

## Stereotactic Body Radiotherapy for Isolated Para-aortic Lymph Node Recurrence after Curative Resection in Gastric Cancer

The aim of this study was to investigate whether stereotactic body radiotherapy (SBRT) can salvage gastric cancer patients with para-aortic lymph node (PALN) recurrence. From January 2003 to December 2006, 7 patients were treated for isolated PALN recurrence from gastric cancer after curative resection. Follow up durations ranged from 19 to 33 months (median; 26 months), and SBRT doses from 45 Gy to 51 Gy (median 48 Gy) in 3 fractions. Disease progression-free and overall survivals and toxicities were recorded. Response to treatment was assessed by computed tomography. Final patient outcomes were as follows: 2 were alive without evidence of disease, 3 remained alive with disease, and 2 patients died of disease. Five of 7 patients showed complete response and 2 patients partial response between 3 and 11 months after SBRT. Three-year overall and disease progression-free survival rates post-SBRT were 43% and 29%, respectively. No severe complication was detected during follow-up. Selected patients with isolated PALN recurrence can be salvaged by SBRT without severe complications.

Key Words : Stomach Neoplasms; Recurrence; Radiotherapy

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## INTRODUCTION

Gastric cancer is the most common malignancy in Korea (1). Early detection, surgical technique refinements, and appropriate adjuvant therapy have improved the survival rates of primary gastric cancer patients. However, despite recent advances, gastric cancer is still the second most leading cause of cancer-related death in Japan (2) and Korea (1), and even after complete surgical resection, a substantial proportion of patients succumb to local recurrence or distant metastasis.

Lymph node (LN) metastasis is one of the most important prognostic factors after stomach resection (3). Appropriate extent of lymph node dissection during surgery has been debatable. Though the randomized trials did not support the routine use of extended LN dissection (4, 5), the possibility for extended LN dissection to decrease locoregional recurrences seems plausible. Nashimoto et al. (6) reported that paraaortic lymph node (PALN) metastasis was detected in 25% of gastric cancer patients that had undergone extensive lymphadenectomy, and that the 5-yr survival rate of these patients was 23.1%. Other institutes have reported corresponding 5-yr survival rates of 15.2% (7), 16.0% (8), and 18.6% (9) for gastric cancer patients with PALN metastasis, respectively.

Peritoneal recurrence is regarded to be the most common

type of recurrence after gastric cancer surgery, followed by hematogenous, local, and regional recurrence. When recurrence is discovered after radical surgery in gastric cancer, no standard salvage treatment has been established yet for such patients. This is because almost all recurrent gastric cancers represent advanced cancer progression, such as, peritoneal seeding or extensive LN metastasis. However, few studies (10-12) have been performed on liver resection for metastatic gastric cancer, although it is known that fewer patients with gastric liver metastases are good candidates for resection than among those with metastases from colorectal cancer. Koga et al. (13) reported outstanding 5-yr survival rate of 42% post-diagnosis after the complete resection of isolated liver recurrence, and 8 (19%) of the 42 patients involved remained alive for over 5 yr after the initial hepatectomy. Therefore, we hypothesized that some selected cases among patients with localized gastric recurrences, as like recurrent colorectal cancer, might have indolent disease course and be salvaged by local treatment even the number of cases is limited. The aim of this study was to investigate whether stereotactic body radiotherapy (SBRT) can salvage gastric cancer patients with PALN recurrence. Accordingly, we reviewed 7 patients who underwent SBRT for isolated PALN recurrence from gastric cancer to clarify patient outcome.

## MATERIALS AND METHODS

### Patients

From January 2003 to December 2006, 7 patients with isolated PALN recurrence from gastric cancer after curative resection were treated with SBRT using a CyberKnife (Accuray Inc., Sunnyvale, CA, U.S.A.). Isolated PALN recurrence was initially detected by computed tomography (CT), and was confirmed by elevated standardized uptake values on a paraaortic lesion by positron emission tomography (PET) or PET/CT. Patient characteristics are summarized in Table 1. Briefly, patient ages ranged from 41 to 68 yr (median 56), and the male:female ratio was 5:2. All patients underwent subtotal or total gastrectomy. Adjuvant chemotherapy was performed in 4 patients. Initial pathologic stages were; stage II in 2, stage III in 3, and stage IV in 2. Pathologic diagnoses were poorly differentiated adenocarcinoma or signet ring cell carcinoma in 5 patients and moderately differentiated adenocarcinoma in 2. Interval between operation and first relapse ranged from 10 to 40 months (median 22 months). Six patients showed a conglomerated LN and the other (case 6) had two separate enlarged lymph nodes on a paraaortic lesion. Greatest tumor diameters and heights were obtained after delineating tumors on CT scans during planning, and are itemized in Table 1. Recurrent tumor volumes ranged from 5.6 to 83 mL (median 21 mL). After recurrence had been detected, all patients received chemotherapy based on 5-FU before SBRT.

### SBRT technique

SBRT doses ranged from 45 to 51 Gy (median 48 Gy) and

were administered in 3 fractions. For SBRT, we used gold fiducials (4 mm long and 0.8 mm in diameter) as markers for tumor localization. Six fiducials were placed percutaneously at transverse processes of the spine located nearest tumors using an 18 gauge spinal needle under fluoroscopic guidance. Patients were immobilized using an Alpha Cradle (Smithers Medical Products, North Canton, OH, U.S.A.) for 5-7 days after fiducial placement. Panning CT scans were performed with patients in the treatment position, and these images were then processed for the CyberKnife planning system. Gross tumor volume (GTV) determined based on CT tumor visualizations. To better delineate tumor volume, PET/CT images were used as a reference. Planned target volumes (PTV) were GTV plus a 2-3 mm margin. Radiation doses were prescribed to the 80-83% isodose line of the maximum dose covering the PTV (Fig. 1).

### Survival, response, and toxicity assessments

Overall survival was calculated from the start date of SBRT using the Kaplan-Meier method; median values are reported. Disease progression free survival was also measured from date of the first SBRT to the date of local progression, distant metastasis, or both. All statistical calculations were performed using SPSS, version 13.0 (SPSS, Inc., Chicago, IL, U.S.A.).

On CT scans, complete response (CR) was defined as complete tumor resolution without new lesion development. Partial response (PR) was defined as at least a 50% volume reduction of conglomerated or distinct tumors without new lesion development. Stable disease (SD) was defined as a change in tumor volume ranging from <50% reduction to <25% in-

Table 1. Demographic and clinical data of the 7 patients

Case	Age /sex	Pathology	Initial staging	Adjuvant chemotherapy	Latent time*	Tumor size (longest D* height)	GTV (mL)	Radiation dose (Gy)	Response of tumor (months after SBRT)	Disease progression site	F/U <sup>†</sup> (months)	Final status
1	52/M	P/D	III	Yes	10	3.5*4.0	13	48	CR (11)	-	26	CDF
2	60/M	P/D	II	No	17	6.0*5.9	83	45	CR (5)	-	33	CDF
3	68/F	P/D	IV	Yes	22	2.5*2.0	5.6	48	CR (3)	Rt retrocural LN, mediastinal LN, Lt SCL LN	23	AWD
4	49/M	M/D	III	No	29	4.0*3.9	21	48	CR (5)	PALN, Bone	25	AWD
5	59/M	M/D	IV	Yes	15	3.0*6.2	18	48	PR (3)	PALN, common iliac LN	31	AWD
6	41/M	P/D	II	No	40	4.0*2.6 2.5*1.3	21	45	CR (3)	Local recur subcutaneous multiple brain SCL LN	32	DOD
7	56/F	P/D	III	Yes	25	4.2*4.0	36	51	PR (5)	Liver, peritoneum	14	DOD

\*Latent time, disease free interval from operation to first relapse; <sup>†</sup>F/U, Follow-up duration.

GTV, Gross tumor volume; CR, complete response; PR, partial response; LN, lymph node; Rt, right; Lt, left; SCL, supraclavicular lymph node; PALN, paraaortic lymph node; DOD, died of disease; AWD, alive with disease; CDF, continuously disease-free; SBRT, Stereotactic body radiotherapy.

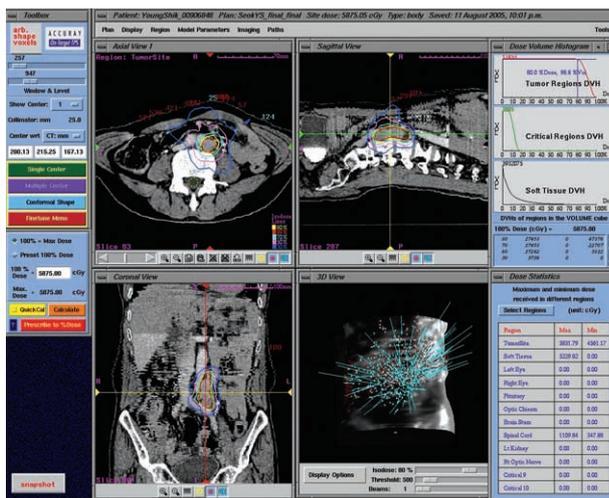


Fig. 1. Planning of 48 Gy SBRT. Gross tumor volume (GTV) was defined as the volume (mL) of the visible LN (innermost line). Radiation dose was prescribed to the 80% isodose line of the maximum dose covering the GTV plus a 2 mm margin. The outermost line is the 30% isodose line.

crease. Progressive disease (PD) was defined as an increase in tumor size of  $\geq 25\%$ . Local progression was defined as increase in tumor size of before CT image or the development of a new lesion in the radiation field.

Acute and late toxicities were defined as symptoms that developed within or after 3 months of treatment completion, respectively.

## RESULTS

Follow up ranged from 14 to 33 months (median; 26 months). Final outcomes were as follows: 2 patients were alive without evidence of disease; 3 remained alive with disease; and 2 patients died of disease (Table 1). Case 7 developed solitary liver metastasis at 5 months after SBRT and subsequent peritoneal seeding, and died after 9 months. However, no local progression in the radiation field was observed in this patient until final follow up. The remaining 5 patients survived longer than 20 months (range; 23–33 months). Among them, two patients (Case 1 and 2) did not show recurrence for 26 and 33 months, respectively. Case 3 developed nodal metastasis in the mediastinal and left supraclavicular areas. Case 4 had PALN metastasis located outside the radiotherapy field and a single bone metastasis, and received repeat SBRT to PALN as well as bone metastasis. Case 5 also developed nodal metastasis in PALN and in the common iliac area. Case 6 developed local relapse at 23 months after SBRT, and died after 9 months due to multiple brain metastases with leptomeningeal seeding.

On CT scans, 5 of the 7 patients showed complete response and 2 patients partial response between 3–11 months post

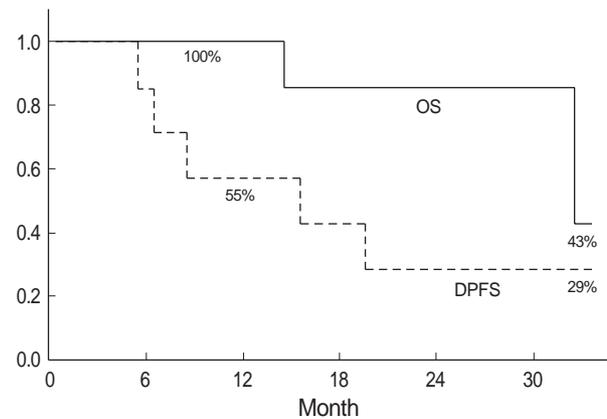


Fig. 2. Three-year overall survival (OS) and disease progression-free survival rates (DPFS) were 43% and 29%, respectively.

first SBRT session. The 3-yr overall survival and disease progression free survival rates were 43% and 29%, respectively (Fig. 2). Grade I acute toxicity such as nausea and vomiting was observed in 2 patients at the first date of SBRT, and relieved without medication. And late complication was not detected during follow-up period.

## DISCUSSION

Peritoneal recurrence or hematogenous metastasis are common type of recurrence after surgery for gastric cancer, and, if extensive LN dissection performed, isolated lymphogenous recurrences are not frequently observed. Roderich et al. (14) reported distant hematogenous metastasis only in 13 (18%) of 73 patients, and peritoneal seeding alone in 8 (11%), and locoregional alone in 2 (3%). Yoo et al. (15) reported peritoneal recurrence alone in 172 (33.9%) of 508 recurrent patients, hematogenous metastasis alone in 133 (26.2%), and locoregional recurrence alone in 98 (19.3%). In these series, most recurrence appeared diffusely at distant or peritoneal sites, and most locoregional recurrences occurred in conjunction with relapse at extraregional sites.

For recurrent gastric cancer after curative resection, repeat surgery was conducted in 12–20% of recurrent gastric cancer patients, as a salvage treatment for local recurrence, for an isolated liver/lung metastasis or for a single peritoneal mass, or for palliative purposes to relieve gastrointestinal obstruction, obstructive jaundice, or ureter obstruction (16–18). Then, 50–85% of patients with re-operation underwent a palliative procedure (17, 18). Park et al. (18) reported 86 reoperation experiences in recurrent gastric cancer. The operative mortality rate was 9 (10.5%) in 86 patients. Excluding the mortality cases, among 77 patients, complete resection was possible in only 13 (17%) patients, and these 13 patients achieved a 50% 5-yr survival rate and a median survival of 21 months, whereas 13 patients that underwent simple laparo-

tomy without any aid had a median survival of only 3.8 months. The other 51 patients received palliative procedure and achieved a median survival of 7.8 months. Ha et al. (19) reported that 241 (20%) of 1,223 gastric cancer patients who underwent curative gastric resection recurred over a 13 yr follow up. In their study, median survival durations were 7, 9.5, and 12.5 months, respectively after the detection of peritoneal seeding, hematogenous metastasis, and locoregional recurrence. However, extent of resection was not specified.

Recently, several studies (20, 21) investigated the therapeutic efficacy of combinatorial chemotherapy in recurrent gastric cancer, and demonstrated excellent responses in a limited number of cases. However, because the numbers of patients enrolled were small and follow up durations were short, further trials must be undertaken to evaluate the role of chemotherapy.

Conventional radiotherapy has played a limited palliative role in the treatment of recurrent gastric cancer involving locoregional recurrence, especially PALN. The proximity between involved lymph nodes and critical organs, such as, the spinal cord, intestine, and colon, often prevents the delivery of sufficient radiation dose for local control when conventional radiation modalities are used. However, SBRT is an emerging technology in the radiation oncology field. This system utilizes stereotactic principles of localization and multiple beams to target lesions accurately. SBRT can deliver higher doses to tumor and cause less tissue damage than other methods. Furthermore, it can have three times the biological effect of fractionated radiation therapy.

Reports on salvage treatment for isolated PALN metastasis are rare. Nashimoto et al. (6) reported a case with a disease-free survival of 6 yr after the dissection of recurrent abdominal PALN in gastric cancer. Also Teraishi et al. (22) reported a recurrence case of gastric cancer with PALN metastasis that showed a marked response to systemic chemotherapy consisting of S-1 alone. After chemotherapy, the patient has remained in remission for more than 21 months with no severe adverse events. In the present study, two (29%) among 7 patients achieved disease free survivals of 26 and 33 months (from the start date of SBRT) without complications, and only one patient showed local progression at 23 months after SBRT. In these studies about PALN recurrence from gastric cancer treated by operation, chemotherapy or SBRT, existence of long term survivors seems to assist our hypothesis which selected cases among recurrent gastric cancer patients with isolated metastasis, as like recurrent colorectal cancer, may have indolent disease course and be salvaged by adjustable treatments.

In conclusion, the present study reports that selected isolated PALN recurrence can be salvaged by SBRT without severe complications. However, further studies are required to confirm our preliminary results in a large number of patients.

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