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Original research

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A retrospective study of the effectiveness of hemostatic radiotherapy with conventional fractionation in patients with advanced cancer

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Abstract

The aim of this study was to assess the efficacy of hemostatic radiotherapy (HRT) in patients with advanced cancer. Eighteen patients with advanced cancer treated with HRT at the Fukuoka University and Kyushu Rosai Hospitals in Japan between July 2010 and February 2015 were retrospectively assessed. The hemostatic effect of tumor-related bleeding was assessed by the clinical course of bleeding, laboratory data, the endoscopic study, and the number of blood transfusion units (BTRUs) for one month before and after HRT. The median follow-up time was 2.6 months (range, 0.7 to 36.2 months). The median age of the patients was 77 years (range, 51 to 93). The primary diseases with tumor-related bleeding included gastric cancer, urinary bladder cancer, gynecological cancer, prostate cancer, non-small-cell lung cancer, and breast cancer. The median overall survival time was three months, and the one year survival rate was 22.9% of all patients. The HRT regimens ranged from 30 Gy in 10 fractions to 40 Gy in 20 fractions. In all patients, the anemia grade and the number of BTRUs decreased for 1 month after RT. The percentage of patients who were diagnosed as "successful" for hemostasis was 83% (15 of 18 patients). HRT is therefore strongly suggested as effective for the control of tumor-related bleeding in patients with advanced cancer. The optimal radiation doses and fractions are controversial; however, this treatment should be offered for patients with a poor life expectancy.

Keywords: retrospective study; hemostatic radiotherapy; conventional fractionation; advanced cancer

Introduction

Tumor-related bleeding occurs in approximately 6–10% of patients with advanced cancer [1, 2]. Active and/or continuous tumor-related bleeding is distressing to patients, their families, and their caregivers, and greatly diminishes patients' quality of life (QOL). Procedures for hemostatic treatment have been previously reported in the literature. The main treatment modalities were hemostatic agents, radiotherapy (RT), surgery, and interventional radiology (IVR) [2]. The efficacy of HRT has been reported in several types of cancers. However, the optimal doses and number of fractions remain controversial. In this study, 18 patients with active tumor-related bleeding were treated with conventional fractionated radiotherapy (CFRT). The aim of this study is to evaluate the outcome in patients with tumor-related bleeding from advanced cancer treated with CFRT.

Materials and methods

Patients

Eighteen patients with active tumor-related bleeding who had been treated with HRT at Fukuoka University Hospital (n = 13) and Kyushu Rosai Hospital (n = 5) in Japan, between July 2010 and February 2015, were retrospectively recruited. The bleeding sites were identified by medical history, physical examination, and radiological or endoscopic examination. The median follow-up time was 2.6 months (range 0.7 to 36.2 months). All of the patients provided written informed consent.

Treatment

All patients were treated with 3-dimensional conformal RT (3D-CRT). Radiation was administered with high-energy photons of 4, 6, or 10 MV from a linear accelerator. The clinical target volume (CTV) was defined as the whole organ of the tumor-related bleeding site or the bleeding tumor. For example, the CTV of urinary bladder carcinoma was the whole urinary bladder, that of gastric cancer was the partial stomach including the bleeding tumor, and

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that of uterine cervical cancer was the cervical tumor. The planning target volume (PTV) was defined as the CTV with a 1 to 2cm margin in all directions. Patients were irradiated using a conformal anteroposterior/posteroanterior or multiple-field technique. A total dose of 30 to 40 Gy in daily fractions of 2 to 3 Gy was delivered to all patients. An example of dose distribution for advanced gastric cancer is shown in Figure 1. The active bleeding site was marked with three metallic clips by endoscopic examination in this patient. Patients with symptomatic anemia and active bleeding with decreasing hemoglobin levels were given blood transfusions before, during, and after HRT.

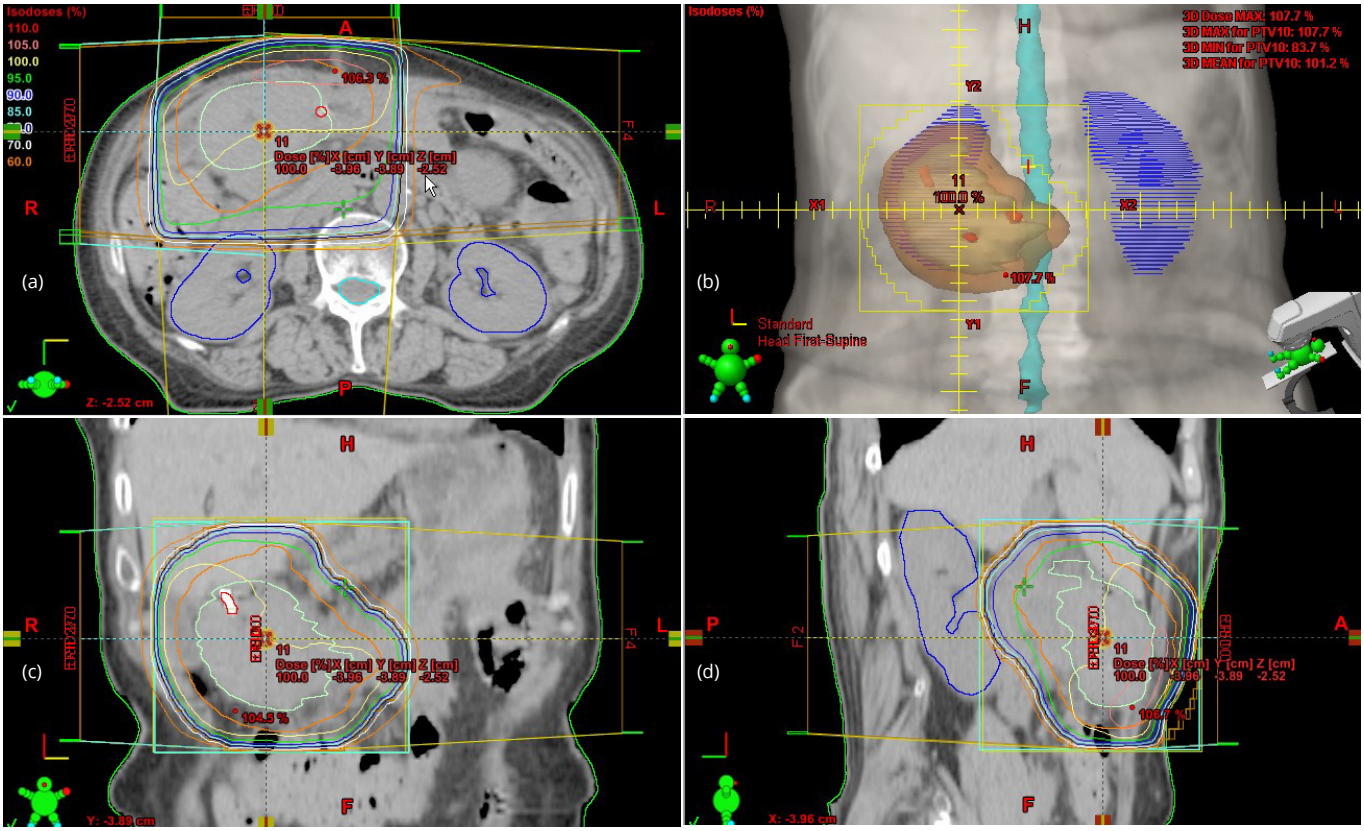

Figure 1a,b,c,d An example of dose distribution for advanced gastric cancer.

Assessment and evaluation

The hemostatic effect of tumor-related bleeding was assessed by the clinical course of bleeding, the laboratory data (hemoglobin levels), an endoscopic study, and the number of BTRUs for 1 month before HRT and 1 month after the end of HRT. The grade of anemia was assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0) for 1 month before and after HRT. The hemostatic effect was estimated as "successful" for patients who showed stable or elevated hemoglobin levels and were not performed to transfuse for 1 month after HRT.

Method of data analysis

The overall survival rate was estimated with the Kaplan-Meier method. The times of overall survival were calculated from the start of HRT.

Results

Patient characteristics

The patient characteristics are shown in Table 1. The median age was 77 years (range, 51 to 93). The disease states that caused bleeding were 16 primary or locally recurrent tumors and 2 metastatic tumors. The grade of anemia before HRT was grade 1 to 2 in 5 patients (28%)

Table 1 Patient characteristics.

Characteristic		*Number of patients (N = 18)*	*Percentage (%)*
Age (y)	51-93 (median 77)		
Sex	Male	6	33
	Female	12	67
Primary disease	Gastric cancer	5	28
	Urinary bladder cancer	5	28
	Gynecological cancer	4	22
	Prostate cancer	2	11
	Non-small-cell lung cancer	1	6
	Breast cancer	1	6
Disease status	Primary or local recurrence	16	89
	Metastatic	2	11
Anemia grade before RT	G1	2	11
	G2	3	17
	G3	5	28
	G4	8	44
Blood transfusion units before RT	0	7	39
	1-10	7	39
	> 11	4	22

and grade 3 to 4 in 13 patients (72%). The number of BTRUs given before HRT were none in 7 patients (39%), 2 to 10 in 7 patients (39%) and 11 or more in 4 patients (22%). The median overall survival time was 3.0 months, and the one year survival rate was 22.9% of all patients.

Treatment

The HRT regimens ranged from 30 Gy in 10 fractions to 40 Gy in 20 fractions. Most patients were treated with a total of 30 Gy, with 3 Gy in 5 fractions per week. The distribution of total radiation doses and fractions is shown in Table 2.

Table 2 Radiation doses and fractions.

Dose/Fractions	*Number of patients*	*Percentage (%)*
30 Gy/10 fractions	11	61
40 Gy/16 fractions	3	17
40 Gy/20 fractions	4	22

Control of tumor-related bleeding

The number of BTRUs given after HRT was none in 15 patients (83%), and 4 to 6 in 3 patients (17%). Thus, the BTRUs were decreased after HRT in all patients. The percentage of patients in the "successful" group for hemostasis was 83% (15 of 18 patients). Three patients (17%) did not benefit from HRT. At the end of HRT, complete hemostasis was achieved in 3 of 18 patients (17%). Clinical course of the anemia grade and the number of BTRUs of each patient before and after HRT is shown in Table 3 and Figure 2.

Acute toxicity

No grade 3 or higher acute toxicities of CTCAE, ver.4.0 was observed. All patients were accomplished to irradiate continuously in CFRT.

Discussion

The prognosis for patients with advanced cancer and tumor-related bleeding is poor. In this study, the median overall survival time was 3 months in all patients, and the one year survival rate was 22.9%. Tumor-related bleeding

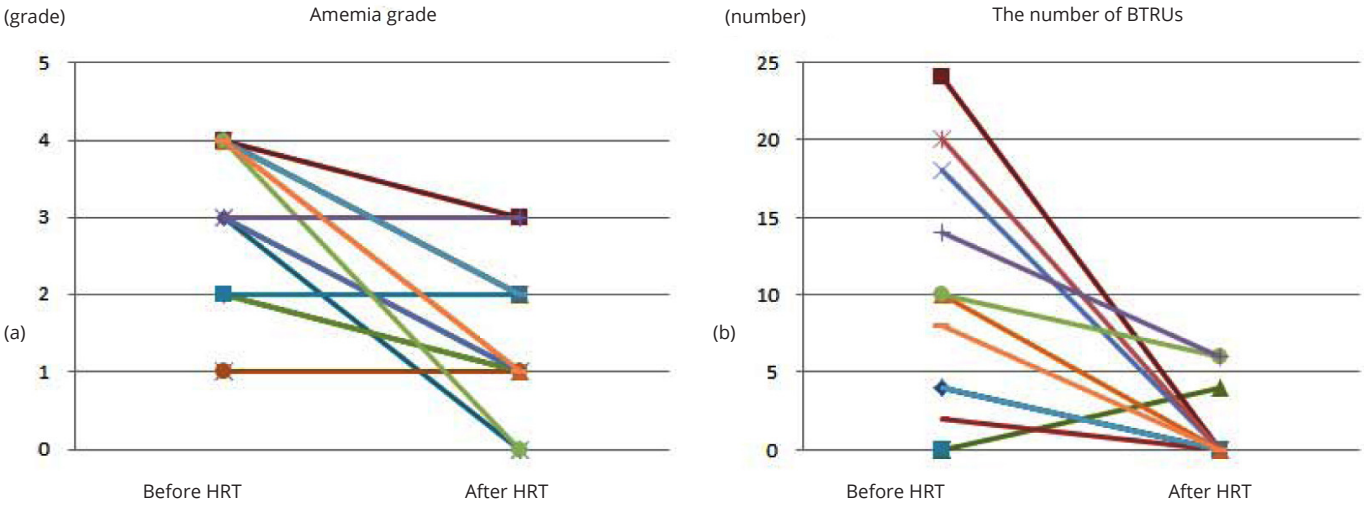

Figure 2a,b Clinical course of the anemia grade and the number of BTRUs of each patient before and after HRT.

diminishes the QOL of these patients, due to anemic symptoms, intensive management for hemorrhage, including repeated blood transfusions, and systemic coagulopathy caused by paraneoplastic syndrome [3].

It has been reported that HRT may affect the pathophysiological process of malignant vessels by inducing malignant endothelial cell damage secondary to extensive DNA damage, and it may also activate signal transduction pathways that can lead to cell cycle arrest or apoptosis [4]. Radiation increases adhesion of platelets to the vascular endothelium. The long-term effects could be due to the formation of vessel fibrosis combined with tumor remission. Fajardo et al. reported that endothelial cell damage was induced by RT, leading to small and medium vessel rupture or thrombosis, and in the longer term, to microvascular network destruction [5]. However, there are few published papers focusing on the effect of HRT. In our study, the clinical success rate of HRT was 83% in all patients.

For gastric cancer, the response rate was 80% (4 of 5 patients) in our study. Previous studies have reported a response rate of 50–70% for controlling bleeding from advanced gastric cancer, and our results were in concordance with these studies. Tey et al. reported that 13 of 24 patients (54.2%) who had received from 8 Gy in a single fraction to 40 Gy in 16 fractions responded with hemostasis [6]. Kim et al. reported that the rate of bleeding control with RT was 14 of 20 patients (70%). In their series, the most common radiation doses and number of fractions were 35 Gy in 14 fractions [7]. Chaw et al. reported a response rate of 50% with 8 Gy in 1 fraction to 20 Gy in 5 fractions [8].

For urinary bladder cancer, the response rate was 60% (3 of 5 patients) in our study. Locarriere et al. reported that 22 of 32 patients (69%) who had received 20 Gy in 5 fractions or 30 Gy in 10 fractions became hematuria-free after RT; the response rate of patients who received 20 Gy in 5 fractions was 79% [9].

Table 3 Clinical course of the anemia grade before and after RT in all patients.

Primary malignancy	*Bleeding site*	*Anemia grade*		*Number of blood transfusions*		*Course of hemostasis*	*Time of followup (months)*	*Disease status*
		Before RT	*After RT*	*Before RT*	*After RT*			
Gastric cancer	Stomach	4	2	4	0	S*	2.8	DOD**
		4	3	0	4	U↯	3	DOD
		4	2	24	0	S	5.2	DOD
		4	1	10	0	S	1.6	DOD
		3	1	18	0	S	1	DOD
Urinary bladder cancer	Bladder	2	1	4	0	S	1.5	DOD
		2	2	0	0	S	0.6	AWD↯
		4	2	20	0	S	3	DOD
		4	0	10	6	U	10.7	AWD
		3	3	14	6	U	1.2	DOD
Gynecologic cancer	Uterus vagina	1	1	0	0	S	0.4	AWD
		3	0	0	0	S	19.6	AWD
		1	1	0	0	S	36.2	DOD
		4	1	8	0	S	0.7	AWD
Prostate cancer	Bladder	3	1	2	0	S	11.2	DOD
		2	1	0	0	S	3.3	DOD
Non-small-cell lung cancer	Bronchus	4	2	4	0	S	1.3	AWD
Breast cancer	Vagina	3	3	0	0	S	2.3	AWD

Abbreviations: *Successful (stable/elevated hemoglobin and not transfused after RT); **DOD (dead of disease); ↯ : Unsuccessful; ↯: AWD (alive with disease).

For gynecological cancer, the response rate was 100% (4 of 4 patients) in our study. Cihoric et al. reported that bleeding control improved in 94.7% of patients with uterovaginal cancer at the end of RT [10]. Other reports have described the excellent efficacy for hemostasis with RT doses and fractions in a single fraction or multiple monthly 10-Gy fractions [11, 12]. The radiosensitivity of squamous cell carcinoma, which is the major histological type of uterovaginal cancer, may at least partly explain this relatively good response to HRT, as compared to bleeding cancers in other organs.

HRT for hematuria due to advanced prostate cancer was described in a review by Cameron et al. [13]. With hypofractionated and conventional fractionated RT, the dose and fraction size of RT ranged from 20–60 Gy and from 2–15 Gy, respectively. The response rate of hemostasis ranged from 42–100%. In our series, there were only 2 cases of prostatic cancer, both of which were successfully controlled using CFRT.

Our study included only 1 patient with non-small-cell lung cancer, who showed a complete response to hemostatic RT. Previous papers have shown up to an 80% response rate in bleeding control for lung cancer. It has been suggested that hypofractionated RT appears to be as effective as CFRT [10, 14].

Our study included only one breast cancer. This patient had vaginal metastasis of breast cancer, and gynecological bleeding. We treated for vaginal tumor as HRT for gynecological cancer, and gained hemostasis. In acute toxicities, no grade 3 or higher was observed, and all patients were accomplished to treat continuously in CFRT.

Study limitations were the small sample size, the different treatment sites and histological types, and the method of evaluation of hemostatic efficacy by the hemoglobin level as reflected by the number of blood transfusions before and during HRT.

Conclusion

RT with conventional fractionation is generally effective for the control of tumor-related bleeding in patients with advanced cancer. The radiation doses and fractions of HRT are controversial; however, this treatment should be offered for patients with poor life expectancy. In order to further demonstrate the efficacy of HRT, retrospective studies of a larger series or prospective randomized studies are needed.

Conflicts of interest

Authors declare no conflicts of interest.

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