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Radiation therapy for gastric cancer bleeding

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ABSTRACT

Aims and background. To evaluate the outcome of palliative radiotherapy (RT) for patients with gastric cancer bleeding.

Methods. A retrospective review of 30 patients with gastric cancer bleeding who underwent palliative RT was conducted. Twenty-three patients who received a dose of ≥30 Gy in 10 fractions were eligible. The palliative effect was evaluated both in a subjective and objective manner. Subjective symptomatic relief of bleeding was determined and an objective response was evaluated by identifying the amount of transfused packed red blood cells (PRBC) and the mean hemoglobin (Hb) level of patients before and after RT.

Results. Subjective symptom relief was observed in 21 patients. The number of transfused PRBC units was 2 to 25 (median, 6) during the month before RT and 0 to 16 (median, 0) during the month after RT (P <0.001). The average level of Hb increased from 9.1 ± 1.6 g/dL to 10.6 ± 1.6 g/dL (P <0.001). In 9 patients whose laboratory findings were available for ≥3 months after RT, the mean Hb at one, two, and three months after RT was 10.7 ± 1.7 g/dL (P = 0.004), 10.5 ± 1.0 g/dL (P = 0.039), and 9.9 ± 1.0 g/dL (P = 0.164), respectively. The median number of transfused PRBC units decreased from 6 to 0 during the three months after RT.

Conclusion. RT may be an effective treatment for gastric cancer bleeding when other modalities are not feasible. In this study, 91% of the patients experienced symptomatic palliation with an elevated Hb level and a decreased number of transfusions after RT.

Introduction

Gastric cancer is one of the most common cancers in Korea[1] and the leading cause of cancer-related death worldwide[2]. In a patient with locally advanced gastric cancer, various symptoms such as bleeding, obstruction, and pain can develop and these symptoms can compromise the patient's quality of life. For palliation of such symptoms, several surgical and non-surgical approaches including radiation therapy (RT) should be considered[3-5].

Bleeding is one of the most frequent causes of emergency abdominal surgery in cancer patients. Gastritis and ulcerative disease account for 44% to 76% of bleeding cases and a second source of bleeding is from the tumor itself, occurring in 10% up to 27% of cases[6-8]. In particular, bleeding from gastric cancer accounts for approximately 2% of total upper gastrointestinal bleeding, and less than 10% of gastric cancer patients show bleeding at initial presentation. Most tumors that cause severe upper gastrointestinal bleeding are of a malignant histological type and are already at an advanced stage[9,10]. Treatment options for bleeding control are palliative surgery[11-13], endoscopic intervention (electrocautery, laser resection, and ligation)[10,14,15], diagnostic angiography with vasoconstrictor injection or embolization[16,17], and RT[4,5]. The purpose of this study is to evaluate the outcome of palliative RT for patients with gastric cancer bleeding.

Key words: gastric cancer, cancer bleeding control, palliative radiation therapy.

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Materials and methods

Patient characteristics

Patients with gastric cancer bleeding who underwent RT for symptom palliation were thoroughly reviewed in this retrospective study. From March 1996 to April 2006, 30 patients were treated with RT at the Samsung Medical Center and all of the patients were confirmed to have gastric cancer bleeding by means of gastroduodenoscopy. Seven patients were excluded from the study because they had received a suboptimal radiation dose, and a total of 23 patients who received a radiation dose of more than 30 Gy in 10 fractions were eligible for inclusion. The cause of the suboptimal radiation dose in the 7 patients who were excluded was as follows: refusal of further treatment after the first day of RT in 1 patient, suspension of RT due to a cerebral infarction episode in 1 patient, cessation of RT due to severe abdominal pain, diarrhea or massive upper gastrointestinal bleeding from disease progression during RT in 3 patients, total radiation dose of 20 Gy in 2.5 Gy per fraction in 1 patient, and expiration after the first RT due to massive upper gastrointestinal bleeding and respiratory arrest from progression of local and distant metastasis in 1 patient.

Radiation therapy

All patients were treated with external-beam RT after a median of 6 months (range, 0-33 months) from the initial diagnosis of gastric cancer. Two-dimensional simulation with administration of 10 to 20 mL of barium-containing contrast medium after 4 to 6 hours' fasting to visualize diaphragmatic and gastric motion during respiration was carried out. The target volume was delineated including partial or whole stomach according to the tumor location with a generous margin. Radiation was delivered with high-energy photons of 10 or 15 MV from a linear accelerator. The radiation dose was 30-44 Gy in 10-22 fractions (median, 30 Gy in 10 fractions).

Response evaluation

The palliative effect of RT was evaluated as follows. First, subjective symptom relief was assessed by checking if any signs of upper gastrointestinal bleeding (hematemesis or melena) resolved after RT. Second, for objective response evaluation, changes in the number of transfused packed red blood cell (PRBC) units and the mean hemoglobin (Hb) level before and after RT were calculated. Wilcoxon's signed rank test was used to compare the mean Hb levels pre- and post-RT.

Results

Patient characteristics

Twenty-three patients with gastric cancer bleeding were analyzed with a median follow-up of 4 months (range, 1-12 months) after RT. The patient characteristics are shown in Table 1. The median age was 61 years (range, 31-71 years), and there was a male predominance. As far as tumor pathology is concerned, adenocarcinoma was present in 20 patients, signet-ring-cell carcinoma in 2 patients, and an undifferentiated carcinoma was found in 1 patient. The majority of cases were initially diagnosed as being at the terminal stage of gastric cancer. Two patients had recurrent disease in the remnant stomach with metastasis to the regional lymph nodes, peritoneum, and liver after 7 and 12 months, respectively, following a curative subtotal gastrectomy.

As initial treatment for gastric cancer, palliative chemotherapy was given to 14 patients (61%) including the 2 patients with recurrent disease after curative subtotal gastrectomy. Palliative surgery was performed in 6 patients (26%): 5 patients underwent a palliative gastrojejunostomy and 1 patient an exploratory laparotomy. In 3 patients, RT was given as the initial treatment.

Before palliative RT, the presence of tumor bleeding foci was endoscopically confirmed in all patients and 2 patients underwent electrocautery for hemostasis. In the remaining patients, RT was the only active treatment provided for bleeding control. Bleeding from the gastric cardia including the esophagogastric junction was identified in 7 patients, in the gastric fundus in 5 patients, and the antrum in 8 patients. Two patients showed bleeding from the remnant stomach, and specific endoscopic findings were not described in 1 patient. When the palliative RT was administered, 22 patients (96%) had synchronous distant metastasis. The sites of distant metastasis were the peritoneum in 13 patients, liver in 11 patients, lung in 2 patients, supraclavicular lymph nodes in 2 patients, and bone in 1 patient. All patients had expired by the time of the study analysis and the median survival was 4 months (range, 1-12 months) after RT.

Table 1 - Characteristics of the study patients (n = 23)

	Patient characteristics	No. of patients (%)
Age	≤60 years	10 (43)
	>60 years	13 (56)
Gender	Male	18 (78)
	Female	5 (22)
ECOG performance status	1	8 (35)
	2	9 (39)
	3	4 (17)
	4	2 (9)
Pathology	Adenocarcinoma	20 (87)
	Signet ring cell carcinoma	2 (9)
	Undifferentiated carcinoma	1 (4)
Initial AJCC stage	II	1 (4)
	IVA	2 (9)
	IVB	20 (87)

1997 AJCC staging criteria.

Response to radiation therapy

Subjective symptom relief of hematemesis or melena was observed in 21 of 23 patients (91%) within 1 month after RT and was maintained for a median of 2 months (range, 1-9 months). In the 21 patients with symptom improvement, there were changes in the number of transfused PRBC units and mean Hb levels for the periods before and after RT. The number of transfused PRBC units was 2 to 25 (median, 6) during the month prior to RT and 0 to 16 (median, 0) during the month following RT (P <0.001). The average level of Hb increased from a mean of 9.1 ± 1.6 g/dL (before RT) to 10.6 ± 1.6 g/dL (after RT); this change was statistically significant (P <0.001) (Table 2).

To evaluate the long-term effects of RT, we analyzed the data of 9 patients whose laboratory findings included a complete blood count and transfusion history that were available for more than 3 months after RT. In this subgroup, the mean Hb level at 1, 2, and 3 months after RT was 10.7 ± 1.7 g/dL (P = 0.004), 10.5 ± 1.0 g/dL (P = 0.039), and 9.9 ± 1.0 g/dL (P = 0.164), respectively. There was a statistically significant increase in the mean hemoglobin level for 2 months after RT. The median number of transfused PRBC units decreased from 6 (range, 2-14) prior to RT to 0 (range, 0-2), 0 (range, 0-4), and 0 (range, 0-6) at periods of 1, 2, and 3 months after RT, respectively (Table 3 and Figure 1). Figures 2 and 3 show an example of a patient with effective bleeding control after RT.

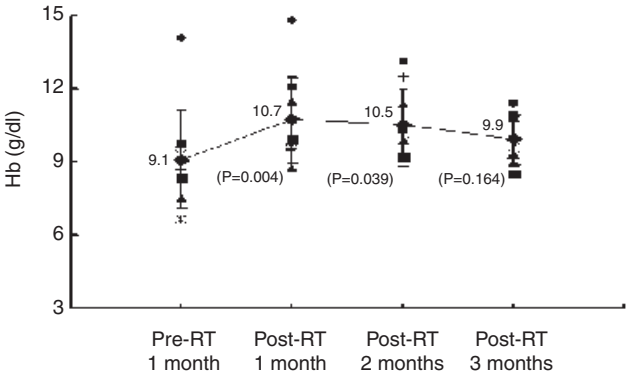

Figure 1 - Changes in hemoglobin levels in 9 patients.

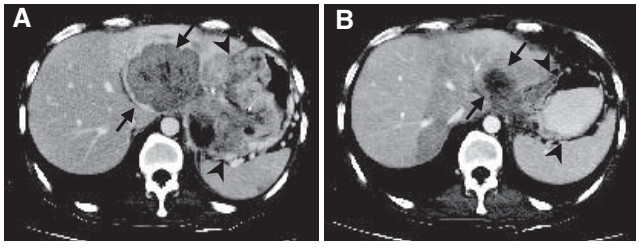

Figure 2 - Images before radiothearpy (A) and 1 month after radiotherapy (B). The recurrent gastric cancer in the remnant stomach and perigastric lymph node developed in a 31-year-old woman. The patient suffered from hematemesis due to tumor bleeding and poor oral intake due to gastric outlet obstruction. After radiation therapy with 30 Gy in 10 fractions, effective palliation was achieved but the patient died 8 months following RT (arrowhead: remnant stomach; arrow: perigastric lymph node.)

Table 2 - Changes in mean number of transfused packed red blood cell units and mean hemoglobin level (n = 23)

	Pre-RT 1 month	post-RT 1 month	P value
Mean number of PRBC units	9.5 (±6.51)	2.8 (±6.8)	<0.001
Mean Hb level (g/dL)	9.1 (±1.6)	10.6 (±1.6)	<0.001

PRBC, packed red blood cells; Hb, hemoglobin; RT, radiation therapy; Wilcoxon signed-rank test.

Table 3 - Changes in mean number of transfused packed red blood cell units and mean hemoglobin level (n = 9)

	Pre-RT	Post-RT		
	1 month	1 month	2 months	3 months
Mean number of PRBC units	7.1 ± 4.0	0.2 ± 0.6	0.6 ± 1.4	1.3 ± 2.2
Mean Hb level (g/dL)	9.1 ± 2.0	10.7 ± 1.7 (P <0.004)	10.5 ± 1.0 (P <0.039)	9.9 ± 1.0 (P <0.164)

PRBC, packed red blood cells; Hb, hemoglobin; RT, radiotherapy; Wilcoxon signed-rank test.

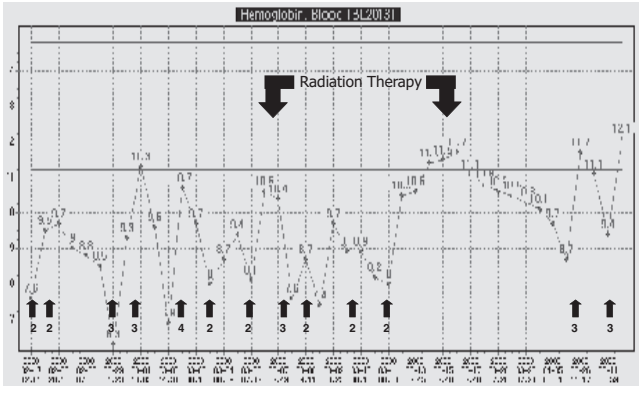

Figure 3 - A graph of the sequential hemoglobin level in the same patient. Note the change in the frequency of transfusion (small arrow) before and after radiotherapy.

Toxicity

A toxicity profile is shown in Table 4. There was no RTOG grade 3 or 4 toxicity during RT. In 3 patients, the bleeding worsened after the initiation of RT but was

Table 4 - Acute toxicities during radiation therapy

	RTOG grade			
	1	2	3	4
Nausea	11	1	0	0
Vomiting	5	0	0	0
Diarrhea	1	1	0	0

RTOG, Radiation Therapy Oncology Group.

soon resolved with supportive management including transfusion. These patients resumed RT after a week's rest and successfully finished their scheduled dose. There was no treatment-related mortality.

Discussion

Gastrointestinal bleeding in cancer patients is mainly due to gastritis or ulcerative disease, but bleeding from the tumor itself accounts for 10% to 27% of all bleeding[6,8]. Gastric cancers that cause severe bleeding are already at an advanced stage and need immediate treatment to control the bleeding. Surgical approaches including palliative gastrectomy or a bypass operation are generally recommended for massive upper gastrointestinal bleeding[11-13] and various endoscopic or angiographic interventions[10,14-16] are useful in terms of diagnosis and treatment. For symptomatic palliation, RT is also worth considering[4,5].

For the selection of an appropriate treatment modality, the performance status of the patient, the expected duration of survival, and the anticipated operative morbidity and mortality must be taken into consideration. Considering the higher risk of surgery in severely ill patients, however, surgical palliation is not commonly used in the clinical setting[12,18]. Selection criteria for patients who can receive the best benefit from surgery need to be evaluated.

Endoscopy has an important role in the diagnosis and treatment of upper gastrointestinal bleeding. Endoscopic hemostasis of bleeding from advanced gastric cancer may provide temporary symptom relief and sufficient time for elective surgical palliation[10,14,15]. In the present study, endoscopic intervention was undertaken only in 2 patients. Because massive bleeding interrupted an opportunity to obtain an adequate visual field for the endoscopic procedure, therapeutic intervention was impossible in many cases.

The symptoms associated with locally advanced gastric cancer can be alleviated with RT. Most reports have revealed that 50% to 75% of patients treated with chemoradiation may experience symptomatic improvement for a median duration of response ranging from 4 to 18 months[5,19-21]. RT has been considered for bleeding control in cancer lesions of the head and neck, lung, rectum, bladder, vagina, and skin. In particular, radiation has been shown to resolve hemoptysis caused by lung cancer, hematochezia from rectal cancer, and hematuria from bladder cancer with reported control rates up to 80%, 85%, and 60%, respectively[22]. Bleeding control can often be accomplished using a relatively low radiation dose, while pain from local tumor invasion may require a higher dose of over 45 Gy[2]. The indication of RT for gastric cancer bleeding has never been proposed before. With this study, one may consider RT for gastric cancer bleeding under the following conditions.

1. ECOG performance status score 3 or better
2. Expected survival duration of more than a few months
3. Failure or contraindication of other treatment modalities
4. Oozing cancer bleeding accompanied by intractable pain.

Tey *et al.*[5] reported the results of palliative RT in 24 gastric cancer patients with bleeding symptoms. With a median RT dose of 30 Gy over 10 fractions, 13 of 24 patients (54%) showed a response for a median duration of 140 days. The definite site of tumor bleeding, however, was not confirmed at the time of active bleeding even though the patients were initially diagnosed as having histologically confirmed gastric cancer. According to the study of Sherlock and Winawer[7], if a tumor is located in the stomach, the probability that it is the source of bleeding is about 50%, and if the tumor is a primary gastric cancer or a gastric lymphoma, the probability increases to 75%. Thus, endoscopic confirmation of cancer bleeding is important to avoid unnecessary RT for bleeding from possible benign causes. This study was based on endoscopically confirmed gastric cancer bleeding. Twenty-one of 23 patients treated with more than 30 Gy of radiation experienced symptom relief of a median duration of 2 months.

The mechanism of radiation on tumor vessels is well understood. The newly formed tumor vessels are different from normal vessels on account of their rapid growth[23]. Tumor vessels are composed of irregular channels with patchy endothelium and are lined by tumor cells. Elastic tissue or smooth muscle is generally absent from the vessel walls[24]. Radiation gives rise to denudation of the surface of blood vessels, leading to formation of thromboses and capillary necroses blocking the lumen. Consequently, hemostasis is achieved.

Several criteria have been used to evaluate the effect of palliative RT on metastatic bone lesions. However, it is remarkably challenging to create the objective parameters for the evaluation of palliative RT for cancer bleeding. The Hb level does not reflect acute bleeding directly and the individual baseline Hb level varies according to gender and underlying comorbidity. Therefore, it is not desir-

able to set a transient Hb level as a standard evaluation tool for determining a treatment result. In this study, the mean Hb level of each individual patient was calculated by summing up all of the peripheral blood exams performed monthly pre- and post-treatment and the total number of transfused PRBC units was also counted during the same period. To assess the effect of treatment, the average of the individual mean Hb level per month and the total number of transfused PRBC units was taken at the same time. A single transient Hb level is an inappropriate criterion to evaluate bleeding control after treatment. Yet, by summing up all of the laboratory results in a given period, minimal objectivity could be achieved. We found that the number of transfused PRBC units decreased following RT, while there was a significant increase in the mean Hb level. It is reasonable to interpret this result as a radiation effect because no other treatment except RT was given during that period.

In conclusion, when acute bleeding from gastric cancer develops, appropriate supportive treatment should be provided including transfusion and fluid replacement. Diagnostic and therapeutic endoscopy can then be performed, but repetitive procedures may be required due to the high rebleeding rate after endoscopic hemostasis. Palliative surgery can be considered as an option if the patient has a good performance status and a long life expectancy. When palliative surgery is not indicated or endoscopic intervention is not effective, RT may be an attractive alternative. In this study, 91% of patients experienced symptomatic palliation with an elevated Hb level and decreased number of transfusions after external-beam RT at a median dose of 30 Gy. Thus, RT may be an effective tool for gastric cancer bleeding when other modalities are not feasible.

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