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Palliative radiotherapy for bleeding control in patients with unresectable gastric cancer

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Abstract

Introduction: Gastric cancer is a significant global health concern, frequently diagnosed at an advanced, unresectable stage. This often leads to severe symptoms, such as bleeding, pain, and malnutrition, which greatly affect patients' quality of life. Tumor-induced bleeding is a particularly critical issue requiring urgent intervention. While palliative treatments like surgery, endoscopy, and arterial embolization are available, radiotherapy (RT) has become an important non-invasive option for controlling bleeding, especially when other treatments are not viable.

Materials and Methods: This retrospective study reviewed medical records of patients with unresectable advanced gastric cancer who received palliative RT for bleeding control between January 2012 and December 2021 at University Hassan II Hospital. Patients were included if they had a histologically confirmed diagnosis of gastric cancer and confirmed tumor bleeding. Successful hemostasis was defined as survival for at least one month without further bleeding or transfusions. Survival outcomes were analyzed using Kaplan-Meier methods.

Results: The study included 23 patients, with a median age of 59.21 years. Radiation doses ranged from 6.5 to 45 Gy, with a median dose of 32 Gy. Hemostasis was successfully achieved in 86.95% of patients, with a significant increase in hemoglobin levels from a baseline of 7.15 g/dL to 10.72 g/dL post-treatment (p=0.0001). However, two patients experienced re-bleeding during the follow-up period, with a median time to recurrence of 3.3 months. The median overall survival was 15.44 months. Radiation therapy was generally well-tolerated, with mild side effects such as grade 1 anorexia and nausea.

Conclusion: Palliative RT is an effective, well-tolerated treatment for bleeding control in patients with unresectable advanced gastric cancer, providing significant clinical benefits and prolonging survival in certain cases. Further research is necessary to refine radiotherapy strategies for this patient population.

Keywords: Palliative radiotherapy; Unresectable gastric cancer; Bleeding control; Hemostasis; Clinical outcomes

1. Introduction

Gastric cancer remains a major global health concern, ranking as the fifth most common malignancy and the third leading cause of cancer-related mortality worldwide [1]. Although its incidence has shown a decline in recent years, it continues to be a prevalent cancer diagnosis and a leading cause of cancer-related deaths in many regions [2]. The standard treatment for localized gastric cancer involves gastrectomy with extended lymphadenectomy, either alone or

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in combination with perioperative chemotherapy [3, 4]. However, despite surveillance programs aimed at early detection, many patients are diagnosed at an unresectable, advanced stage. These patients often experience severe symptoms, including pain, obstruction, anorexia, vomiting, and malnutrition, all of which significantly deteriorate their quality of life (QoL) [5]. Among these complications, tumor-induced bleeding is particularly concerning, as it can lead to life-threatening anemia, requiring urgent medical intervention [6].

To manage bleeding in advanced gastric cancer, several palliative treatment modalities are available, including surgery, endoscopic interventions, and angiographic procedures [6–10]. While palliative gastrectomy can provide immediate bleeding control, it is an option only for a small subset of patients who are hemodynamically unstable, refractory to conservative measures, and fit for surgery [11.12]. Endoscopic techniques such as laser photocoagulation, argon plasma coagulation, and the application of hemostatic nanopowders have shown efficacy in achieving hemostasis, but their cost and limited availability in resource-constrained settings pose significant challenges [13.14]. Additionally, other endoscopic methods like thermal probes or epinephrine injections can provide temporary bleeding control but often require repeated interventions due to high recurrence rates [15]**.** Arterial embolization has also been explored as a safe and effective method in selected cases [16,17]**.**

Although radiotherapy (RT) is not a primary treatment for gastric cancer, it has been increasingly recognized for its role in controlling tumor-associated bleeding in advanced cases. Studies have reported bleeding control rates ranging from 53% to 80% following palliative RT [18.19]. In cases where surgery and other hemostatic interventions are not feasible, RT emerges as a valuable non-invasive alternative [20.21]**.** This is particularly relevant in developing countries, where access to advanced endoscopic or interventional radiology techniques is often limited, making palliative RT one of the most viable options for bleeding control [22]**.**

Given the limitations of existing therapeutic approaches and the critical need for effective bleeding management in advanced gastric cancer, further research is required to better define the role of palliative RT. This study aims to assess the clinical outcomes of patients with unresectable advanced gastric cancer who received palliative RT, focusing on its efficacy in achieving hemostasis.

2. Material and methods

2.1. Study Design

We conducted a retrospective review of medical records for patients diagnosed with unresectable advanced gastric cancer who received palliative radiotherapy for bleeding control. The study was carried out at the Department of Radiation therapy of University Hassan II Hospital between January 2012 and December 2021.

The inclusion criteria for this study were as follows: Patients had to have a histologically confirmed diagnosis of gastric cancer. Gastric tumor bleeding had to be confirmed by upper gastrointestinal endoscopy. Palliative radiotherapy had to be administered specifically for hemostasis.

Patients who received radiotherapy for indications other than tumor-related bleeding, such as alleviating gastric obstruction or pain, were excluded from the analysis.

2.2. Definition of Hemostasis and Survival Analysis

Successful hemostasis was defined as survival for more than one month following the initiation of radiotherapy, without requiring blood transfusions, experiencing a drop in hemoglobin levels, or showing clinical signs of persistent bleeding, such as melena or hematemesis.

Overall survival (OS) was calculated from the first day of radiotherapy to the date of death or last follow-up. Survival probabilities were estimated using the Kaplan-Meier method.

2.3. Response Assessment

Patients were classified as responders if they met at least one of the following criteria: They had a complete resolution of bleeding symptoms, with no recorded episodes of hematemesis or melena within one month after completing radiotherapy. They survived for at least one month post-radiotherapy without the need for blood transfusions. Their hemoglobin (Hb) levels recorded one month after radiotherapy were higher than the lowest Hb level observed during the one-month period preceding treatment.

2.4. Statistical Analysis

Survival curves were estimated using the Kaplan-Meier method. All statistical analyses were performed using R software (Version 4.3.1).

3. Results

3.1. Patient Characteristics and Treatment

A total of 23 patients were included in the analysis. The cohort was predominantly male, representing 73.9% of the population, with a median age of 59.21 years (range: 39-73). The majority of patients (69.6%) had an ECOG (Eastern cooperative oncology group)performance status of <2 before radiation therapy, indicating relatively preserved functional status, while 30.4% had a poorer performance status (≥2).

Before radiation therapy, 73.9% of patients had locally advanced disease, whereas 26.1% had both locally advanced and metastatic disease. The predominant histological type was tubular adenocarcinoma (73.9%), followed by signet ring cell carcinoma (4.3%) and other histologies (21.7%).

The most frequently reported symptom associated with gastric tumor bleeding was melena, observed in 52.2% of cases, followed by hematemesis in 30.4% of patients. A smaller proportion (17.4%) experienced both melena and hematemesis simultaneously. The median baseline hemoglobin level before radiation therapy was 7.15 g/dL, with a range from 3.6 to 12.5 g/dL.

Regarding treatment, the median radiation therapy dose was 32 Gy, with a range of 6.5 to 45 Gy. Daily fractionation varied between 1.8 and 8 Gy. The majority of patients (81.8%) received additional chemotherapy after radiation therapy, whereas 18.2% did not undergo further systemic treatment. Table 1 summarizes the patient characteristics and treatment details

Table 1 Summary of Patient Characteristics and Treatments

Characteristics	**Number of Patients (%) or Median (Range)**
Gender	
Male	73.9%,
Female	26.1%
Age (Years)	39-73 (59.21)
ECOG Performance Status before Radiation therapy	
<2	69.6%,
≥2	30.4%
Disease Status before Radiation therapy	
Locally advanced	73.9%,
Combined locally advanced and metastatic	26.1%
Histopathology	
Tubular adenocarcinoma	73.9%,
Signet ring cell carcinoma	4.3%,
Other	21.7%
Initial Symptoms	
Melena	52.2%,
Hematemesis	30.4%,
Melena + Hematemesis	17.4%

Baseline Hemoglobin (g/dL)	3.6-12.5 (7.15)
Radiation therapy Dose (Gray)	32 (6.5-45)
Additional Chemotherapy after Radiation therapy	
Yes	81.8%,
No	18.2%

ECOG : Eastern cooperative oncology group

3.2. Bleeding Control

Bleeding control was successfully achieved in 86.95% of patients, demonstrating the efficacy of radiation therapy in managing gastric tumor bleeding. The mean hemoglobin level at two months after the completion of radiation therapy increased significantly to 10.72 g/dL, compared to the baseline value of 7.15 g/dL (p=0.0001), indicating effective hemostasis and recovery of hematologic parameters.

Among the patients who achieved bleeding control, two (8.7%) experienced re-bleeding during the follow-up period. The median time to re-bleeding was 3.3 months, highlighting the potential for recurrence in a small subset of patients despite initial successful treatment. Table 2 presents the statistical comparison of hemoglobin levels before and after radiation therapy.

Table 2 Comparison Between Hemoglobin Levels Before and After Radiation Therapy

	Appariated differences				**t**	**ddl**	**Sig. (bilateral)**
	Mean	**Ecart -Type**	**IC 95% of the difference**				
			Inf	**Sup**			
Baseline Hb level (g/dL) – Hb after radiotherapy (g/dL)	-3.5696	2.1775	-4.5112	-2.6280	-7.862	22	*0.0001*

3.3. Survival Outcomes and Follow-Up Results

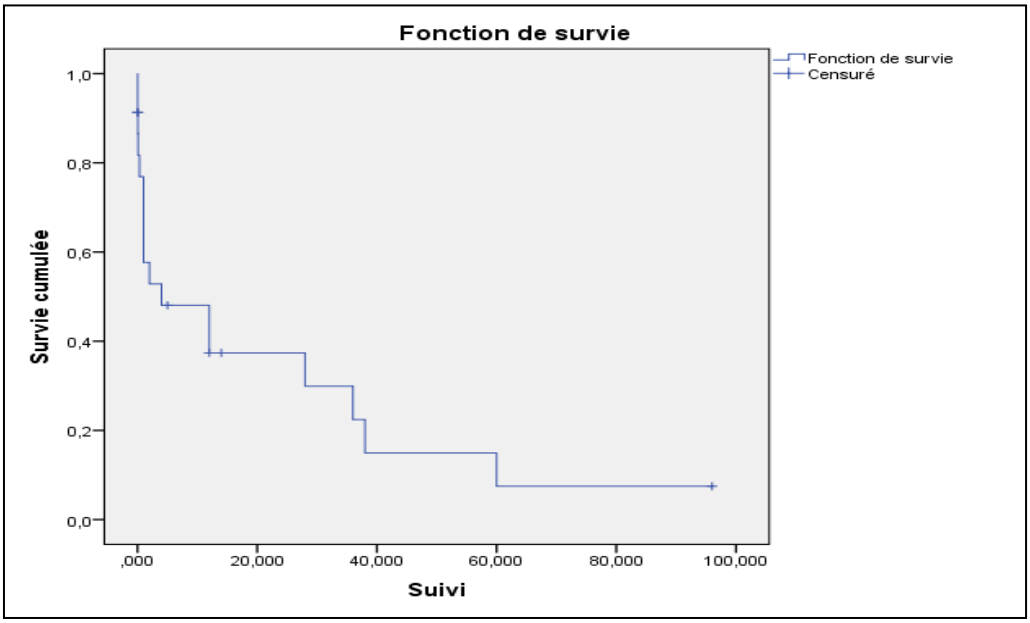

Figure 1 Overall Survival

The median follow-up period for the cohort was 14.07 months. The median overall survival (OS) was 15.445 months, as depicted in Figure 1. These results suggest that palliative radiation therapy for hemostasis in patients with

unresectable gastric cancer does not only provide bleeding control but may also contribute to prolonged survival in select patients.

3.4. Treatment-Related Toxicity

The toxicity profile of radiation therapy in this cohort was generally mild. Only one patient developed acute grade 2 esophagitis, which was managed symptomatically. Other treatment-related side effects, including anorexia, nausea, fatigue, and abdominal pain, were mostly grade 1 and effectively controlled with medication. Importantly, no grade 3 or higher toxicities were observed, confirming the tolerability of palliative radiation therapy in this setting.

Overall, these findings suggest that palliative radiation therapy is an effective and well-tolerated approach for bleeding control in patients with advanced gastric cancer, with significant improvements in hemoglobin levels and an acceptable safety profile.

4. Discussion

Endoscopic hemostasis is the preferred approach for managing bleeding in advanced gastric cancers, achieving initial success in many instances [8.23.24]. However, recurrence rates of bleeding are notably higher in cancers involving tumors, compared to benign ulcers, where recurrences are less common [9, 25]. The efficacy of endoscopic procedures is restricted by factors such as the lesion's location, size, and the nature of the bleeding (e.g., severe or widespread) [7, 10, 26]. In advanced gastric cancers, bleeding is frequently linked to tumor infiltration, making endoscopic treatments inadequate for long-term control. In such cases, transcatheter arterial embolization (TAE) is often considered as an alternative after failed endoscopy. This procedure, however, comes with challenges, including the need to accurately locate the bleeding site and the technical skill required [7, 27].

Radiotherapy (RT), typically used as palliative care, has shown significant effectiveness in controlling bleeding, likely due to its direct impact on reducing tumor mass and stabilizing blood vessels [18]. Although the relationship between radiation dose and bleeding control remains debated, some studies indicate that a biologically effective dose (BED10) ≥ 36 Gy is significantly linked to improved bleeding control [18]. In contrast, other studies do not report a significant difference in response rates between lower and higher doses [28]. Studies by Chaw et al. [29] and Kawabata et al. [30] also suggest that relatively low radiation doses can effectively palliate advanced gastric cancer patients.

A critical factor affecting patients' quality of life is the duration of bleeding control. In Jesang Yu et al.'s study [31], patients who received higher radiation doses (BED10 ≥ 39 Gy) had a significantly longer period before bleeding recurred (19.3 months vs. 2.6 months, $p = 0.008$). This aligns with findings by Tey et al. [28], who noted that bleeding recurred more often in patients who received radiation doses lower than 39 Gy. Furthermore, Hashimoto et al. observed that a BED10 ≥ 50 Gy was strongly associated with successful bleeding control in patients with unresectable gastric cancer-related bleeding [19]. These findings suggest that higher radiation doses might delay symptom recurrence after treatment, though further studies are needed to determine the optimal dose based on a patient's prognosis.

In the management of advanced gastric cancer, chemotherapy is central, although symptoms like bleeding, dysphagia, and vomiting can interfere with treatment. As such, palliative interventions such as radiotherapy, which help manage these symptoms, may allow chemotherapy to continue or resume. In Jesang Yu et al.'s study [31], nearly half of the patients (49.2%) could continue chemotherapy after radiotherapy, with the treatment significantly reducing the risk of bleeding recurrence (HR = 0.276; 95% CI, 0.114–0.670; $p = 0.004$). These results suggest that combining palliative radiotherapy with chemotherapy may enhance clinical outcomes in certain cases.

Radiotherapy is well recognized for controlling bleeding in various malignancies, including cervical, rectal, bladder, lung, and gastric cancers. For instance, Rasool et al. recommended radiotherapy to reduce bleeding caused by cancers directly related to tumor invasion, pointing out that short fraction regimens are as effective as those involving multiple fractions [22]. Halle et al. used a single fraction of 1000 cGy to control bleeding in incurable gynecological cancers, achieving bleeding control in 60% of patients [32]. Biswal et al. showed that radiotherapy (either external beam or brachytherapy) was effective in controlling bleeding in cervical cancers, achieving complete control within 12 to 48 hours after treatment, with doses ranging from 5 Gy in a single fraction to 20 Gy in five fractions [33].

In gastric cancer, success rates of 50 to 91% have been reported for bleeding control with radiotherapy [20.21.34.35], and our study observed a success rate of 86.95%. While the mechanisms behind radiotherapy's effectiveness in controlling bleeding remain partially understood, it is generally accepted that platelet aggregation and endothelial cell

damage induced by radiotherapy contribute to bleeding control, resulting in vascular embolization, as observed in both in vivo and in vitro studies [36.37].

Several fractionation schemes have been used in radiotherapy for bleeding control in advanced gastric cancer, ranging from 8 Gy in a single fraction to 50 Gy in 25 fractions. For example, Asakura et al. reported a response rate of 73% in patients receiving 30 Gy in 10 fractions, with those receiving concurrent chemotherapy showing a significantly lower rate of bleeding recurrence compared to those receiving radiotherapy alone [21]. Although chemoradiotherapy seems to provide better clinical outcomes, it must be used cautiously, particularly in patients with a good performance status. Hashimoto et al. and Kim et al. suggested that radiation doses with a BED greater than 39 Gy offer better local control and extended overall survival [19, 34], though Tey et al. also noted that higher doses are associated with longer survival, despite the median survival difference not being significant [20].

Some studies have also shown the effectiveness of lower doses of radiotherapy in specific situations, such as Kawabata et al.'s study, where a dose of 6 Gy administered in three fractions was effective and safe for controlling bleeding in gastric cancer [30]. These results suggest that, in some cases, especially for patients with a limited prognosis, short-course radiotherapy could be a viable option.

5. Conclusion

While our study has limitations, such as its retrospective nature, small sample size, and variations in physician dosing decisions, it provides valuable insights into the use of radiotherapy for bleeding control in advanced gastric cancer. Further prospective studies are necessary to confirm these findings and refine radiotherapy dosimetry strategies in this clinical context.

Compliance with ethical standards

Disclosure of conflict of interest

All authors have no conflict of interest to declare.

Statement of ethical approval

This retrospective study was conducted in accordance with ethical guidelines.

Statement of informed consent

Patients provided informed consent for the publication of this study.

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