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Original Article

Radical Radiotherapy for Hemodialysis Patients with Esophageal Cancer

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Abstract

The aim of this study was to assess outcomes of radical radiotherapy for eight hemodialysis patients with esophageal cancer. A total of eight hemodialysis patients with esophageal cancer were treated by radical radiotherapy at Kyushu University Hospital in January 2008–June 2016. Their clinical stages were IA–IV. Radiation doses ranged from 60 to 70 Gy (median 65.4 Gy). Docetaxel was administered weekly to three patients. The initial response was graded according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 and acute adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0. The complete response (CR) rate was 50% (n=4). The T-stage of all four CR patients was T1b. The 1-year cumulative survival rate was 35%. Esophagitis (≥grade 3) was observed in four patients. Gastrointestinal bleeding occurred in two patients ; life-saving efforts were not successful. Dialysis patients with T1b esophageal cancer could achieve good initial treatment response by radical radiotherapy. However, their risk of severe mucosal disorders might be higher than that of non-dialysis patients. Chemotherapy in particular might make adverse events more severe.

Key words : esophageal cancer, hemodialysis, radical radiotherapy, chemoradiotherapy

Introduction

Esophageal cancer, a highly virulent malignancy, was responsible for 9,500 deaths in Japan in 2015, accounting for 4% of total cancer deaths[1)]. The number of hemodialysis patients in Japan in 2011 was over 300,000 and is now increasing, and some of the hemodialysis patients in Japan who also have esophageal cancer are treated by radiotherapy[2)].

It is well known that the risk of upper gastrointestinal bleeding is increased among hemodialysis patients, and it is a concern that serious adverse events could be induced in hemodialysis patients by radiotherapy, such as mucositis, ulcer, bleeding increase[3)~5)]. However, there are few reports about treatment outcomes after radiotherapy for hemodialysis patients with esophageal cancer. Here we report the treatment outcomes of radical radiotherapy for a small series of hemodialysis patients with esophageal cancer.

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Table 1 Patient characteristic

Patient	Sex	Age	Stage	TNM	Comobidity	Dose (Gy)	Chemo
1	M	71	IIIA	T2N2M0	DM, HT, IHD	65.4	+
2	M	63	IV	T3N3M1	DM	65.4	+
3	M	70	IA	T1bN0M0	−	61.4	+
4	F	80	IIIB	T3N2M0	−	60	−
5	M	82	IA	T1bN0M0	DM, HT	66	−
6	F	66	IA	T1bN0M0	DM, HT	64	−
7	M	73	IIIC	T4bN2M0	DM, HT	60	−
8	M	64	IIB	T1bN1M0	−	70	−

Chemo : chemotherapy, DM : diabetes mellitus, HT : hyper tension, IHD: ischemic heart disease

Patients and Methods

We evaluated the cases of eight hemodialysis patients with esophageal cancer who were treated by radical radiotherapy at Kyushu University Hospital between January 2008 and June 2016. The ethic committee of our institution approved this study. Table 1 shows the characteristics of all patients. Six patients were male and two were female. The ages ranged from 63 to 82 years (median 70.5 years old). The clinical stage was IA in three patients, IIB in one patient, IIIA in one patient, IIIB in one patient, IIIC in one patient and IV in one patient according to the International Union Against Cancer 2009. Of all patients, five (62.5%) had comorbidities. They all had diabetes ; four patients (50%) had hypertension and one patient (12.5%) had ischemic heart disease.

Radiotherapy was delivered using 10 megavoltage (10MV) X-rays. The eight patients received a total dose of 60 to 70 Gy (median 65.4 Gy). The clinical target volume (CTV) encompassed the esophageal tumor with a 30-mm longitudinal margin and a 10-mm radial margin, any grossly involved nodal site, the supraclavicular nodes in cervical lesions and the upper thoracic esophageal lesions, the supraclavicular nodes and celiac nodes in the middle thoracic esophageal lesions, and celiac nodes in the lower thoracic esophageal lesions. However, for a patient with middle thoracic esophageal cancer, the supraclavicular nodes and celiac nodes were not included. Weekly docetaxel 10 mg/mm^2 (weekly DOC) chemotherapy was administered to three patients.

We calculated the cumulative survival rate at 1 year from the start of radiotherapy, using the Kaplan-Meier method. In some cases, we were unable to acquire CT images after treatment, and we therefore evaluated the initial response of the primary lesions after radiotherapy by performing endoscopy. The initial response was graded according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1. We divided the eight patients into three groups : complete response (CR), non-complete response (non-CR) or progressive disease (PD). Acute adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0. Adverse events that were grade 3 or greater were defined as severe adverse events.

Results

Local treatment response

Four of the patients (50%) achieved a CR, three of the other patients had a non-CR and the other patient had a PD. The T-stage of all four CR patients was T1b. Of the patients with T1b esophageal cancer, chemotherapy was administered to only one patient, and the other three patients were treated by radiation therapy alone. In those patients, a radiation dose of 60-70 Gy (median 65 Gy) was delivered. In contrast, all

Table 2 Treatment response, severe adverse event and survival

Patient	Initial treatment response	Follow-up period (month)	Acute adverse event	Survival
1	PD	4.5	esophagitis (G4), bleeding (G5)	Treatment related death
2	non-CR	3	esophagitis (G4), bleeding (G4), DIC (G5)	Treatment related death
3	CR	4	esophagitis (G3), infection (G3)	Alive without disease
4	non-CR	6	anorexia (G3)	Death from disease
5	CR	58	none	Death from other disease
6	CR	49.5	none	Death from late adverse event
7	non-CR	3	none	Alive with disease
8	CR	6	esophagitis (G3)	Alive without disease

CR : complete response, G : grade, DIC : disseminated intravascular coagulation

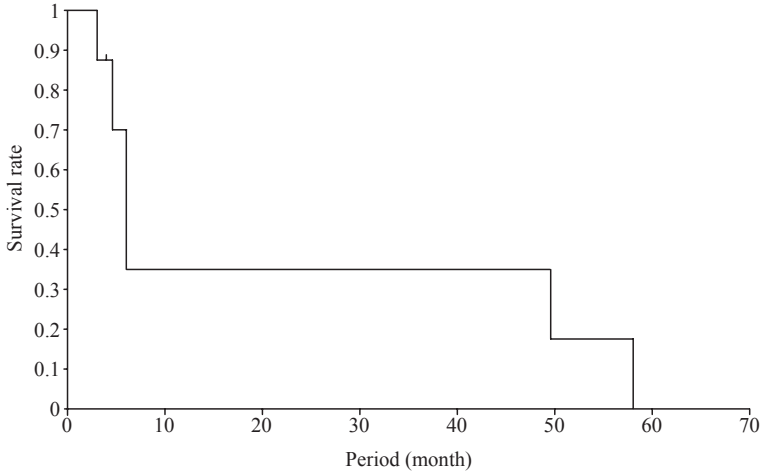

Fig. 1 The cumulative survival rate
The cumulative survival rate at 1 year was 35%.

non-CR patients had advanced esophageal cancer. Of the three patients who received chemoradiotherapy (CRT), only one patient (33%) achieved a CR ; another patient (33%) had a non-CR and the other patient (33%) had a PD. Of the five patients who were treated by RT alone, three patients (60%) achieved a CR and the other two (40%) had a non-CR (Table 2).

Survival

Two patients survived without recurrence, five patients died, and one patient dropped out during the follow-up. The cumulative survival rate at 1 year was 35% (Fig. 1). The T-stage of both patients who survived without recurrence was T1b. Two patients died from treatment-related toxicity, another patient's death was related to esophageal cancer, one death was related to a late adverse event, and the cause of one death was unknown. One of the two treatment-related deaths was caused by gastrointestinal bleeding from an aortoesophageal fistula after treatment, and another was caused by gastrointestinal bleeding from esophagitis during treatment and subsequent infection. One patient died of uncontrollable pleural effusion which was considered to be a late adverse event after 49 months of treatment. The longest-surviving patient died after 58 months of treatment. Although recurr-

Table 3 Mucosal disorder in chemoradiotherapy for non-dialysis patients with esophageal cancer

Author	Radiation dose	Chemotherapy	Mucosal disorder
Kato K	60 Gy/30 Fr	5-FU + CDDP	13/76 (17%)
Crosby T	50 Gy/25 Fr	CDDP + CAP	7/129 (5%)
Crosby T	50 Gy/25 Fr	CDDP + CAP + Cmab	3/129 (2%)
Font A	66 Gy/33 Fr	DOC	6/34 (17%)
Kubo N	60 Gy/30 Fr	DOC	1/8 (12.5%)
Maruyama S	60 Gy/30 Fr	DOC	0/10 (0%)
Nagahama T	60 Gy/30 Fr	DOC	0/4 (0%)

5-FU : 5-fluorouracil, CDDP : cisplatin, CAP: capecitabine, Cmab: cetuximab, DOC : docetaxel

ence was not observed in this patient, the cause of death could not be specified.

Acute adverse events

Mucosal disorders of grade 3 or greater were observed in four of the eight patients. In three of these patients, chemoradiotherapy (CRT) with weekly DOC was administered, and the cessation of radiotherapy and/or chemotherapy was required due to severe mucosal disorders. Gastrointestinal bleeding was observed in two patients, and life-saving efforts were not successful. The other patients did not need a prolongation of the treatment period that was associated with acute adverse events.

Discussion

We have analyzed and reported the outcomes of eight dialysis patients treated by radical radiotherapy for esophageal cancer. There has been no comprehensive report about radical radiotherapy for esophageal cancer of dialysis patients, to our knowledge ; this is the first such report. Our analyses indicated that the patients with advanced esophageal cancer could not achieve a CR by radical radiotherapy. However, all of the patients with a T1b tumor achieved a CR. This proportion of CR was equivalent to a result reported for CRT in Stage I patients (87.5%)[6], suggesting that dialysis patients with T1b esophageal cancer might achieve good local control by a radical dose (60-70 Gy) radiotherapy. Some case reports also showed successful treatment for esophageal cancer of hemodialysis patients with CRT[7)~9)]. Radical radiotherapy could be one of the treatment options for hemodialysis patients with esophageal cancer.

Table 3 summarizes the incidence of mucosal disorder following chemoradiotherapy for non-dialysis patients with esophageal cancer[10)~15)]. Kato et al. reported that grade 3 or 4 esophagitis occurred in 13 of 76 non-dialysis patients (17%) with esophageal cancer treated by CRT (60 Gy/30 Fr) combined with cisplatin (CDDP) and 5-fluorouracil (5-FU) [10]. According to a report by Font et al., of the 34 non-dialysis patients treated by CRT combined with weekly DOC, only 6 (17%) had grade 3 or higher esophagitis[12]. They reported two treatment-related deaths due to radiation pneumonitis. Kubo et al. reported that an esophagomediastinal fistula was observed in 1 of 8 non-dialysis patients treated by CRT (60 Gy/30 Fr) combined with DOC, but the others were treated very safely[13]. There were some reports of no serious complications in CRT (60 Gy/30 Fr) combined with DOC[14)15)]. In the present study, grade 3 or more severe esophagitis and esophageal bleeding were observed in all three of the patients treated with DOC. This result suggested that dialysis might be a high risk for conducting CRT.

CDDP and 5-FU are commonly used for CRT for locally advanced esophageal cancer. CDDP is

metabolized in the kidneys, and thus dialysis patients need dialysis at appropriate timing[9]. DOC is metabolized in the liver, and it is not affected by dialysis ; DOC was thus used for the present patients. DOC inhibits the polymerization of intracellular microtubules and suppresses cell division, thereby exerting an antitumor effect. As a result, tumor cells stop in the G2M phase, when cells are radiosensitive[16]. In previous reports[12)~15)], most of the DOC toxicities were mild, but some severe adverse events such as radiation pneumonitis and esophagomediastinal fistula were described. Two of the present patients' treatment-related deaths might have been related to the toxicity of DOC. In the CRT for dialysis patients, the choice of chemotherapy drug must be considered carefully.

In one of our five patients treated by RT alone, grade 3 mucositis as an acute adverse event occurred. This patient received 70-Gy irradiation. Although 70 Gy is a safe dose as radical irradiation for the esophageal cancer of non-dialysis patients, it might cause severe acute toxicity in dialysis patients. This is because the mucosal layer of the gastrointestinal tract decreases or weakens with malnutrition, and the mucosal membrane breakdowns due to repeated ischemia during dialysis[17)~21)]. However, the patients who was treated by RT alone did not need a prolongation of the treatment period that was associated with acute adverse events. A radical radiotherapy had good tolerability for dialysis patients with T1b esophageal cancer.

In conclusion, a radical radiotherapy for dialysis patients with T1b esophageal cancer had good tolerability and achieved good initial treatment response. However, the risk of severe mucosal disorders might be higher in dialysis patients than in non-dialysis patients. Chemotherapy in particular might make adverse events more severe.

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（和文抄録）

透析中の食道癌患者に対する根治的放射線治療の成績

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目的：透析中の食道癌患者 8 名に対する根治的放射線治療の成績について後方視的に検討する．
対象，方法：2008 年 1 月から 2016 年 6 月に九州大学病院にて根治的放射線治療を受けた透析中の食道癌患者 8 名を対象とした．臨床病期は IA 期から IV 期で，照射線量は 60～70 Gy（中央値 65.4 Gy）だった．3 名の患者に化学療法として，weekly docetaxel を投与した．初期治療効果は the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1, 急性期有害事象は the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0 に基づいて評価した．
結果：完全奏効率は 50%（n=4）で，いずれも T ステージが T1b の症例だった．1 年累積生存率は 35%だった．Grade 3 以上の重篤な食道炎を 4 例で認めた．2 例で致死的な消化管出血を認めた．
結語：透析患者において，T1b の食道癌に対する根治的放射線治療は良好な初期治療効果を示した．一方で，重篤な粘膜炎のリスクが非透析患者に比べて高い可能性が示唆された．特に化学療法を併用する際には注意が必要である．

キーワード：食道癌，透析，根治的放射線治療，化学療法