Usefulness of chemoradiotherapy for inoperable gastric cancer

T Taki¹, Y Hoya¹, A Watanabe¹, T Nakayoshi¹, T Okamoto¹, H Sekine², N Mitsumori², K Yanaga³

¹Department of Surgery, Jikei University Daisan Hospital, Tokyo, Japan

²Department of Radiology, Jikei University Daisan Hospital, Tokyo, Japan

³Department of Surgery, Jikei University School of Medicine, Tokyo, Japan

ABSTRACT

INTRODUCTION Radiotherapy is not commonly used for the treatment of gastric cancer in Japan, where surgery is the standard local treatment. 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 sixteen with advanced/recurrent gastric cancer and five with poor general condition) underwent chemo-radiotherapy, for whom the therapeutic efficacy, toxicity and survival period were analysed.

RESULTS The tumour response to chemoradiotherapy was categorised as complete, partial, stable or progressive 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, 18 died of primary cancer and the cause of death was unknown in 2 patients.

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

KEYWORDS

Non-curative resection – Advanced gastric cancer – Recurrent gastric cancer – Chemo-radiation therapy

Accepted 5 September 2016

CORRESPONDENCE TO

Yoshiyuki Hoya, E: hoya@jikei.ac.jp

Introduction

In Japan, advanced or recurrent gastric cancer is usually treated by palliative surgery and/or chemotherapy.^{1–5} The development of new anticancer drugs has led to improved survival in patients with advanced or recurrent gastric cancer, and has increased the chances of surgical treatment as a part of a combined modality therapy. However, the oncological benefit of aggressive resection and tumour reduction therapy for advanced or recurrent gastric cancer remains unclear. Radiotherapy is not commonly used for the treatment of gastric cancer in Japan, where surgery is the standard local treatment,^{1–5} and adenocarcinoma is not generally regarded as radiosensitive. Furthermore, radiotherapy is associated with adverse effects. Among gastrointestinal cancers, squamous cell carcinomas such as oesophageal and anal cancers are often treated with radiotherapy but adenocarcinomas are generally treated with surgery and/or chemotherapy. However, recent reports from Europe and the

United States have demonstrated the usefulness of radiotherapy as a local treatment for gastric cancer, and adjuvant and neoadjuvant chemoradiotherapy have attracted attention.^{4–7}

Methods

We examined the characteristics of 21 patients with gastric cancer who underwent chemoradiotherapy as a first-line treatment between January 2005 and May 2013, and evaluated the safety, feasibility, response rate, toxicity and survival rate in comparison with chemotherapy alone. Patient characteristics are shown in Table 1. Gastric carcinoma was diagnosed by endoscopy and biopsy. Endoscopic ultrasound and contrast-enhanced computed tomography (CE-CT) were operated for clinical TNM stages. The indications for chemoradiotherapy consisted of extensive invasion of the surrounding organs in 16 patients with unresectable primary advanced (2 patients) and recurrent (14 patients) gastric cancer with no distant metastases or carcinomatous

Table 1 Patient characteristics

Characteristic	Tumour stage					Value
	I	II	III	IV	Unknown	
Age (years)						76.1 ± 7.1
Sex (male : female)						15 : 6
Stage:	1	2	1	16	1	
Reason for selecting CR ¹ :						
Unresectable	0	0	0	16	0	
Poor general condition	1	2	1	0	1	
Hystological type:						
Well						3
Mod						7
Por						5
Sig						3
NEC ²						1
Unknown						2
Chemotherapy regimen:						
TS-1						15
5-FU+Low-dose cisplatin						5
None						1
Mean irradiation dose (Gy)						50.4 ± 4.5

¹CR, chemo-radiotherapy; ²NEC, neuroendocrine carcinoma

peritonitis, and because of advanced age and poor general condition in the other 5 patients. Gastrojejunostomy was performed to the 2 patients with primary advanced gastric cancer before chemo-radiotherapy; 9 of 14 patients with recurrent advanced gastric cancer were included after distal gastrectomy and 5 patients after total gastrectomy. All cases of residual stomach cancer were treated as recurrent gastric cancer.

In this study, the patients had no distant metastases or carcinomatous peritonitis on preoperative imaging and lesions were confined to the intended radiation field. The chemotherapy regimen for patients who tolerated oral intake consisted of TS-1 (80mg/m² of body surface area) given orally every day for 4 weeks followed by a 2-week rest. The regimen for those who had difficulty with oral intake consisted of 5-fluorouracil (5-FU; 250mg/m² of body surface area) plus cisplatin (5mg/m² of body surface area) given for 4 weeks. 5-FU was administered intravenously as a 24-hour continuous infusion on days 1–5, 8–12, 15–19 and 22–26. Cisplatin was administered intravenously as a bolus infusion at least 1 hour prior to starting irradiation on days 1–5, 8–12, 15–19 and 22–26.

Patients underwent CT simulation (Aquilion LB, Toshiba Medical Systems) from lower thorax to lower abdomen. The

primary lesion was contoured on axial slices of the planning CT images (slice thickness 2mm) to define as the gross tumour volume (GTV). Typically, a 5-mm margin was added to the GTV to form clinical target volume (CTV) including micro-invasion. A 5–10mm margin was also added to the CTV to form the planning target volume (PTV) for internal movement and/or set up error. For compensation of the beam penumbra, a 5-mm leaf margin was added to the PTV. Treatment planning goals included covering the PTV with more than 95% of the prescription dose, with placement of the normalised point within the GTV.

As illustrated by the patient treatment planning examples in Figure 1 by XiO (Elekta), treatment was delivered using a 6-MeV photon beam (Primus, Toshiba). Treatments were usually delivered using three-dimensional conformal therapy from four field portals and a total of 50 Gy was given in 25 fractions over 5 weeks.

After chemo-radiotherapy, tumour response was evaluated based on the findings of CE-CT, endoscopy and endoscopic ultrasound according to Response Evaluation Criteria in Solid Tumours (version 1.1) criteria.⁸ Overall survival was defined as the interval in months measured between the starts of the treatment and death from any cause, or the last examination of the patient. The analysis of overall survival was calculated using the Kaplan-Meier method. Each patient enrolled in the study provided written informed consent.

Results

The regimen for chemotherapy was TS-1 (15 patients), 5-FU plus low-dose cisplatin (5 patients) and radiotherapy alone (1 patient.) Mean irradiation dose was 50.4 ± 4.5 Gy (Table 1). Tumour response to chemoradiotherapy was as follows: complete response (5 patients; Fig 2), partial response (9 patients), stable disease (3 patients) and progressive disease (4 patients), with an overall response rate of 67%. Eighteen patients resumed an oral diet and were discharged. No serious complications such as gastrointestinal perforation or bleeding were encountered, and no cardiac, hepatic or renal dysfunction developed during the follow-up period. Chemotherapy was discontinued in nine patients because of grade 1 leucopenia, but radiotherapy was continued. The mean survival time was 19.8 months (range 3–51 months); for patients with unresectable disease survival was 22.3 ± 14.6 months (range 5–51 months); and for patients in poor general condition it was 12 ± 7.68 months (range 3–23 months); 1 patient died of aspiration pneumonia, 18 died of primary cancer and the cause of death is unknown in 2 patients (Table 2). The main cause of death due to the primary disease is peritoneal dissemination and distant metastasis out of the radiation field. The survival curve is depicted in Figure 3.

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 In Japan, therefore, 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 5-year survival rate was significantly higher in patients with gastric cancer treated with postoperative chemotherapy (5-FU + leucovorin) and radiotherapy than in those treated by surgery alone (50% vs. 41%, respectively).

In the present study, chemoradiotherapy for localised, invasive gastric cancer with no distant metastases or peritoneal dissemination caused only mild adverse effects during short-term follow-up and achieved a good response rate. Mean survival period for patients with unresectable advanced and recurrent gastric cancer was 22.3 ± 14.6 months (range 5–51 months).

The SPIRITS trial concluded that overall survival was better in patients treated with advanced gastric cancer treated with S-1 plus cisplatin over S-1 alone.¹⁵ The background of patients in this trial is different from this study, so a comparison of both groups would not be accurate. However, the mean survival time in the current study was longer than that found in the SPIRITS trial ($n = 148$, survival time 13 months) and the response rate of this study was better than that of the SPIRITS trial ($n = 87$ target tumours 54%).

These results suggest that chemoradiotherapy deserves serious consideration in patients with gastric cancer who are not amenable to curative resection or are difficult to

Table 2 Summary of the treatment results	
Over all response rate	67%
CR/PR/SD/PD	5/9/3/4
Serious side effects (gastrointestinal perforation and bleeding)	None
Chemotherapy discontinued due to leukopenia (radiotherapy could be completed in all patients)	9 (all grade 1)
Mean survival period	19.8 (3–51) months
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

treat by surgery because of advanced age or poor general condition.^{14–17} Accurate identification of the lesions involved, including peritoneal dissemination and the setting of the radiation field, is important to avoid recurrence after chemo-radiotherapy. Reported serious adverse effects of chemoradiotherapy for gastric cancer include gastrointestinal perforation and bleeding,^{18–20} which did not occur in this study. In addition, no cardiac, hepatic or renal dysfunction developed during the follow-up period. However, these adverse effects may cause problems in the future if long-term survival is achieved.^{21–24} Moreover, for patients with advanced or recurrent gastric cancer which was deemed difficult to treat surgically, we believe that the survival benefit is greater than any long-term adverse effects.

Mean survival period of patients with poor general condition was 12 ± 7.68 months (range 3–23 months) and the adverse effects of chemoradiotherapy and the progression of the cancer was not a cause of death. We were therefore able

to avoid unnecessary surgery for patients with poor general condition.

In conclusion, chemoradiotherapy for patients with inoperable gastric cancer was successful with no serious short-term adverse effects, and yielded a response rate of as high as 67%. Chemoradiotherapy appears to be effective in the treatment of localised lesions with no 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 late-onset adverse effects, as well as the chemotherapy regimens to be used. Moreover, it is our opinion that a prospective study would be useful to compare chemoradiotherapy with chemotherapy looking at patients with unresectable advanced and recurrent gastric cancer without distant metastasis.

References

1. Degiuli M, Sasako M, Ponti A *et al.* Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer. *Br J Cancer* 2004; **90**: 1,727–1,732.
2. Degiuli M, Sasako M, Ponti A *et al.* Morbidity and mortality after D2 gastrectomy for gastric cancer: results of the Italian Gastric Cancer Study Group prospective multicenter surgical study. *J Clin Oncol* 1998; **16**: 1,490–1,493.
3. Sasako M. What is reasonable treatment for gastric adenocarcinoma? *J Gastroenterol* 2000; **12**: 116–1,120.
4. Ajani JA, Winter K, Okawara GS *et al.* Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. *J Clin Oncol* 2006; **24**: 3,953–3,958.
5. Bora H, Unsal D, Akmansu M. Results of chemoradiation after curative resection of locally advanced gastric cancer. *Int J Clin Pract* 2004; **58**: 451–456.
6. Surenkok S, Beyzadeoglu M, Oysul K *et al.* The management of gastric adenocarcinoma with postoperative chemoradiation. A non-randomized comparison of oral UFT and 5-FU. *Tumori* 2008; **94**: 70–74.
7. Roukos DH. Adjuvant chemoradiotherapy in gastric cancer: wave goodbye to extensive surgery? *Ann Surg Oncol* 2002; **9**: 220–221.
8. Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–247.
9. Fu S, Lu JJ, Zhang Q *et al.* Intraoperative radiotherapy combined with adjuvant chemoradiotherapy for locally advanced gastric adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2008; **72**: 1,488–1,494.
10. Saikawa Y, Kubota T, Takahashi T *et al.* Is chemoradiation effective or harmful for stage IV gastric cancer patients? *Oncol Rep* 2005; **13**: 865–870.
11. Shigeoka H, Imamoto H, Nishimura Y *et al.* Complete response to preoperative chemoradiotherapy in highly advanced gastric adenocarcinoma. *World J Gastrointest Oncol* 2010; **15**: 282–286.
12. Macdonald JS, Smalley SR, Benedetti J *et al.* Chemoradiation therapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**: 725–730.
13. Koizumi W, Narahara H, Hara T *et al.* S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9**: 215–221.
14. Henning GT, Schild SE, Stafford SL *et al.* Results of irradiation or chemoradiation for primary unresectable, locally recurrent, or grossly incomplete resection of gastric adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2000; **46**: 109–118.
15. Warenus HM, Britten RA, Peacock JH. The relative cellular radiosensitivity of 30 human in vitro cell lines of different histological type to high LET 62.5 MeV (p→Be+) fast neutrons and 4 MeV photons. *Radiother Oncol* 1994; **30**: 83–89.
16. Warenus HM, Britten RA, Browning PG *et al.* Identification of human in vitro cell lines with greater intrinsic cellular radiosensitivity to 62.5 MeV (p→Be+) neutrons than 4 MeV photons. *Int J Radiat Oncol Biol Phys* 1994; **28**: 913–920.

17. Suit H, Skates S, Taghian A *et al.* Clinical implications of heterogeneity of tumor response to radiation therapy. *Radiother Oncol* 1992; **25**: 251–260.
18. Mackay RI, Hendry JH. The modelled benefits of individualizing radiotherapy patients' dose using cellular radiosensitivity assays with inherent variability. *Radiother Oncol* 1999; **50**: 67–75.
19. Martel P, Deslandes M, Dugue L *et al.* Radiation injuries of the small intestine. Surgical treatment. *Ann Chir* 1996; **50**: 312–317.
20. Yamashita H, Nakagawa K, Tago M *et al.* Small bowel perforation without tumor recurrence after radiotherapy for cervical carcinoma: report of seven cases. *J Obstet Gynaecol Res* 2006; **32**: 235–242.
21. Wals A, Contreras J, Macías J *et al.* Damage assessment in gastric cancer treatment with adjuvant radiochemotherapy: calculation of the NTCP's from the differential HDV of the organs at risk. *Clin Transl Oncol* 2006; **8**: 271–278.
22. Leong T, Willis D, Joon DL *et al.* 3D conformal radiotherapy for gastric cancer—results of a comparative planning study. *Radiother Oncol* 2005; **74**: 301–306.
23. Ringash J, Perkins G, Brierley J *et al.* IMRT for adjuvant radiation in gastric cancer: a preferred plan? *Int J Radiat Oncol Biol Phys* 2005; **63**: 732–738.
24. Wieland P, Dobler B, Mai S *et al.* IMRT for postoperative treatment of gastric cancer: covering large target volumes in the upper abdomen: a comparison of a step-and-shoot and an arc therapy approach. *Int J Radiat Oncol Biol Phys* 2004; **59**: 1,236–1,244.