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Original article

Usefulness of Chemoradiotherapy for Inoperable Gastric Cancer

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Abstract

Purposes: Surgery is the standard local treatment for gastric cancer and radiotherapy is not commonly used in Japan. We report the results of chemoradiotherapy in patients with advanced or recurrent gastric cancer which was deemed difficult to treat surgically.

Methods: Twenty-one patients with gastric cancer (including 16 with advanced/recurrent gastric cancer and 5 with poor general condition) underwent chemoradiotherapy, for whom the therapeutic efficacy, toxicity, and survival period were analyzed.

Result: The tumor response to chemoradiotherapy was as follows: CR, PR, SD, and PD in 5, 9, 3, and 4 patients, respectively, with an overall response rate of 67%. No serious complications such as gastrointestinal perforation or bleeding occurred, and no cardiac, hepatic, or renal dysfunction developed during the follow-up period. The mean survival time was 19.8 months (range, 3-51 months). One patient died of another disease, 17 died of primary cancer, and the other patient is alive, respectively, while the cause of death is unknown is 2 patients.

Conclusion: Chemoradiotherapy appears to be an effective treatment for localized gastric cancer without distant metastases, but further studies are needed to determine the indications for chemoradiotherapy and the late side effects, as well as the chemotherapy regimens to be used.

Keywords: Non-Curative Resection; Advanced/Recurrent Gastric Cancer; Chemo-Radiation Therapy

Introduction

In Japan, advanced or recurrent gastric cancer is usually treated by palliative surgery and/or chemotherapy[1-3]. The development of new anticancer drugs has led to improved survival in patients with advanced or recurrent gastric cancer, and increased the chance of surgical treatment as a part of combined-modality therapy. However, the oncological benefit of aggressive resection and tumor reduction therapy for advanced or recurrent gastric cancer remain unclear. On the other hand, radiotherapy is not commonly used for the treatment of gastric cancer in Japan, where surgery is the standard local treatment[1-3], and adenocarcinoma is not generally regarded as radiosensitive. Furthermore, radiotherapy is associated with side effects. Among gastrointestinal cancers, squamous cell carcinomas such as esophageal and anal cancers, are often treated with radiotherapy, but adenocarcinomas are generally treated by surgery and/or chemotherapy. However, recent reports from Europe and the Unites States demonstrated the usefulness of radiotherapy as local treatment for gastric

cancer, and adjuvant and neoadjuvant chemoradiotherapy have attracted attention[4-7].

Methods

We examined the characteristics of 21 patient with gastric cancer underwent chemoradiotherapy as first treatment between January 2005 and May 2013, and evaluated the safety, feasibility, response rate, toxicity, and survival, without the comparison with the chemotherapy alone. The patient characteristics are shown in Table 1.

Age (years)	76.1 ± 7.1
Sex (Male:female)	15:6
Stage (I/II/III/IV/unknown)	1/2/1/16/1
Unresectable Poor general condition Histological type (Well/Mod/Por/Sig/NEC*/unknown)	0/0/0/16/0 1/2/1/0/1 3/7/5/3/1/2
Reason for selecting chemoradiotherapy	
(Unresectable/Poor general condition)	16/5
Chemotherapy regimen	
(TS-1/5-FU+Low-dose CDDP/none)	15/5/1
Mean irradiation dose (Gy)	50.4 ± 4.5

NEC*: neuroendocrine carcinoma

Table 1. Patients' characteristics

Gastric carcinoma was diagnosed by endoscopy and biopsy. Endoscopic ultrasound (EUS) and enhanced CT scan were operated for clinical T and N stages. The indication for chemoradiotherapy consisted of extensively invasion of the surrounding organs in 16 patients with unresectable advanced and recurrent gastric cancer, and due to advanced age and poor general condition in the other 5 patients. In this study, patients studied consisted of those who had no distant metastases or carcinomatous peritonitis on preoperative imaging and whose lesion was confined to the intended radiation field. The chemotherapy regimen for patients who tolerated oral intake consisted of TS-1 (80-100 mg/body) given for 4 weeks followed by a 2-week off drugs, and that for those who had difficulty with oral intake consisted of 5-FU (250-500 mg/body) plus CDDP (5-10 mg/body) given for 4 weeks. Bilateral irradiation (2 Gy/day) was given using a LINAC. The mean irradiation dose was 50.4 ± 4.5 Gy. After chemoradiotherapy, tumor response was evaluated based on the findings of contrast-enhanced computer tomography (CE-CT) and EUS according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Each patient enrolled in the study provided written informed consent.

Results

The tumor response to chemoradiotherapy was as follows: CR (Figure. 1, case 10), PR, SD, and PD in 5, 9, 3, and 4 patients, respectively, with an overall response rate of 67%. Eighteen patients resumed oral diet, and were discharged.

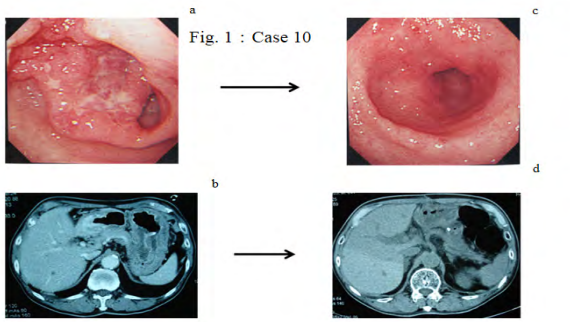

Figure 1

a, b: A Type 3 lesion involved 4/5 of the circumference on the lesser curvature side of the gastric antrum.

c, d: The tumor disappeared, with only mild residual erosions.

Over all response rate	67%
CR/PR/SD/PD	5/9/3/4
Serious side effects	None
(gastrointestinal perforation and bleeding)	
Chemotherapy discontinued due to leukopenia	9 (all grade 1)
(radiotherapy could be completed in all patients)	19.8 (3-51)months
Mean survival period	
Unresectable	22.3±14.6(5-51)months
Poor general condition	12±7.68(3-23)months

CR= complete response, PR= partial response,
SD= stable disease, PD= progressive disease

Table 2. Summary of clinicopathologic features

No serious complications such as gastrointestinal perforation or bleeding were encountered, and no cardiac, hepatic, or renal dysfunction developed during the follow-up period. While

chemotherapy was discontinued in nine patients because of grade 1 leukopenia, radiotherapy was continued. The mean survival time was 19.8 months (unresectable patients: 22.3±14.6months, poor general condition: 12±7.68months). Because the patients background with The SPIRITS trial [8] is different from this study, the comparison of both groups is not accurate. However, the mean survival time of this study was longer than The SPIRITS trial (n=148: 13 months), and the response rate of this study was better than The SPIRITS trial (n=87target tumors: 54%). One patient died of aspiration pneumonia, 17 died of primary cancer, and one patient is alive, while the cause of death is unknown in 2 patients (Tables 2). The main cause of death due to the primary disease is peritoneal dissemination and distant metastasis out of the irradiation range.

Discussion

According to the Japanese gastric cancer treatment guidelines, gastric cancer has a low sensitivity to radiotherapy, and cannot be cured by radiotherapy alone, although it is effective in relieving pain and other symptoms due to cancer invasion and bone metastasis [9-11]. Therefore, in Japan, radiotherapy is not commonly used to prolong life in patients with gastric cancer. However, in the United States, MacDonald et al.[11,12] reported that the 3-year survival rate was significantly higher in patients with gastric cancer treated with postoperative chemotherapy (5-FU + leucovorin) and radiotherapy than that in those treated by surgery alone (50% vs. 41%, respectively). In the present study, chemoradiotherapy for localized, invasive gastric cancer without distant metastases or peritoneal dissemination caused only mild side effects during short-term follow-up, and achieved a good response rate. These results suggest that chemoradiotherapy deserves serious consideration in patients with gastric cancer who are not amenable to curative resection or difficult to treat by surgery because of an advanced age or poor general condition [13-16]. Accurate identification of the lesions involved including peritoneal dissemination and the setting of the irradiation range are important to avoid recurrence after the chemoradiotherapy. Reported serious side effects of chemoradiotherapy for gastric cancer include gastrointestinal perforation and bleeding [17-19], which did not occur in this study. In addition, no cardiac, hepatic, or renal dysfunction developed during the follow-up period. However, these side effects may cause problems in the future if long-term survival is achieved [20-23]. Moreover, for the patients with advanced or recurrent gastric cancer which was deemed difficult to treat surgically, we believe that the survival benefit is more important than the long-term side effect.

In conclusion, chemoradiotherapy for patients with inoperable gastric cancer was successful without the short-term serious side effect, and yielded a response rate of as high as 67%. Chemoradiotherapy appears to be effective in the treatment of localized lesions without distant metastases. However, further robust clinical studies and the collection of large-scale data are still required to determine the indications for chemoradiotherapy for gastric cancer and on late side effects, as well as the chemotherapy regimens to be used. Moreover, we think that prospective study which compares chemoradiotherapy with chemotherapy should be planed for the patients of unresectable advanced and recurrent gastric cancer without distant metastasis.

Conflict of interest statement: Yoshiyuki Hoya and other co-authors have no conflict of interest.

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