shorter, higher dose treatments increase the risk of acute reactions whereas

KEY POINTS

- Palliative radiotherapy to the oesophagus and stomach is an effective treatment for bleeding tumours in stable patients who do not require active resuscitation.
- The mechanisms by which radiotherapy causes haemostasis are not well established.
- Time from referral to completion of treatment can be a matter of days as treatment can be quickly delivered in a small number of fractions (1–10 treatments), making it appropriate even for patients with a poor performance status and/or active bleeding.
- Palliative radiotherapy is well tolerated with few significant toxicities reported.
- Priority for treatment is to achieve effective clinical palliation of symptoms.
- The prognosis for these patients remains poor. There is no clear evidence that longer higher dose treatment regimens are more effective.

higher doses per fraction increase the risk of long-term side effects. Prolonging treatment can alleviate acute side effects but potentially compromise efficacy.

The published retrospective cohorts demonstrated survival of 2.8 months (Tey et al, 2014), 3.6 months (Asakura et al, 2011) and 3.4 months (Hashimoto et al, 2009) – in the majority of these patients long-term sequelae of radiotherapy are unlikely to have a significant impact on their quality of life. Therefore shorter radiotherapy regimens with higher dose per fraction may be more appropriate if the acute side effects are tolerable. The majority of papers use regimens such as 20 Gy in five treatments or 30 Gy in 10 treatments. However, there is evidence that a single 8 Gy fraction is effective, with 75% (39/52) of patients in the study by Chaw et al (2014) receiving this. Many of the retrospective cohorts suggest that a higher total radiation dose may be associated with an improved survival outcome (Kim et al, 2008; Hashimoto et al, 2009; Asakura et al, 2011; Lee et al, 2017). This needs to be interpreted with caution as with the absence of prospective randomized trial data it is difficult to confirm this effect. Across other tumour sites such as lung cancer despite level 1 evidence (meta-analysis) there is no clear benefit that higher dose regimens are more effective in the palliative setting (Fairchild et al, 2008; Stevens et al, 2015).

It is therefore essential that patients are assessed to determine the most appropriate fractionation schedule of radiation therapy. For patients with poor performance and/or limited projected survival times, shorter treatment schedules, with the aim of optimizing quality of life (e.g. improvements in symptoms of bleeding and anaemia), remain the preferred choice.

Endoscopic and surgical management

Most patients who present with upper gastrointestinal bleeding will have an upper gastrointestinal endoscopy. In the non-malignant setting endoscopic interventions are the first-line interventions to control upper gastrointestinal bleeding. However, the role of endoscopy is more limited in the context of malignancy where clips, injection therapy and argon laser lack effectiveness. A systematic review by Chen and Barkun (2015) identified Hemospray (TC-325) as a potential option in the management of acute upper gastrointestinal bleeding from malignancies. Hemospray is an inorganic molecule that forms a haemostatic barrier when in contact with water. Hemospray is a bridging solution to definitive management such as palliative radiotherapy. The rate of re-bleeding (in the 28 cases in the literature) at 7 days following Hemospray was 25%.

Palliative gastrectomies have been performed to palliate local symptoms including bleeding. The REGATTA trial was performed to compare survival in patients undergoing a palliative gastrectomy in stage 4 gastric cancer (followed by chemotherapy) to chemotherapy alone. This trial was stopped early because of futility in the gastrectomy arm (Fujitani et al, 2016).

Conclusions

Palliative radiotherapy is a widely available treatment for patients who present with upper gastrointestinal bleeding secondary to advanced upper gastrointestinal malignancies. The evidence available to help make decisions is low quality with the majority being non-comparative retrospective cohort studies (level 4). However, from the limited data available it appears that radiotherapy is effective, well tolerated and safe treatment for patients who are haemodynamically stable with symptomatic bleeding. From these retrospective reviews the median survival of these patients is often short. There is no conclusive evidence that high dose prolonged treatment confers benefit to patients and this needs to be considered when deciding treatment strategy. **BJHM**

Conflict of interest: none.

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