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ORIGINAL PAPER

Palliative radiation therapy for hemorrhage of unresectable gastric cancer: a single institute experience

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Abstract
Purpose To clarify the toxicity of palliative radiotherapy (RT) and its efficacy against bleeding of unresectable gastric cancer.
Methods Clinical data of 19 patients received palliative RT for bleeding from unresectable gastric cancer were reviewed. The median total dose and dose per fraction were 40 Gy (range 2–50 Gy) and 2.5 Gy (range 1.8–3 Gy).
Results The treatment success rate was 68.4%. By using a tumor alpha/beta ratio of 10, biological effective dose of 50 Gy_{10} or more was significantly correlated with treatment success ($P = 0.040$). The median event-free survival was 1.5 months after RT and the median overall survival from starting RT was 3.4 months. Grade 3 nausea and anorexia were recorded in 1 and 3 patients, respectively.
Conclusion Palliative RT was effective for hemostasis in patients with gastric cancer bleeding with minor adverse events.

Keywords Gastric cancer · Radiotherapy · Bleeding · Hemostasis

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Introduction

Gastric cancer is the fourth most common malignancy and is the second leading cause of death, accounting for 700,000 confirmed deaths annually with about 930,000 new cases in the world (Kamangar et al. 2006). In Japan, about 100,000 patients suffer from gastric cancer, and roughly half of them died in 2002. These patients were unfortunately not localized at the first diagnosis. Unresectable gastric cancer has poor prognosis, with the 5-year overall survival (OS) rate of 10%. Fluorouracil-based chemotherapy for patients with unresectable gastric cancer has shown some benefits in improving survival compared with the best supportive care (Glimelius et al. 1994; Murad et al. 1993; Pyrhönen et al. 1995). However, no international standard regimens have been established to date (Ohtsu et al. 2006).

Gastric cancer induces various local symptoms such as bleeding, obstruction, anorexia and pain. Chronic bleeding from gastric cancer can lead to anemia, anorexia, dehydration or hypoalbuminemia. Anemia, in particular, occasionally interrupts the continuity of chemotherapy, and thus control of bleeding is important to improve the quality of life (Pereira and Phan 2004).

Several modalities can be considered as the treatment of choice against bleeding from gastric cancer; nevertheless, which treatment is more effective remains a matter of debate. For example, palliative gastrectomy may be appropriate only for well-selected patients with severe hemorrhage refractory to conservative treatment. Endoscopic hemostasis achieved using thermal probes or by epinephrine injection is temporarily effective in limited cases (Savides et al. 1996). Endoscopic intervention including argon plasma coagulation (APC) has achieved hemostasis in 67% of patients with gastroduodenal tumor bleeding (Loftus et al. 1994).

However, APC sometimes causes severe complications such as perforation in 5–15% of patients, and recurrence of bleeding was frequently found (Loftus et al. 1994). Some investigators have applied gastrointestinal arterial embolization to stop bleeding from gastric cancer, and they have proven its safety and efficacy in limited cases (Encarnacion et al. 1992; Srivastava et al. 2000).

Radiation therapy (RT) has been shown to palliate bleeding from every type of malignant tumors, such as cervical, lung and bladder cancers (Ferris et al. 2001; Onsrud et al. 2001; Hoskin 1998). Recently, two retrospective analyses have been reported regarding the benefit of palliative RT for symptomatic advanced gastric cancer (Kim et al. 2007; Tey et al. 2007). In these reports, palliative RT successfully controlled tumor bleeding in 53–70% of patients without causing severe toxicity. As a clinical practice, we have applied RT for the palliation of bleeding from gastric cancer at our institution. We report here the results of our retrospective analysis of palliative RT for patients with bleeding from gastric cancer, particularly focusing on the dose–fractionation relationship and treatment outcome.

Methods

We retrospectively reviewed the clinical data from the database of our institution of patients with advanced gastric cancer receiving palliative RT between January 1994 and October 2007. Of these patients, those who received RT for a primary lesion for the purpose of palliating tumor bleeding were identified. This study was performed in accordance with Declaration of Helsinki in 1964.

The following clinical characteristics of the patients were reviewed: age, Eastern Cooperative Oncology Group performance status (PS), endoscopic findings, primary site, tumor histology, oral intake status, serum hemoglobin (Hb) level, chemotherapy regimens, dose fractionation of RT, adverse events and treatment outcome. The amount of transfused red blood cells (RBCs) within 1 month before RT was also recorded. Successful treatment was defined as a patient being alive with no need for blood transfusion after more than 1 month following RT. Even if endoscopy proved bleeding improvement, patients who did not meet the successful treatment criterion were considered as treatment failure.

All patients included in this study received external beam RT. They were treated with 6–25 MV X-ray beams from a linear accelerator or microtron. All patients were conformally treated based on CT planning. The typical irradiation technique applied was opposed anterior–posterior two fields. Oblique opposed two fields were sometimes used to avoid irradiation of the right kidney or spinal cord. The biological effective dose (BED) was calculated using a tumor alpha/beta ratio of 10 using the linear-quadratic formalism. Adverse events were retrospectively recorded according to the Common Terminology Criteria for Adverse Events version 3.0.

We defined event-free survival (EFS) as the interval from the last day of RT to the first day of an event including blood transfusion or any cause of death. OS was defined as the interval from the first day of RT to the day of death. Survival curve was estimated by the Kaplan–Meier method (Kaplan and Meier 1958). Univariate analysis was performed using the Fisher's exact test to determine the factors correlating with treatment success. Statistical analysis was performed using StatView version 5.0 (SAS Inc., USA).

Results

Patients' characteristics

Nineteen patients with advanced gastric cancer receiving RT for the palliation of bleeding from primary gastric cancer ($n = 18$) or with postoperative local recurrence

Table 1 Patients' characteristics at the time of starting radiation

$n = 19$	Number
Male/female	13/6
Median age (range)	61 (33–78)
Performance status	
1	5
2	10
3	3
4	1
Histopathology	
Adenocarcinoma	18
Interstitial	11
Diffuse	6
Unknown	1
Squamous cell carcinoma	1
Location	
Upper	7
Middle	5
Lower	6
Stamp	1
Macroscopic type classification	
Type1	2
Type2	4
Type3	11
Type4	2
Median quantity of transfusion one month prior to radiation (range) (ml)	2,400 (0–4,600)

Table 2 Dose, fractionations of radiation therapy, regimens of chemotherapy and clinical outcomes in each case

Patient no.	Age	Sex	Performance status	Total dose (Gy)	Fractions	BED (Gy)	Completion of RT	Prior chemotherapy	Concurrent chemotherapy	Post RT chemotherapy	Lowest Hb level prior to RT (g/dl)	Prior transfusion one month before RT (ml)	Hb level one month after RT (g/dl)	Oral intake before RT	Oral intake after treatment	Treatment outcome	OS (days)	EFS (days)	Status
1	70	M	2	5,000	25	60	Complete	1. CDDP/CPT 2. S1	None	None	4.7	1,700	9.5	Possible	Possible	Succeeded	248	56	Death
2	68	F	2	4,000	16	50	Complete	None	None	S1	7.1	1,000	10	Possible	Possible	Succeeded	1,157	1,136	Alive
3	60	M	4	4,000	16	50	Complete	5FU	None	1. PTX 2. CPT/MMC	6	3,400	10.1	Impossible	Possible	Succeeded	340	318	Death
4	68	M	2	4,000	16	50	Complete	1. 5FU 2. CDDP/CPT 3. PTX	None	None	4.3	1,200	8.3	Possible	Possible	Succeeded	275	254	Death
5	33	M	1	4,000	16	50	Complete	5FU	FP	1. S1 2. CDDP/CPT	6.6	500	8.6	Possible	Possible	Succeeded	194	173	Unknown
6	62	M	3	4,000	16	50	Complete	5FU	None	None	6.8	0	10.1	Impossible	Possible	Succeeded	191	66	Death
7	46	M	1	4,000	16	50	Complete	CDDP/CPT	None	S1	5	2,400	8.4	Possible	Possible	Succeeded	125	38	Death
8	69	M	2	4,000	16	50	Complete	CDDP/S1	None	PTX	5.1	1,700	9.2	Possible	Possible	Succeeded	101	56	Death
9	78	F	1	4,000	16	50	Complete	S1	None	None	5.3	700	7.6	Possible	Possible	Succeeded	88	66	Death
10	53	M	2	4,000	16	50	Complete	S1	S1	None	6.1	1,000	10.2	Possible	Possible	Succeeded	66	41	Death
11	62	M	3	4,000	16	50	Complete	CDDP/CPT	PTX	None	3.5	3,100	NE	Possible	Possible	Failed	29	7	Death
12	53	M	2	4,000	20	48	Discontinue[a]	1. FP 2. CDDP/CPT 3. DTX 4. MMC/CPT	None	None	4.9	1,900	10.2	Impossible	Possible	Succeeded	75	45	Death
13	61	F	3	3,500	14	44	Suspend[b]	1. S1 2. CDDP/CPT	None	None	7	1,000	NE	Possible	Possible	Failed	29	3	Death
14	57	M	1	2,700	9	35	Discontinue[a]	CDDP/CPT	None	PTX	5.4	4,600	8	Impossible	Possible	Succeeded	265	32	Death
15	51	M	2	2,000	10	24	Complete	None	MF	PTX	8.4	3,400	12.3	Impossible	Impossible	Succeeded	77	64	Death
16	51	F	2	2,000	10	24	Discontinue[a]	None	None	None	5.9	1,200	NE	Impossible	Impossible	Failed	30	3	Death
17	71	M	2	1,800	9	22	Suspend[b]	1. 5FU 2. CDDP/CPT	None	None	4.8	1,900	6.4	Possible	Possible	Failed	39	1	Death
18	71	F	2	720	4	8.5	Suspend[c]	S1	None	None	6.5	1,000	NE	Impossible	Impossible	Failed	30	21	Alive
19	33	F	3	200	1	2.4	Suspend[c]	CDDP/CPT	None	None	4.6	2,500	NE	Impossible	Impossible	Failed	3	2	Death

CDDP cisplatin, *CPT* irinotecan, *FP* 5FU/cisplatin, *DTX* docetaxel

MMC mitomycin C, *PTX* paclitaxel, *MF* methotrexate/5FU

RT radiation therapy, *BED* biological effective dose (α/β ratio of 10), *OS* overall survival, *EFS* event free survival, *NE* not examined

[a] Stopped because bleeding improved

[b] No clinical symptom improved

[c] General condition deteriorated

($n = 1$) were identified. The median age of the patients was 61 years (range 33–71) and the median PS was 2 (range 1–4). Table 1 shows the characteristics of the patients. All patients were classified as stage IV at the time of RT and ineligible for surgery because of tumor invasion to other organs. To confirm the bleeding site, all patients underwent endoscopy before RT.

Radiotherapy and patient condition

The dose fractionation of RT, prior chemotherapy, previous blood transfusion and treatment outcomes are shown in Table 2. All but one patient received blood transfusion to improve serum Hb level within 1 month prior to RT. The lowest serum Hb level before RT ranged from 3.5 to 8.4 g/dl (median 5.4 g/dl; Table 2). RBCs corresponding to a median of 1,700 ml of total blood (range 700–4,600 ml) were transfused prior to RT.

The prescribed dose–fractionation regimen ranged from 20 Gy in 10 fractions to 50 Gy in 25 fractions. The median BED was 50 Gy_{10}, which corresponds to a dose of 40 Gy in 16 fractions. Thirteen of 19 (68%) patients completed the total prescribed dose. Three discontinued the prescribed irradiation course because they were clinically judged as treatment success, while another three did not complete the planned irradiation course because of deterioration of general condition.

Treatment outcomes

Treatment success was observed in 13 of 19 patients (68%). The typical endoscopic findings of patients successfully treated are shown in Fig. 1. Complete hemostasis was confirmed in six of seven patients who underwent endoscopy after RT. The median BED was 50 Gy_{10}. Of those who completed the total prescribed dose, successful hemostasis was observed in 11 (92%) of 12 patients. In contrast, of those who were unable to complete the planned irradiation course, successful hemostasis was seen in only two of seven (29%) patients. Treatment success group received significantly higher dose than failure group (median total dose 40 Gy vs. 19 Gy, $P = 0.026$; Fig. 2). The causes of treatment failure ($n = 6$) were deterioration of general condition ($n = 2$), poor treatment effect ($n = 2$) and re-bleeding ($n = 2$). A BED of 50 Gy_{10} or more was significantly correlated with treatment success compared with a BED of <50 Gy_{10} ($P = 0.040$). Other factors considered to affect treatment success such as good PS (1 or 2) and Hb level before RT were not correlated with outcome ($P = 0.26$ and $P > 0.99$, respectively).

After completion of RT, two of three patients without prior chemotherapy could switch to chemotherapy, whereas seven of ten patients with one previous chemotherapy regimen could shift to second-line chemotherapy. Only one of six patients with two prior chemotherapy regimens could continue chemotherapy. Of eight patients in whom oral

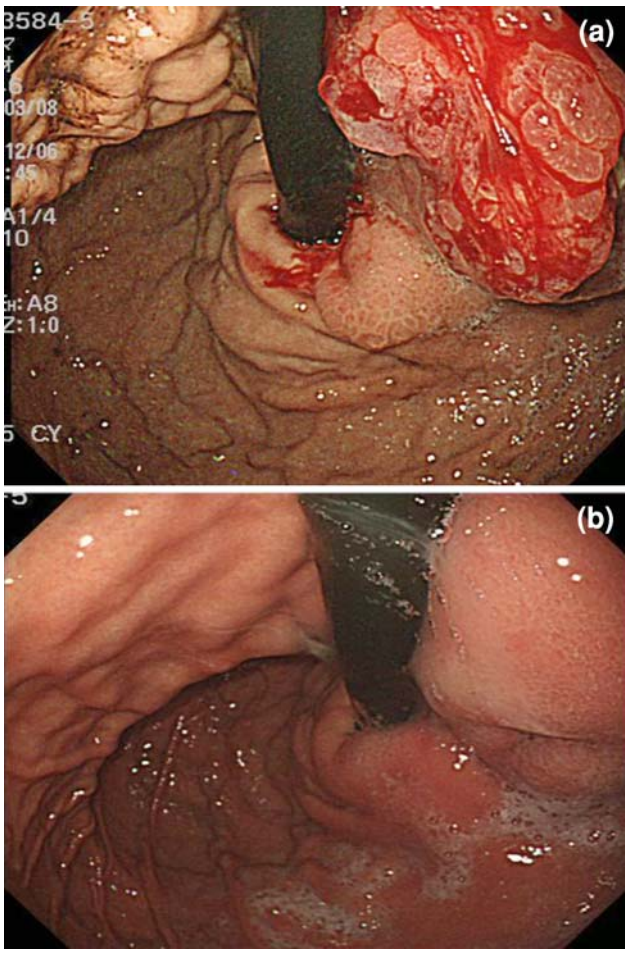

Fig. 1 Typical endoscopic findings. **a** Hemorrhagic gastric cancer of stomach body before radiation therapy. **b** Complete hemostasis following radiation therapy (40 Gy) of the same site

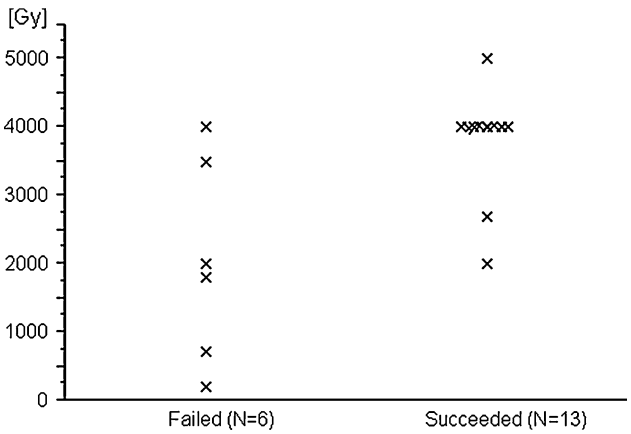

Fig. 2 Dose–effect relationship

intake was prohibited due to gastric bleeding before RT, four (50%) resumed oral intake after RT.

Survival analysis and adverse events

As shown in Figs. 3 and 4, the median EFS from the end of RT and the OS from the first day of RT were 1.5 and 3.4 months, respectively. For EFS, one patient underwent blood transfusion after RT because of anemia, which was supposed to be caused by the subsequent chemotherapy following RT. The median survival time of all patients from the first diagnosis was 12.7 months.

The observed adverse events presented in Table 3 show the frequent occurrence of hematological adverse events. However, most of the patients with grade 3–4 hypohemoglobinemia showed the same grade before, during and after RT. One patient who received chemoradiotherapy developed grade 3 leukocytopenia with no sign of infection. Although there were three patients with grade 3 anorexia (one patient underwent chemoradiation), all of them recovered immediately after completion of RT.

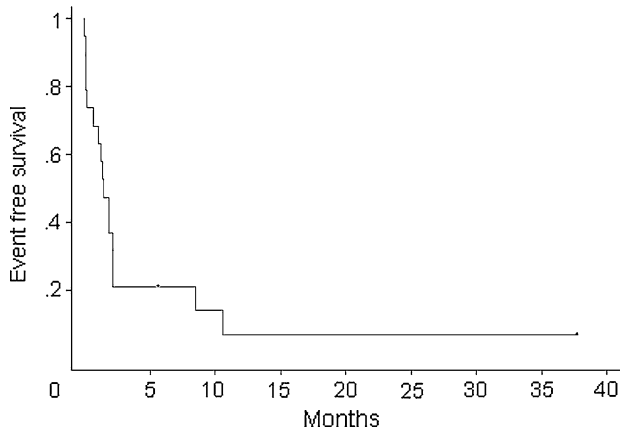

Fig. 3 Event-free survival from the day of completing radiation

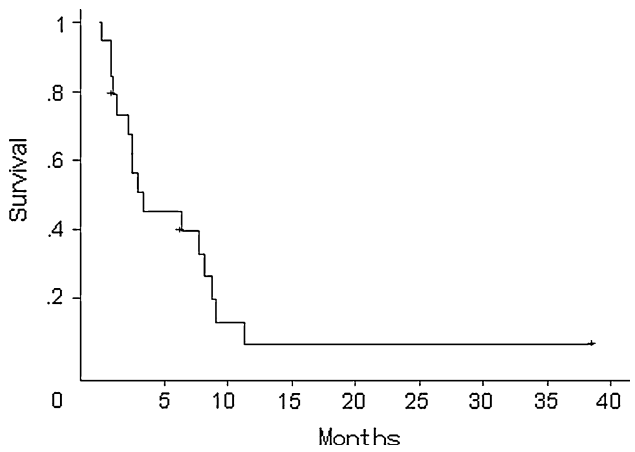

Fig. 4 Survival from the day of starting radiation

Table 3 Toxicity in patients receiving radiation

	Grade 1	Grade 2	Grade 3	Grade 4
Leukocyte	0	2	2[a]	0
Hemoglobin	0	4	9[b]	6[c]
Platelet	0	0	0	0
Anorexia	3	4	3	0
Nausea	3	1	1	0
Lethergy	3	2	0	0
Diarrhea	1	0	0	0
Dysphagia	0	1	0	0

[a] One patient received chemoradiation

[b] Ten patients had grade 3 hemoglobin at start of radiation

[c] Two patinets had grade 4 hemoglobin at start of radiation

Discussion

We confirmed here the efficacy of palliative RT in achieving hemostasis in patients with bleeding from gastric cancer. In our clinical experience, successful hemostasis was observed in 13 of 19 patients (68%), without severe adverse effects.

Several reports of palliative RT for local symptom control in patients with unresectable or metastatic gastric cancer are found in the literature. Moreover, several investigators have applied RT for the palliation of obstructive symptoms. Mantell (1982) reported that palliative RT improved dysphasia in 13 of 17 patients (76%). Coia et al. (1998) showed that a combination of RT, fluorouracil and mitomycin successfully relieved dysphasia in six of nine patients (67%). More recently, Kim et al. (2007) have reported that 13 (81%) of 16 patients with dysphasia/obstruction positively responded to RT.

For bleeding control, Tey et al. (2007) reported that 13 of 24 patients (54%) with bleeding from gastric cancer were responsive to RT. However, they simply defined a positive response as improvement or stabilization of the Hb level without providing any discussion on blood transfusion. Kim et al. (2007) have also reported that palliative RT was successful in achieving hemostasis in 14 (70%) of 20 patients. Bleeding was controlled for a median of 11.4 months, which corresponded to 81% of the patients' remaining life (Kim et al. 2007).

In the present analysis, we defined treatment success as absence of the need for blood transfusion for more than 1 month after RT without any other cause of death. Our results are comparable with those of previous reports. We also demonstrated the median duration of sustained

efficacy; however, the median EFS of 1.5 months here was shorter than that of Kim's report. This can be explained by the difference in the definition of treatment success and cohort differences. We believe that the cohort of this study has limited survival when RT was conducted. Interestingly, Kim et al. simply defined treatment success as the absence of the need for coagulation, or no compliant of symptoms during follow up; however, they made no mention about blood transfusion. Here, the median OS was 3.4 months, also shorter than those reported by Tey et al. (2007) and Kim et al. (2007). Most patients analyzed here had poor PS with severe bleeding, and all of them were classified as stage IV and thus ineligible for operation. Moreover, heterogeneous patients who presented with not only bleeding but also stenosis or pain were included in the analysis in previous reports (Kim et al. 2007; Tey et al. 2007).

The reported palliative RT doses for unresectable gastric cancer range widely from 8 to 60 Gy. Tey et al. found no dose–response relationship between responders and non-responders ($P = 0.078$), whereas Kim et al. suggested that a BED of 41 Gy_{10} or more was correlated with better local symptom control ($P = 0.05$). Our data demonstrated a significant dose–response relationship between BEDs of 50 Gy_{10} or more and <50 Gy_{10} ($P = 0.040$). These results are based on the fact that only patients with bleeding were analyzed, and our definition of hemostasis was a clearer objective endpoint than that of other reports. In our experience, successful hemostasis was observed in as high as 91% of patients who completed an initial planned dose (mostly 40 Gy in 16 fractions: BED of 50 Gy_{10}). Despite this relatively high dose, toxicities were tolerable in most patients similarly to other reports (Kim et al. 2007; Tey et al. 2007).

Kim et al. suggested that a lower RT dose (BED <41 Gy) correlated with poor local control (56 and 70%), while Tey et al. found no evidence suggestive of a dose–response relationship. Most patients received a BED of 39 Gy_{10}, which corresponds to a dose of 30 Gy in ten fractions. Thus, different cut-off points may produce different result from ours.

It remains a matter of debate whether gastrectomy for preventing mortality from local progression can improve survival of patients with metastatic gastric cancer. A previous cohort study has shown that only 7% of gastric cancer patients with metastases not undergoing gastrectomy needed intervention due to bleeding (Sarela et al. 2007). Their median survival time was similar to those of a previous series of patients undergoing gastrectomy. A clinical trial is now underway in Japan and Korea to compare the effects of chemotherapy following gastrectomy with the effects of chemotherapy without gastrectomy in patients with metastatic gastric cancer.

Because of the retrospective nature of the present analysis, there are a number of study limitations that may have affected the interpretation of our findings. The dose used in our facility may not always be valid in other facilities because the best available dose has not yet been established. Also, patient population was not homogenous because palliative RT was not used for initial treatment in most cases. Moreover, patients with gastric cancer who presented with bleeding after the failure of several chemotherapeutic regimens might be more resistant to palliative RT. Additionally, those showing good PS with less bleeding could easily complete the total planned dose, and thus may easily be considered as treatment success. On the other hand, those with pronounced bleeding could hardly complete the planned dose. In the present study, the treatment failure group included patients who discontinued the irradiation course because of deterioration of general condition. The dose–response relationships in our study might also be biased. Further studies in large number of patients are warranted to elucidate the appropriate dose for the palliation of bleeding from gastric cancer.

In conclusion, palliative RT was shown to be a powerful treatment of choice for achieving hemostasis in patients with bleeding from gastric cancer. Successful hemostasis was achieved in as high as 91% of patients who completed the initial planned dose (mostly 40 Gy in 16 fractions). A BED of 50 Gy_{10} or more was significantly correlated with treatment success compared with a BED of <50 Gy_{10} ($P = 0.040$). We recommend 40 Gy in 16 fractions for palliating bleeding from gastric cancer according to our analysis. Palliative RT is considered to be helpful not only in rendering transfusion unnecessary but also in re-starting oral nutrition, as well as in potentiating a positive response to other chemotherapy regimens.

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