Table 4. Details of responders treated with weekly paclitaxel

Patient no.	Age (years)	Sex	Metastatic site	Reduction ratio	Total number of administrations	Response duration (days)
1	68	M	Abdominal wall	61%	44	413
2	57	F	LN, peritoneum	32%	6	41
3	65	F	LN, liver	37%	4	50
4	72	M	Liver, LN, peritoneum	36%	5	99
5	71	M	Liver, LN, lung	35%	13	119
6	66	M	LN, abdominal wall, peritoneum	70%	11	328

LN, lymph node

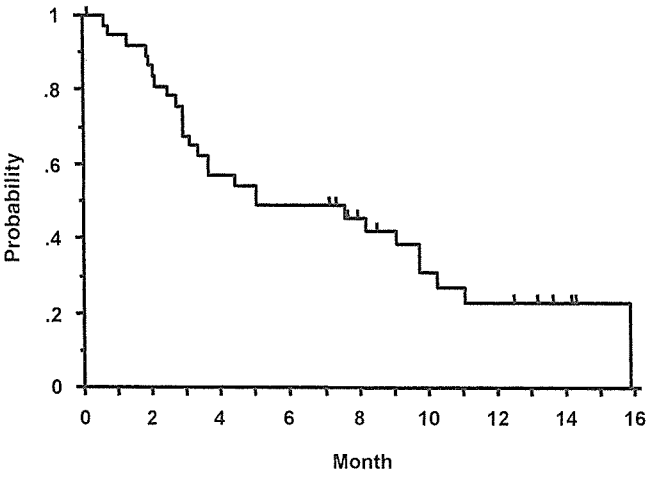

Fig. 1. Kaplan–Meier analysis of overall survival. Median overall survival time was 151 days

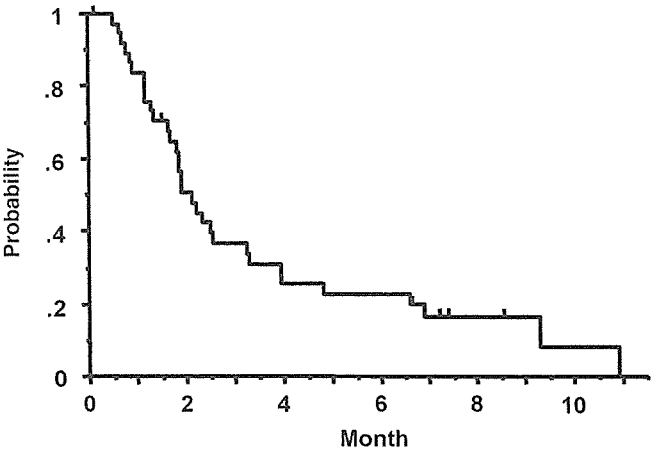

Fig. 2. Kaplan–Meier analysis of time to progression. Median time to progression was 64 days

hematological toxicity. Furthermore, nonhematological toxicities were generally mild.

Seven patients died within 30 days of the last administration of paclitaxel. The causes of the deaths in our study were disease progression in three patients, other medical diseases in two patients, complications due to a metallic stent in one, and treatment-related sepsis in one. These patients had had a severe medical condition or poor oral intake and poor performance status at the last administration of paclitaxel. Therefore, we have to take care regarding the patient's condition and consider cautiously the indications for the administration of paclitaxel.

With weekly paclitaxel therapy, we observed a response rate of 24% in 25 patients with measurable metastatic lesions. Disease stabilization was observed in 40% (10/25). Ascites and pleural effusion decreased or disappeared in 24% (5/21) and 43% (3/7), respectively. Direct comparison of response rates from one trial to another is inherently difficult, given that studies often differ with respect to entry criteria and population characteristics. Nevertheless, overall response rates of 8%–27% have been reported in other trials of single-agent paclitaxel administered for gastric cancer at doses of 210 mg/m^2 by 3-h infusion every 3 weeks for gastric cancer [6–9]. Therefore, our response results are within the range observed in other trials, of paclitaxel given every 3 weeks.

On the basis of previously reported data, the median survival time for metastatic or recurrent gastric cancer is about 7 to 9 months [13–17] with first-line chemotherapy. In the present retrospective study, the median overall survival time after the administration of paclitaxel was about 5 months. These data are the same as the previously reported data [10] for weekly paclitaxel. Our results suggest that weekly paclitaxel may have similar activity to paclitaxel given on a 3-week schedule for patients with metastatic or recurrent gastric cancer after prior therapy.

In conclusion, weekly paclitaxel as second-line chemotherapy was tolerated and demonstrated activity against metastatic and recurrent gastric cancer. How-

ever, its administration in practice must be decided with caution in patients in poor condition. The Japan Clinical Oncology Group (JCOG) is now conducting a randomized phase II trial of weekly paclitaxel versus best available 5-FU for second-line chemotherapy for gastric cancer with peritoneal dissemination.

References

1. Health and Welfare Statistics Association (1999) The movement of population. J Health Welfare Stat 46:41–72.
2. Rowinsky EK, Donehower RC, Jones RJ, Tucker RW. Microtubule changes and cytotoxicity in leukemic cell lines treated with taxol. Cancer Res 1998;48:4093–100.
3. Lopes NM, Adams EG, Pitts TW, Bhuyan BK. Cell kill kinetics and cell cycle effects of taxol on human and hamster ovarian cell lines. Cancer Chemother Pharmacol 1993;32:235–42.
4. Fennelly D, Aghajanian C, Shapiro F, O'Flaherty C, McKenzie M, O'Connor C, et al. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol 1997;15:187–92.
5. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, Gianni L, Myles J, van der Burg ME, et al. European–Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion. J Clin Oncol 1994;12:2654–66.
6. Ajani JA, Fairweather J, Dumas P, Patt YZ, Pazdur R, Mansfield PF. Phase II study of Taxol in patients with advanced gastric carcinoma. Cancer J Sci Am 1998;4:269–74.
7. Yamada Y, Shirao K, Ohtsu A, Boku N, Hyodo I, Saitoh H, et al. Phase II trial of paclitaxel by 3-h infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol 2001; 12:1133–7.
8. Garcia AA, Leichman CG, Lenz HJ, Baranda J, Lujan R, Casagrande Y, et al. Phase II trial of outpatient schedule of paclitaxel in patients with previously untreated metastatic, measurable adenocarcinoma of the stomach. Jpn J Clin Oncol 2001;31:275–8.
9. Ohtsu A, Boku N, Tamura F, Muro K, Shimada Y, Saigenji K, et al. An early phase II study of a 3-h infusion of paclitaxel for advanced gastric cancer. Am J Clin Oncol 1998;21:416–9.
10. Arai T, Hamaguchi T, Shirao K, Shimada Y, Yamada Y, Muro K, et al. Weekly paclitaxel in patients with heavily treated advanced gastric cancer. Proc Am Soc Clin Oncol 2003;22:321.
11. Cho H, Shotsu A, Konishi K, Kanari M, Tsuburaya A, Kobayashi O, et al. Weekly paclitaxel for the second-line treatment of recurrent and advanced cancer (RAGC). Proc Am Soc Clin Oncol 2002;21:357.
12. Gehan EA, Tefft MC. Will there be resistance to the RECIST (Response evaluation criteria in solid tumors)? J Natl Cancer Inst 2000;92:179–81.
13. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol 2003;21:54–9.
14. Boku N, Ohtsu A, Shimada Y, Shirao K, Seki S, Saito H, et al. Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. J Clin Oncol 1999;17:319–23.
15. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium) in advanced gastric cancer patients. Eur J Cancer 1998;34:1715–20.
16. Koizumi W, Kurihara M, Nakano S, Hasegawa K. Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. For the S-1 Cooperative Gastric Cancer Study Group. Oncology 2000;58:191–7.
17. Sugimachi K, Maehara Y, Horikoshi N, Shimada Y, Sakata Y, Mitachi Y, et al. An early phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. The S-1 Gastrointestinal Cancer Study Group. Oncology 1999;57:202–10.

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Original article

Combination chemotherapy with irinotecan and cisplatin in pretreated patients with unresectable or recurrent gastric cancer

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Abstract

Background. **The combination of irinotecan (CPT-11) and cisplatin (CDDP) is an active regimen for metastatic gastric cancer in the first-line setting. The objective of this retrospective study was to clarify its efficacy and safety in patients with prior chemotherapy for advanced or recurrent gastric cancer.**

Methods. **Patients in the study fulfilled the following selection criteria: (1) histologically proven gastric cancer with metastatic lesions; (2) performance status of 2 or less; (3) age of 75 years or younger; (4) at least one prior chemotherapy regimen without CPT-11 or CDDP; (5) adequate bone marrow, liver, and kidney function; (6) normal cardiac function; (7) no other severe medical conditions; (8) no other active malignancy; and (9) the provision of written informed consent. The treatment consisted of CPT-11 (70 mg/m^2) on day 1 and day 15 and CDDP (80 mg/m^2) on day 1; repeated every 4 weeks.**

Results. **Thirty-two patients were recruited, and 28 were assessable for clinical response. There were eight partial responses, resulting in a response rate of 28%. Median time to progression was 104 days (range, 24–863 days) and median overall survival time was 283 days from the initiation of this therapy. The incidences of grade 4 neutropenia, grade 3 or higher infection, and diarrhea were 69%, 9%, and 3%, respectively. Other adverse reactions were mild. No treatment-related deaths occurred.**

Conclusion. **A combination of CPT-11 and CDDP may be active and feasible for gastric cancer patients with prior chemotherapy. Further studies with larger numbers of patients are needed to clarify this regimen's significance in the second-line setting.**

Key words CPT-11 · CDDP · Gastric cancer · Prior chemotherapy

Introductions

Gastric cancer remains one of the major causes of cancer deaths all over the world. In Japan, despite the remarkable improvement in survival through early detection and curative surgery, there were approximately 50 000 deaths from gastric cancer in 1997. Unresectable advanced or recurrent gastric cancer still shows a poor prognosis.

Although chemotherapy for patients with advanced gastric cancer can be palliative, we have made an effort to advance this treatment modality for prolonging survival and improving quality of life. Compared with the best supportive care, combination chemotherapy in these patents has been proven to improve the quality of life and the overall survival in four small randomized trials [1–4]. Recently, several new agents have been developed for advanced gastric cancer, and some promising data have been reported with docetaxel [5,6], paclitaxel [7], irinotecan hydrochloride (CPT-11) [8], and S-1 (tegafur·gimeracil·oteracil potassium) [9]. While a first-line chemotherapy standard has not yet been established, these agents encourage us to define a second-line chemotherapy after failure of the first-line chemotherapy. However, there are only a few reports of the use of second-line chemotherapy for gastric cancer, and no standard regimen has been established. Therefore, investigation of a second-line regimen is very important.

As 5-fluorouracil (5-FU)-based regimens have been widely accepted as a standard first-line regimen at present, non-5-FU regimens are candidates as second-line regimens. Among the new agents mentioned above, CPT-11 is one of the most promising [8]. Boku et al. [10] reported that the response rate for CPT-11 and CDDP as the first-line regimen for advanced gastric cancer was 59% and the median survival time was 322 days. Ajani et al. [11] reported that the response rate for CPT-11 and CDDP therapy for first-line treatment was 58% and the median survival was 270 days. Both reports suggest that this combination therapy may also be very active and promising after the failure of first-line 5-FU-based chemotherapy.

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The objective of this retrospective study was to clarify the efficacy and safety of CPT-11 and CDDP cisplatin therapy in patients with prior chemotherapy for advanced or recurrent gastric cancer.

Patients and methods

Recruitment criteria

The subjects were 32 patients who were treated with CPT-11 and CDDP between September 2002 and September 2004 at the Shizuoka Cancer Center, Shizuoka, Japan. Patients who were recruited into the study fulfilled the following inclusion criteria: (1) histologically proven gastric cancer with metastatic lesions; (2) Eastern Clinical Oncology Group performance status of 2 or less; (3) age of 75 years or younger; (4) at least one prior chemotherapy regimen without CPT-11 or CDDP; (5) adequate bone marrow (WBC count ≥ 4000/μl and platelet count ≥ 10000/μl), liver (serum bilirubin level ≤ 1.5 mg/dl and serum transaminase level ≤ three times the upper limit of normal range), and renal function (serum creatinine level ≤ 1.5 mg/dl, blood urea nitrogen level ≤ 25 mg/dl); (6) normal cardiac function; (7) no other severe medical conditions; (8) no other active malignancy; and (9) the provision of written informed consent.

Statement of patients' informed consent

Patients and their families submitted written informed consent prior to entry into the study. The information supplied covered: (1) the name of the disease and condition; (2) method and contents of the treatment; (3) expected response and side effects; (4) other possible outcomes; (5) advantages and disadvantages; (6) agreement, denial, and retraction; and, (7) human rights protection.

Treatment schedule

CPT-11 (70 mg/m^2) was administered by intravenous infusion for 90 min on day 1; this was followed by a 2-h interval, after which an intravenous infusion of CDDP (80 mg/m^2) was administered over 2 h, with adequate hydration. The same dose of CPT-11 was administered on day 15. This treatment was repeated every 4 weeks until disease progression, patient refusal, or unacceptable adverse reactions. On day 15, if the patient had a WBC count of 2800/μl or less or 12000/μl or more, a platelet count of 100000/μl or less, diarrhea of grade 1 or higher, or an episode of infection, then CPT-11 on day 15 was postponed until recovery from these adverse reactions. If these adverse reactions continued beyond day 22, then the CPT-11 which should have been administered on day 15 was skipped. If a hematological adverse reaction was grade 4, or a nonhematological adverse reaction was grade 3 or higher, then CPT-11 on day 15 was skipped, and the subsequent dose of CPT-11 was reduced to 60 mg/m^2. Granisetron was used routinely before the administration of CPT-11. Granulocyte colony-stimulating factor (G-CSF) was used when necessary.

Evaluation

Tumor measurements for response assessment were obtained every 1–2 months by computed tomography (CT). The objective response to chemotherapy in measurable lesions was evaluated by the Response Evaluation Criteria in Solid Tumors [12]. National Cancer Institute common toxicity criteria (NCI-CTC; version 2) were adopted to evaluate the adverse reactions. The survival time was calculated from the day of the initiation of treatment to the date of death or the last date of confirmation of alive (censored), by the Kaplan–Meier method.

Patient characteristics

Patient characteristics are listed in Table 1. The median age of all patients was 58 years (range, 37–75 years).

Table 1. Patient characteristics

Characteristic	
Age (years)	
Median	58
Range	(37–75)
Sex	
Male	26
Female	6
PS	
0/1/2	16/14/2
Prior chemotherapy	
One regimen	27
Two regimens	5
S-1	18
MTX+5-FU	5
5′-FUDR	2
TXL	3
UFT	1
5-FU	8
Histology	
Intestinal	16
Diffuse	13
Unknown	3
Metastatic site	
Liver	8
Lymph node	23
Peritoneal dissemination	13
Lung	4
Ascites	9

PS, performance status; S-1, tegafur-gimeracil-oteracil-potassium; MTX, methotrexate; 5-FU, 5-fluorouracil; 5′-FUDR, doxifluridine; TXL, paclitaxel; UFT, uracil-futrafur

Thirty patients (94%) had a performance status of 0 or 1. Histologically, 16 patients (50%) had an intestinal type of adenocarcinoma, 13 patients (41%) had diffuse-type gastric cancer, and 3 patients (10%), had adenocarcinoma with unknown differentiation. Eighteen patients (56%) had primary diseases and 28 patients (88%) had measurable metastatic lesions. There were 8 patients (25%) with metastases in the liver, 23 (72%) with metastases in lymph nodes, 4 (13%) with metastases in lung, 13 (41%) with peritoneal dissemination, and 9 (28%) with ascites. Prior chemotherapy regimens are listed in Table 1, and all patients showed progressive disease before the initiation of the regimen used in the present study.

Results

Response and survival

Twenty-eight patients with measurable metastatic lesions were assessable for clinical response. There were eight partial responses, resulting in an overall response rate of 28% (Table 2). Median time to progression was 104 days (range, 24–863 days) and median overall survival time was 283 days, with a median follow-up time of 345 days (Figs. 1, 2).

Adverse reactions

The total number of treatment courses was 109, and the median number in each patient was 2.5 courses (range, 1–6 courses). The adverse reactions to this regimen are summarized in Table 3. The most frequent reaction was neutropenia, with grade 4 neutropenia observed in 22 patients (69%), and grade 3 or higher infection observed in only 3 patients (9%). Other hematologic adverse reactions were mild. Grade 3 diarrhea was observed in 1 patient (3%). Other grade 3 or 4

Table 2. Response

	n	CR	PR	SD	PD	RR
Overall	28	0	8	10	10	28%

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate

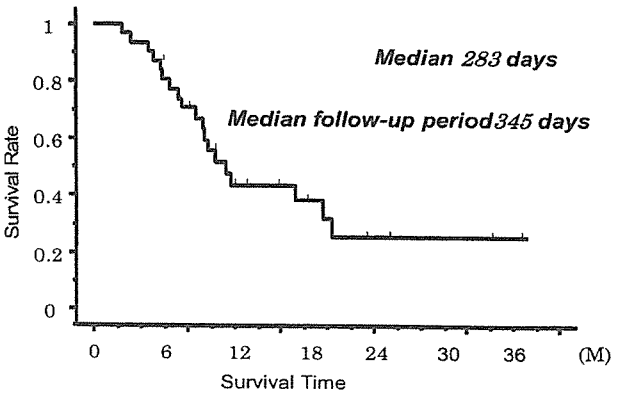

Fig. 1. Overall survival curve. Median overall survival time was 283 days. Median follow-up period was 345 days. The initial date of reckoning was the first day of the irinotecan (CPT-11), cisplatin (CDDP) chemotherapy

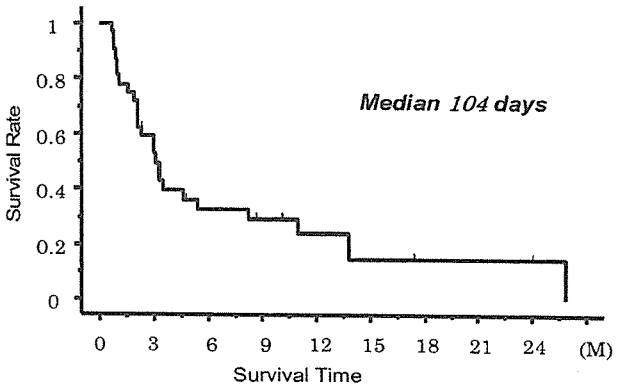

Fig. 2. Progression-free survival curve. Median time to progression was 104 days

Table 3. Adverse reactions

Grade	1	2	3	4 (%)	Percentage of patients with grade 3 or higher
Leukopenia	0	6	17	7 (22%)	75%
Neutropenia	0	4	4	22 (69%)	81%
Thrombocytopenia	5	4	2	0	6%
Anemia	8	3	9	5 (16%)	44%
Nausea	11	13	7	—	22%
Vomiting	7	7	4	2	19%
Anorexia	11	13	4	2	19%
Diarrhea	5	7	1	0	3%
Neutropenic fever	—	—	3	0	9%
Creatinine	8	7	0	0	0%

Table 4. Further chemotherapy

	No. of patients
Further chemotherapy	
Yes	26
No	5
No follow-up	1
Treatment type	
TXL	17
CPT-11	6
CDDPip	2
5-FU+LV	1

TXL, paclitaxel; CPT-11, irinotecan; CDDPip, cispatin intraperitoneal; 5-FU, 5-fluorouracil; LV, leucovorin

nonhematological toxicities were: nausea, in 7 patients (22%); vomiting, in 6 patients (19%); and anorexia, in 6 patients (19%). No patient was taken off treatment because of severe adverse reactions, and no treatment-related deaths occurred.

Dose intensity

The planned administration of CPT-11 on day 15 was not given 27 (25%) times in 15 patients (47%) during the 109 courses. Dose reduction of CPT-11 was required in 7 (22%) patients. Leukopenia was the most common reason for skipping the administration of CPT-11 on day 15 and for the dose reduction of CPT-11 (days 1 and 15). Thus, the dose intensity of CPT-11 was 24.5 mg/m^2 per week and that of CDDP was 15.4 mg/m^2 per week, which corresponded to 70% and 77% of the planned doses, respectively.

Further chemotherapy

Twenty-six patients (81%) received further chemotherapy after failure of the CPT-11 + CDDP regimen (Table 4). The condition of the remaining 6 patients made them unsuitable to receive third-line chemotherapy.

Discussion

Because the administration of CPT-11 is contraindicated for patients with myelosupression, infection, diarrhea, ileus, interstitial pneumonia, and obstructive jaundice, for fear of its severe toxicity, in clinical practice we selected patients with good PS and mild peritoneal dissemination for second-line chemotherapy with CPT-11. Of all the patients, 30 (94%) had a PS of 0 or 1, 13 (41%) had peritoneal dissemination, and 9 (28%) had ascites; however, none had massive ascites. Thus, this study contained a certain level of selection bias.

In our study, the actual dose intensity of CPT-11 was 70% of the planned dose, which was lower than that in a previous report (81.4% [10]). Leukopenia was the most common reason for skipping the administration of CPT-11 on day 15, and for the dose reduction of CPT-11. The incidences of grade 4 neutropenia (69%) and grade 3 or 4 infection (9%) were higher than those in the previous report [10], showing 57% and 5%, respectively. The high incidence of neutropenia in our study may have been caused by the prior chemotherapy. On the other hand, the incidence of grade 3 or 4 diarrhea (3%) was lower than that in the previous report (20% [10]), and other toxicities were mild, with frequencies similar to those in the previous report. Although dose reduction was required in some of our selected patients, this regimen is considered to be feasible for patients with prior chemotherapy.

CPT-11 has activity against gastric carcinoma. When used as a single agent for untreated and treated gastric cancer patients, Kambe et al. [13] reported a response rate of 23%. A recent European study of single-agent CPT-11 therapy reported a response rate of 17% in 34 previously untreated patients with gastric cancer [14]. There are a few reports of CPT-11 used in second-line combination chemotherapy regimens. Boku et al. [10] reported that CPT-11 and CDDP showed a response rate of 27%. In a report by Ajani et al. [15], this combination showed a response rate of 31%, with a median survival of 150 days. In a phase II study of CPT-11 and mitomycin C (MMC) [16], the response rate was 29%, and the median survival was 306 days. Kim et al. [17] reported that CPT-11, 5-FU, and leucovorin showed a response rate of 21%, and the median survival was 273 days. From the results of these studies, it seems that combination chemotherapy with CPT-11 may have a slightly higher response rate in second-line chemotherapy for gastric cancer than CPT-11 alone.

Both paclitaxel and docetaxel have been widely used in second-line chemotherapy for gastric cancer. Arai et al. [18] reported that the response rate to paclitaxel was 23%, and the median survival was 207 days. Park et al. [19] reported that combination chemotherapy with docetaxel and CCDP showed a response rate of 17%, with a median survival of 174 days. These results seem to be comparable with those of CPT-11-containing chemotherapy as a second-line chemotherapeutic regimen for gastric cancer.

In conclusion, the combination of CPT-11 and CDDP may be active and feasible for patients with prior chemotherapy for gastric cancer. To establish standard second-line chemotherapy for gastric cancer, especially after the failure of a 5-FU-based regimen, a CPT-11-based regimen and a taxane-based regimen should be compared in a randomized study.

References

1. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer 1993;72: 37–41.
2. Pyrhonen S, Kuitunen T, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 1995;71:587–91.
3. Glimelius B, Hoffmann K, Haglund U, Nyren O, Sjoden PO. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. Ann Oncol 1994;5:189–90.
4. Scheithauer W, Komek G, Zeh B, et al. Palliative chemotherapy versus supportive care in patients with metastatic gastric cancer. A randomized trial (abstract). Second International Conference on Biology, Prevention, and Treatment of GI Malignancy, Koln, Germany; 1995. p. 68.
5. Taguchi T, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J, et al. Late phase II clinical study of RP56976 (Docetaxel) in patients with advanced/recurrent gastric cancer: a Japanese Cooperative Study Group trial (Group A). Jpn J Cancer Chemother 1998;25:1915–24.
6. Mai M, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J, et al. A late phase II clinical study of RP56976 (Docetaxel) in patients with advanced or recurrent gastric cancer: a Japanese Cooperative Study Group trial (Group B). Jpn J Cancer Chemother 1999;26:1487–96.
7. Hyodo I, Ohtsu A, Shirao K, Miyata Y, Saito H, Taguchi T. Late phase II study of paclitaxel (BMS-181339) in patients with advanced/recurrent gastric cancer; a Japanese Cooperative Study Group trial (group A). The 38th annual meeting of Japan Society for Cancer Therapy 2002;35:443.
8. Futatsuki K, Wakui A, Nakao I, Sakata Y, Kambe M, Shimada Y, et al. Late phase II study of irinotecan hydrochloride (CPT-11) in advanced gastric cancer. Jpn J Cancer Chemother 1994;21:1033–38.
9. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrumidine anticancer drug S-1 (1M tegafur-0.4M gimestat-1M otastat potassium) in advanced gastric cancer patients. Eur J Cancer 1998;34:1715–20.
10. Boku N, Ohtsu A, Shimada Y, Shirao K, Seki S, Saito H, et al. Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. J Clin Oncol 1999;17:319–23.
11. Ajani JA, Baker J, Pisters PW, Ho L, Mansfield PF, Feig BW, et al. CPT-11 plus cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma. Cancer 2002;94: 641–6.
12. World Health Organization. WHO handbook for reporting results of cancer treatment (WHO Offset Publication No. 48). Geneva: World Health Organization; 1979.
13. Kambe M, Wakui A, Nakao I, et al. A late phase II study of irinotecan (CPT-11) in patients with advanced gastric cancer. Proc Am Soc Clin Oncol 1993;12:198.
14. Kohne CH, Thuss-Patience P, Catane R, Klein H, Peretz T, Preusser P, et al. Final results of a phase II trial of CPT-11 in patients with advanced gastric cancer (abstract). Proc Am Soc Clin Oncol 1999;18:258a.
15. Ajani JA, Baker J, Pisters PW, Ho L, Mansfield PF, Feig BW, et al. Irinotecan/cisplatin in advanced, treated gastric or gastroesophageal junction carcinoma. Oncol 2002;16:16–18.
16. Hamaguchi T, Ohtsu A, Hyodo I, Arai Y, Takiuchi H, Fujii H, et al. A phase II study of biweekly irinotecan and mitomycin C combination therapy in patients with fluoropyrimidine-resistant advanced gastric cancer: The Japan Clinical Oncology Group trial (JCOG0109). Proc Am Soc Clin Oncol 2004;22:4071.
17. Kim ST, Kang WK, Kang JH, Park KW, Lee J, Lee SH, et al. Salvage chemotherapy with irinotecan, 5-fluorouracil and leucovorin for taxane- and cisplatin-refractory, metastatic gastric cancer. Br J Cancer 2005;92:1850–4.
18. Arai T, Hamaguchi T, Shirao K, Shimada Y, Yamada Y, Muro K, et al. Weekly paclitaxel in patients with heavily treated advanced pastric cancer: Proc Am Soc Clin Oncol 2003;22:321.
19. Park SH, Kang WK, Lee HR, Park J, Lee KE, Lee SH, et al. Docetaxel plus cisplatin as second-line therapy in metastatic or recurrent advanced gastric cancer progressing on 5-fluorouracil-based regimen. Am J Clin Oncol 2004;27:477–80.

Computer-Assisted Analysis of Biopsy Specimen Microvessels Predicts the Outcome of Esophageal Cancers Treated with Chemoradiotherapy

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Abstract **Purpose:** A computer-assisted microvessel analysis system was developed to evaluate correlations between the architecture of biopsy specimen microvessels and the outcome for patients with esophageal cancer treated with chemoradiotherapy.

Experimental Design: Biopsy specimens from 51 patients with esophageal cancer (T_{2-3}, any N, M_0) treated with chemoradiotherapy were immunostained with an anti-CD31 antibody and quantified using computerized image analysis. We evaluated the association of several microvessel factors with overall survival, including the ratio of total microvessel perimeter to total tumor area (TP/TA), the tumor hypoxic ratio, and the ratio of total microvessel number to total tumor area (TN/TA). Results from traditional manual microvessel density (MVD) hotspot count and computerized hotspot count were compared and the relation between hotspot MVD count and survival rate was evaluated.

Results: The median follow-up time was 32 months. Both univariate and multivariate analyses revealed that computer-counted hotspot MVD and TN/TA and TP/TA ratios correlated significantly with the outcome of chemoradiotherapy. Kaplan-Meier survival curves showed that patients with high computer-counted hotspot MVDs and high TN/TA and TP/TA ratios had better overall survival rate than patients with low MVDs or ratios ($P = 0.025$, 0.008, and 0.031, respectively). Combining computer-counted MVD or TN/TA ratio with TP/TA ratio proved more predictive than any single factor. Two researcher-counted hotspot MVDs had no significant relation with outcome.

Conclusion: Computer-assisted tumor microvessel analysis is a powerful tool in predicting the outcome for patients with esophageal cancer treated with chemoradiotherapy because intraobserver and interobserver variability is minimized.

Esophageal cancer is a common malignancy that causes ~10,000 deaths each year in Japan (1) and >300,000 deaths annually worldwide (2). Surgery with or without preoperative chemoradiotherapy is generally done for resectable cases and chemoradiotherapy is used for unresectable cases or resectable cases where patients do not wish to have surgery. In recent years, chemoradiotherapy is increasingly being reported as a curative treatment modality for clinically resectable cases, which does not compromise disease control. In the Radiation Therapy Oncology Group 85-01 randomized trial, definitive chemoradiotherapy using 5-fluororuracil, *cis*-diammine-dichloroplatinum (cisplatin), and concurrent radiation (50 Gy) has achieved a 26% 5-year survival (3), similar to surgery alone (4, 5). Stahl et al. (6) reported a randomized trial comparing chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma. Chemoradiotherapy resulted in equivalent survival compared with chemoradiotherapy followed by surgery.

Because chemoradiotherapy can achieve similar survival rates to surgery or surgery combined with chemoradiotherapy, patient characteristics and tumor histologic features that favor chemoradiotherapy should be carefully assessed before choosing treatment. However, the factors that can predict the response to treatment of esophageal cancer remain uncertain. In our studies, we reported that hotspot microvessel density (MVD) in biopsy specimen is of strong prognostic significance for patients with laryngeal squamous cell cancers and with hypopharyngeal cancers treated with radiation (7, 8). The ratio of total microvessel perimeter (TP) to total tumor area (TA) of biopsy specimens, the ratio of total microvessel number (TN) to TA, and the tumor hypoxic ratio calculated from microvessel distributions in biopsy specimens have been further proved to

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be good prognostic factors for patients with early stages of laryngeal carcinoma treated with radiation (9). In the present study, microvessel factors, including hotspot MVD and TP/TA, TN/TA, and hypoxic ratios, in biopsy specimens from 51 patients with esophageal cancer treated with chemoradiotherapy were analyzed, and the relations between these factors and overall survival were assessed. All factors including tumor hotspot MVD counts were analyzed using a computer-assisted image analysis system, with the aim of minimizing intraobserver and interobserver variation in microvessel counting and analysis.

Materials and Methods

Patients. A total of 348 patients with esophageal cancers were diagnosed and treated at the National Cancer Center Hospital East between 1992 and 1999. Surgery was done as the main treatment for 139 patients, and 209 received definitive chemoradiotherapy. Among the 209 patients, 51 met the following criteria to be included in this study: (*a*) the tumor was histologically diagnosed as squamous cell carcinoma; (*b*) patient age was ≤75 years; (*c*) sufficient biopsy specimens (tumor area >0.6 mm^2, which is about thrice of ×400 magnification field) were available before treatment; (*d*) performance status on the Eastern Cooperative Oncology Group scale ≤2; and (*e*) stage T_{2-3}, any N, M_0 on the International Union against Cancer tumor-node-metastasis classification. The patients' characteristics are listed in Table 1.

Treatment protocol. Chemotherapy consisted of continuous infusion of 5-fluorouracil (400 mg/m^2/d, on days 1-5 and 8-12) and a weekly infusion of cisplatin (40 mg/m^2, days 1 and 8). Concurrent radiotherapy was given at 2 Gy/d for 5 d/wk with a 2-week break after a dose of 30 Gy, and restarted on day 36 along with the same schedule of chemotherapy as before. The total radiation dose was 60 Gy. After concurrent chemoradiotherapy, two additional courses of chemotherapy (5-fluorouracil, 800 mg/m^2/d, on days 1-5 and 29-33; cisplatin, 80 mg/m^2, on days 1 and 29) were basically administered if patients responded to treatment without serious side effect. Further additional courses were optional although they were limited to a total of four courses.

Definition of tumor response. The first evaluation was done ~1 month after treatment. Patients then received computed tomography scanning and esophagoscopy every 2 or 3 months during the first year and every 6 months thereafter. Tumor recurrences were all proved histologically by biopsy.

Response at the primary site was evaluated by endoscopic examination. The criteria for evaluation were as follows: complete remission was defined as disappearance of tumor lesion and ulceration for ≧4 weeks with negative biopsy results; partial remission was determined when primary tumor was observed on esophagography as being reduced in area by ≧50%. Responses of metastatic lymph nodes were assessed by computed tomography scanning according to the WHO criteria for measurable disease.

Immunohistochemical staining of blood microvessels and computer-assisted image analysis. All biopsy specimens were taken at the time of diagnosis. Immunohistochemical staining of blood microvessels was done with the standard avidin-biotin complex technique using diaminobenzidine as a chromogen and hematoxylin as counterstain. Antigen was retrieved by treating with 0.05% pepsin in 0.01 N HCl for 5 minutes at room temperature. A mouse antibody for CD31 was used as primary antibody (4°C, overnight, 1:50 dilution; DAKO, Glostrup, Denmark). After washing, sections were incubated with an avidin-biotin complex reagent (DAKO). Color reactions were developed for 5 minutes in diaminobenzidine-Tris buffer (pH 7.6) containing 0.3% hydrogen peroxide.

Table 1. Patient characteristics

Characteristic	No. patients
Total number	51
Gender	
Male	43
Female	8
Age	
Mean	61.7
Range	38-75
Performance state	
0	38
1	13
Tumor location	
Upper and middle	36
Lower	15
Histology type	
W/D	1
M/D	36
P/D	14
T stage	
T_2	10
T_3	41
N stage	
N_0	20
N_1	31
Stage	
IIA	20
IIB	6
III	25

Digitized images of immunohistochemically stained sections of whole specimen at ×100 magnification (10× objective and 10× ocular) were obtained using a KS 300 image analysis system (capture resolution 768 × 580, Karl Zeiss Vision K.K., Jena, Germany). Vessels with lumens located around or inside tumor nest were traced by one of the authors (H.S.). The process of image analysis has been described elsewhere (9). Briefly, traced microvessels and the outline of the total specimen were converted to binary images and TN, TP, and TA were calculated. Data were recorded as TN/TA, TP/TA, and TP/TA ratios. As the oxygen diffusion distance from blood vessels is ~150 μm (10), the hypoxic ratio was calculated as the ratio of tumor area >150 μm from blood vessels to the TA (Fig. 1A).

Two of the authors (Z.S. and H.S.) counted hotspot microvessel numbers independently without knowledge of patient outcomes. The immunohistochemically stained specimens were first scanned at low magnification (×10-×100); three high-magnification (×400) fields with plentiful vascular tumor areas were then selected and counted as hotspots. The mean number of vessels from three fields was recorded as the hotspot MVD.

As an alternative for manual counting, a computer-assisted method was used to identify hotspot and count vessels in specimens. The previously traced vessels were converted to binary images and were scanned consecutively. The scanning circle was 500 μm in diameter and 0.196 mm^2 in area, which was the same as a ×400 magnification field. Microvessels within each circle were counted by computer. The overlay of adjacent circles in both the *X* and *Y* axes was set arbitrarily at 375 μm (three fourths of the diameter). The mean number of MVDs in the three circles containing the highest MVD count was recorded as the hotspot MVD of the corresponding specimen (Fig. 1B).

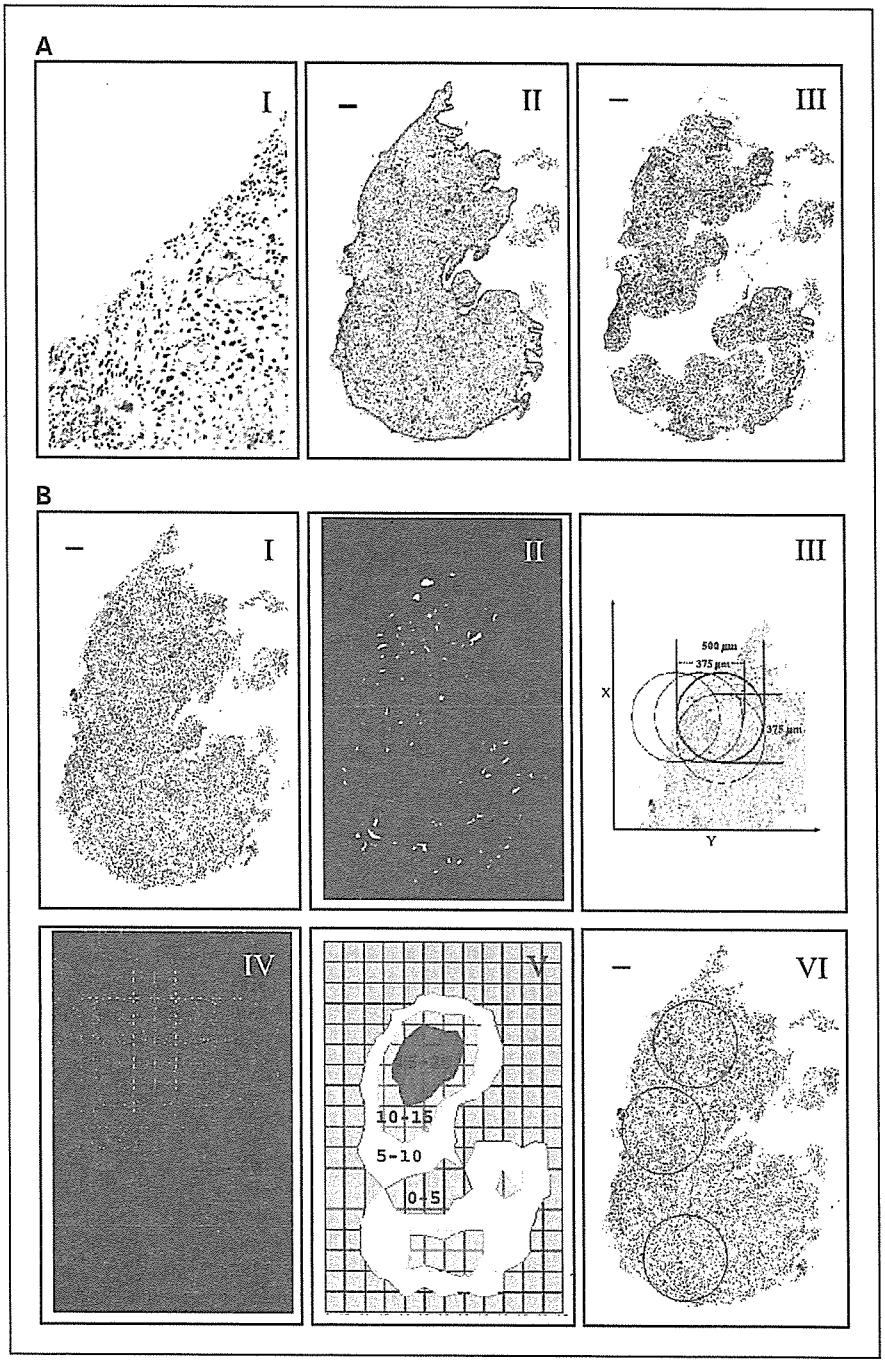

Fig. 1. *A*, image analysis of microvessels. *I*, the lumen of each microvessel was traced by an observer and counted by the computer. The TP was then calculated using the computer. *II*, the tumor region was outlined by the observer and the tumor area was calculated using the computer. *III*, the area of the tumor located >150 μm from the nearest vessel was calculated by the computer (*yellow area*) and then hypoxia ratio was calculated. *B*, microvessel hotspot counted by computer. *I*, microvessels were labeled by an observer. Bar, 100 μm. *II*, labeled vessels were converted to binary images. *III*, the scanning circle is 500 μm in diameter and 0.196 mm^2 in area, which equals the area of a ×400 power field. The overlay of two neighboring circles is 375 μm. *IV*, the binary image was scanned. *V*, a schematic image of microvessel distribution derived from computer analysis. *VI*, areas with the highest microvessel number were identified as microvessel hotspots.

Statistical analysis. Correlations between different factors were assessed using Pearson's correlation coefficient. A Cox proportional hazard analysis was used to evaluate clinicopathologic and microvessel factors in the prediction of treatment outcome. Survival curves were generated using the Kaplan-Meier method and statistical differences between curves were calculated using the log-rank test. For evaluation of continuous variables in survival analysis, patients were divided into two groups based on an optimal cutoff derived from receiver operating characteristic analysis. GraphPad Prism software (GraphPad Software, San Diego, CA) was used for receiver operating characteristic analysis and Statistica (StatSoft, Tulsa, OK) was used for all other analysis.

Results

Treatment outcome. All 51 patients completed the concurrent chemoradiotherapy with a total radiation dose of 60 Gy. Seven patients (14%) received one additional course of chemotherapy, and 25 patients (49%), 2 patients (4%), and 2 patients (4%) received an additional two, three, and four courses, respectively. The median patient follow-up time was 32 months (range, 5.9-121.5 months). Thirty-nine patients (76%) achieved clinical complete remission and 12 patients (24%) achieved partial remission at primary site. Among the

Table 2. Correlation between different MVDs

	r	P
Observer 1 vs observer 2	0.514	0.0001
Observer 1 vs computer	0.579	<0.0001
Observer 2 vs computer	0.472	0.0005

39 with clinical complete remission at primary site, 12 patients developed recurrence in the primary area, 3 in a distant area (a different site in esophagus), and 4 had distant metastases during follow-up (3 in the liver and 1 in the lung). Up to January 1, 2005, 23 patients had died of esophageal cancer, 8 patients died of other disease or accidents, and the other 20 cases were alive at the last follow-up time point.

Image analysis of microvessels in biopsy specimens. Areas of inflammation, sclerotic tumor, and adjacent benign tissue were identified and excluded by observer when calculating the TA, which ranged from 0.99 to 3.37 mm^2, with a median of 1.92 mm^2. The TN varied from 3 to 204, with a median of 100. The TP ranged from 0.35 to 41.26 mm, with a median of 11.81 mm. Tumor hypoxic ratio ranged from 0.11% to 78.63%, with a median of 8.34%.

Comparison of manual MVD counting and computer-assisted MVD counting. The results of two manual MVD counts and the computer-assisted counts are shown in Table 2.

Although hotspot MVD counts for a given patient varied between different observers and the computer, analysis showed that they were correlated linearly (Table 2).

Receiver operating characteristic analysis. To evaluate the ability for the prediction of survival, we evaluated the accuracy of prediction of death of esophageal cancer at 2 years for each microvessel factor. This interval of 2 years was selected because most of the complete cases happened in this interval (19 in 23 cases) and only three patients (all of whom died of other diseases and were excluded from the receiver operating characteristic analysis) censored before the end of 2 years. The predictive power was estimated by calculating the area under receiver operating characteristic curves (11, 12). All factors, including TN/TA, TP/TA, and hypoxic ratios and observer-counted and computer-derived hotspot MVDs, were found to be predictors of 2-year survival (Table 3); the observer-counted MVD showed the weakest power in predicting death 2 years after treatment.

Univariate analysis of survival. Univariate Cox proportional hazard analysis was done to evaluate the relation between clinicopathologic factors and overall survival. The result is presented in Table 4. No clinicopathologic factor correlated with overall survival.

From the receiver operating characteristic curves, the optimal cutoffs for varied microvessel factors were determined to stratify patients into two groups, and univariate Cox proportional analysis revealed that patients with low TN/TA (P = 0.023) or low TP/TA (P = 0.037) had a higher risk of dying of esophageal cancer after chemoradiotherapy (Table 5). Patients with a low ratio of tumor hypoxic area tended to survive longer after treatment but this was not statistically significant (P = 0.329). The hotspot MVDs counted by the two observers had no relation with overall survival (P = 0.203 and 0.119, respectively) whereas hotspot MVDs counted by the computer showed a significant association with survival (P = 0.036).

Multivariate analysis for survival. In the multivariate Cox proportional hazard analysis, computer-derived hotspot MVD counts and the TN/TA and TP/TA ratios were analyzed combined with T and N stage, which showed the highest significance among clinicopathologic factors by univariate analysis. All three microvessel factors proved to be independent predictors for overall survival (P = 0.019 for hotspot MVD, P = 0.018 for TN/TA, and P = 0.044 for TP/TA; Table 6).

Kaplan-Meier survival analysis. Figure 2 shows the survival curves generated using the Kaplan-Meier method. Patients with high MVD and high TN/TA and TP/TA ratios had 5-year survival rates of 73%, 79%, and 73%, respectively, whereas the group of patients with low such factors had 5-year survival rates of 46%, 45%, and 41%, respectively. Log-rank test showed that these differences were statistically significant (P = 0.025 for hotspot MVD, P = 0.008 for TN/TA, P = 0.031 for TP/TA).

Because hotspot MVD count and the TN/TA and TP/TA ratios all proved to be predictive factors for the outcome of patients treated with chemoradiotherapy, we investigated whether combinations of these factors would provide more powerful and more precise predictors. Hotspot MVD showed a strongly positive correlation with TN/TA (Pearson test, r = 0.843, P < 0.000001) whereas TP/TA was independent of hotspot MVD (r = 0.023) and was relatively weakly correlated with TN/TA (r = 0.318, P = 0.022). We therefore selected the combinations of MVD and TP/TA, TN/TA and TP/TA ratios as new factors and investigated if they could

Table 3. Receiver operating characteristic curve analysis

Variable	Area under the curve	95% confidence interval	Best cutoff
Hotspot			
Computer	0.593	0.441-0.732	29
Observer 1	0.529	0.381-0.668	51
Observer 2	0.564	0.418-0.710	15
TN/TA	0.649	0.502-0.779	73.74
TP/TA	0.647	0.504-0.782	9.944
Hypoxic ratio	0.623	0.467-0.748	30.421%

Table 4. Univariate Cox proportional hazard analysis of relations between clinical and pathologic characteristics and overall survival

Variables	No. patients	Risk ratio (95% confidence interval)	*P*
Age (y)			
≦62	27		
>62	24	1.104 (0.491-2.511)	0.809
Performance state			
0	38		
1	13	1.038 (0.381-2.837)	0.946
Tumor location			
Upper and middle	36		
Lower	15	1.011 (0.423-2.455)	0.982
T stage			
T_2	10		
T_3	41	1.443 (0.589-3.514)	0.423
N stage			
N_0	20		
N_1	31	1.664 (0.682-4.077)	0.262
Histology type			
W/D and M/D	37		
P/D	14	1.273 (0.538-3.023)	0.584
Stage			
II	26		
III	25	1.233 (0.542-2.878)	0.625

predict survival of patients. The high hotspot MVD plus high TP/TA group included eight patients and the high TN/TA plus high TP/TA included 11 patients (including all the eight in the high MVD plus high TP/TA group). Surprisingly, none of the patients with both high MVD and high TP/TA ratio died of esophageal cancer during follow-up and only one patient died of esophageal cancer in the high TN/TA plus high TP/TA group. The Kaplan-Meier survival curve of the high TN/TA plus high TP/TA group was presented in Fig. 3.

Table 5. Univariate Cox proportional hazard analysis of relations between microvessel characteristic and overall survival

Variables	No. patients	Risk ratio (95% confidence interval)	*P*
Hotspot MVD			
Computer			
<29	31		
≥29	20	2.892 (1.066-7.80)	0.036
Observer 1			
<51	38		
≥51	13	2.033 (0.679-6.002)	0.203
Observer 2			
<15	15		
≥15	36	2.024 (0.833-4.909)	0.119
TN/TA			
<73.741/mm^2	35		
≥73.741/mm^2	16	4.208 (1.252-14.208)	0.023
TP/TA			
<9.944 mm/mm^2	28		
≥9.944 mm/mm^2	23	2.617 (1.058-6.477)	0.037
Hypoxic ratio			
<30.421%	39		
≥30.421%	12	1.597 (0.623-4.093)	0.329

Table 6. Multivariate Cox proportional hazard analysis of relations between microvessel characteristic and overall survival

Variables	Risk ratio (95% confidence interval)	P
Model 1		
T stage	1.023 (0.402-2.552)	0.966
N stage	1.988 (0.813-4.903)	0.133
Hotspot MVD	3.233 (1.139-9.113)	0.019
Model 2		
T stage	1.074 (0.428-2.646)	0.877
N stage	1.784 (0.733-4.335)	0.214
TN/TA	4.263 (1.235-14.646)	0.018
Model 3		
T stage	1.214 (0.488-2.987)	0.674
N stage	1.653 (0.676-4.045)	0.271
TP/TA	3.591 (1.046-12.239)	0.044

Discussion

We previously reported that hotspot MVD and the TN/TA, TP/TA, and hypoxic ratios in biopsy specimen are prognostic factors for laryngeal cancer patients treated by radiotherapy (9). Here we found that, for patients with T_{2-3} esophageal cancers, hotspot MVD, TN/TA, and TP/TA were favorable predictors for overall survival. The combinations of hotspot MVD with TP/TA, or TN/TA with TP/TA, may provide more powerful predictors for predicting the outcome of such patients scheduled to undergo chemoradiotherapy.

It is likely that a low density of microvessels will lead to a decrease in oxygen transport and drug delivery into local tumor environments. Bhattacharya et al. (13) investigated avascular regions of human head and neck cancer xenografts and found that cells in these areas were hypoxic and chemotherapy resistant. Hypoxia-related factors, such as hypoxia-induced factor 1α and carbonic anhydrase IX, and hypoxic area imaging by pimonidazole or misonidazole binding have been discussed as prognostic factors for radiotherapy of cancers (14-17). Although there are substantial data implying that poorly vascularized tumors are resistant to chemotherapy and/or radiotherapy, no definitive conclusion has been drawn at present on the clinical usefulness of MVD as a marker for prognosis. There are some studies that did not show a relationship between MVD and survival (18, 19) and a reverse relationship between MVD and survival has been reported by some groups (20, 21).

These contradictory conclusions might be explained by the difficulty in evaluating MVD accurately. Manual hotspot MVD counting has been the predominant method for analysis. The observer first scans a section at low magnification (×10-×100). High angiogenesis areas can be recognized as hotspots and a higher magnification (×200-×400) is then selected to count the number of microvessels in these areas (22). All procedures, including screening hotspot area and counting vessels, are done subjectively and intraobserver or interobserver variability is almost inevitable. Our study presents one resolution of this problem. Because pathologic section is converted into digitized image, the observer only needs to trace the outlines of the microvessels and the following work is all accomplished by the computer with minimum variability and perfect reproducibility. When two observers counted the microvessels of the same patients in our study using the manual hotspot counting method, the results differed and both failed to predict the survival of patients.

Using a computerized system to evaluate tumor microvessels has been reported by some groups (23-26). The present method has two novel features. The first is observer intervention in microvessel tracing. Although completely automated analysis will undoubtedly be developed, the nonspecific

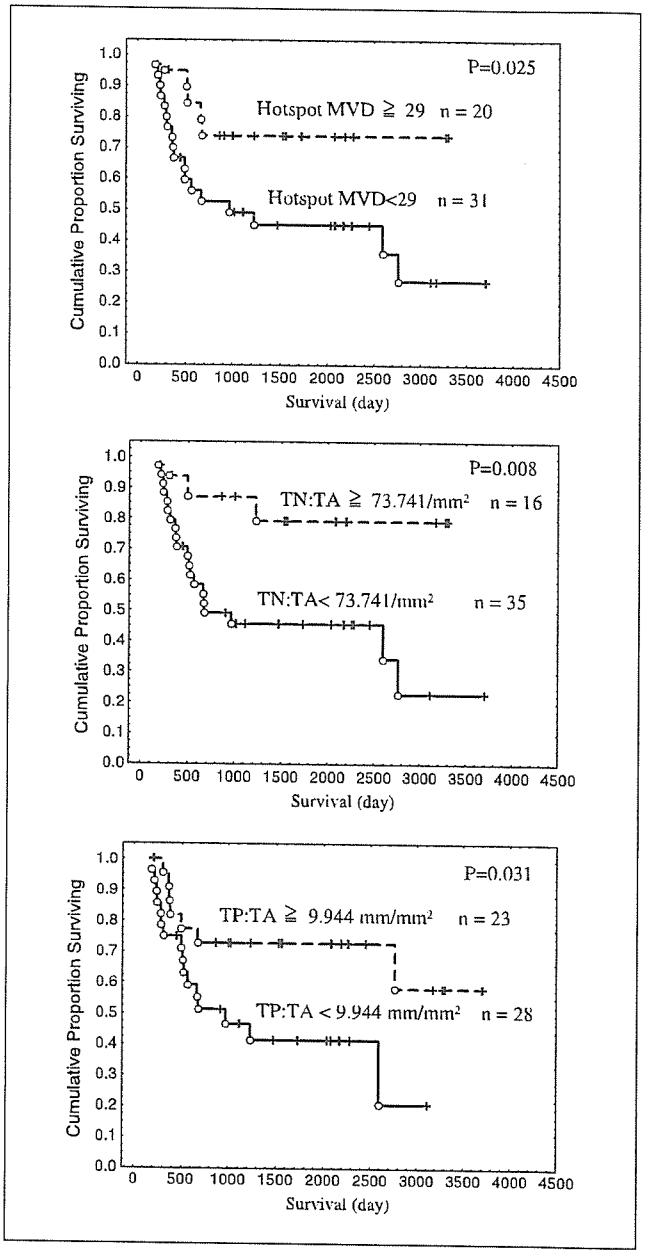

Fig. 2. Kaplan-Meier overall survival curves for patients with T_{2-3} M_0 esophageal cancer treated with chemoradiotherapy.

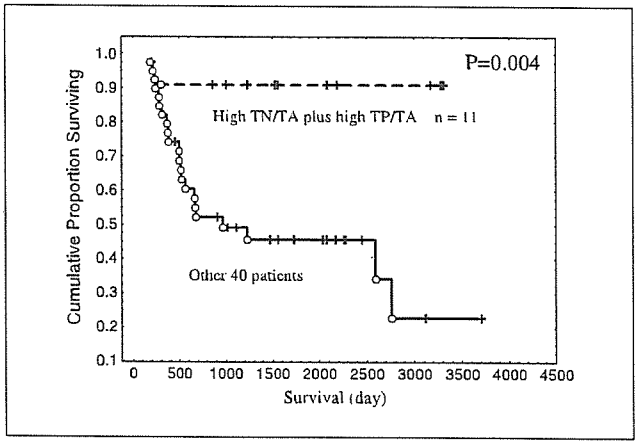

Fig. 3. Kaplan-Meier overall survival curves for patients with high TN/TA and high TP/TA.

staining and the varying threshold for positive endothelial staining are likely to comprise this. Manual tracing ensures the accuracy of microvessel recognition and therefore maintains a high specificity of this analysis. The second feature is the use of full section scanning to determine microvessel hotspots, which provides the most objective information on microvessel distribution within any biopsy sample.

The tumor hypoxic ratio counted by computer has been shown as a predictor for radiosensitivity (9). In the present study, there was a tendency for a low hypoxic ratio to show good patient prognosis, but this was not statistically significant. The predictive power of the hypoxic ratio for the outcome of chemoradiotherapy thus needs further investigation.

A surprising finding in our study is that in the group of patients with both high hotspot MVD and high TP/TA ratios, none died of esophageal cancer, and in the group with high TN/TA and TP/TA ratios, only one patient died of esophageal cancer during follow-up. Six of eight patients (75%) in the high hotspot MVD plus high TP/TA ratio group and 8 of 11 patients (73%) in the high TN/TA plus high TP/TA ratio group survived longer than 3 years, compared with the average level of 45% (23 of 51) for all patients. These data suggested that well-vascularized tumor may be more sensitive to chemoradiotherapy.

The subjects of this study were patients who received definitive chemoradiotherapy. Because induction chemoradiotherapy before surgery is one of the most adopted multimodal treatments for esophageal cancer, whether the computer-assisted microvessel analysis is useful in predicting the outcome in these patients remains to be determined. After induction chemoradiotherapy, only 15% to 56% of patients achieved pathologic complete remission (27, 28). This method may be extremely helpful for treatment selection in residual disease after induction chemoradiotherapy. Similarly, the usefulness of this method in assessing treatment advantage of postoperative chemoradiotherapy is also an interesting topic needing further investigation.

Esophageal adenocarcinomas were not included in this study because most esophageal cancers in Japan (>90%) histologically are squamous cell carcinoma (29). However, in western countries, adenocarcinomas account for >60% of all esophageal cancers (5, 30). An independent study is needed to investigate whether microvessel analysis is suitable for adenocarcinoma when this method is expected to be used in these countries.

High MVD was reported to correlate with distant metastasis and short survival in solid tumors (31, 32). It should be noted that surgery was the main treatment modality in most of these prognosis analysis studies. For esophageal cancer, if it is proved that patients with a high MVD have short survival after surgery, chemoradiotherapy should then be more strongly recommended for these patients.

In conclusion, using a computer-assisted image analysis system for biopsy specimens, we found that hotspot MVD and the TN/TA and TP/TA ratios were powerful predictors for the outcome of patients with esophageal cancer treated with chemoradiotherapy. Compared with manual microvessel counting, this computer-assisted method produced lower variability and higher reproducibility for the evaluation of tumor vasculature.

References

1. Fujita H. Present status of esophageal cancer and its treatment in Japan. Ann Thorac Cardiovasc Surg 2004;10:135–9.
2. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. Eur J Cancer 2001;37: 4–66.
3. Cooper JS, Guo MD, Herskovic A, et al. for the Radiation Therapy Oncology Group. Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01). JAMA 1999;281: 1623–7.
4. Mullrt JM, Erasmi H, Stelzner M, et al. Surgical therapy of osesophageal carcinoma. Br J Surg 1990;77: 845–57.
5. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without pre-operative chemotherapy in oesophageal cancer: a randomized controlled trial. Lancet 2002;359: 1727–33.
6. Stahl M, Stuschke M, Lehmann N, Meyer HJ. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 2005;23: 2310–7.
7. Kamijo T, Yokose T, Hasebe T, Yonou H, et al. Potential role of microvessel density in predicting radiosensitivity of T1 and T2 stage laryngeal squamous cell carcinoma treated with radiotherapy. Clin Cancer Res 2000;6: 3159–65.
8. Zhang SC, Miyamoto S, Kamijo T, et al. Intratumor microvessel density in biopsy specimens predicts local response of hypopharyngeal cancer to radiotherapy. Jpn J Clin Oncol 2003;33:613–9.
9. Kamijo T, Yokose T, Hasebe T, et al. Image analysis of microvessel surface area predicts radiosensitivity in early-stage laryngeal carcinoma treated with radiotherapy. Clin Cancer Res 2001;7:2809–14.
10. Thomlinson RH, Gray LH. The histological structure of some human lung cancers and the possible implications for radiotherapy. Br J Cancer 1955;9: 539–49.
11. Wensel R, Opitz CF, Anker SD, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation 2002;106:319–24.
12. Grieco A, Pompili M, Caminiti G, et al. Prognostic factors for survival in patients with early-intermediate hepatocellular carcinoma undergoing non-surgical therapy: comparison of Okuda, CLIP, and BCLC staging systems in a single Italian centre. Gut 2005;54: 411–8.
13. Bhattacharya A, Toth K, Mazurchuk R, et al. Lack of microvessels in well-differentiated regions of human head and neck squamous cell carcinoma A253 associated with functional magnetic resonance imaging detectable hypoxia, limited drug delivery, and resistance to irinotecan therapy. Clin Cancer Res 2004;10: 8005–17.
14. Hutchison GJ, Valentine HR, Loncaster JA, et al. Hypoxia inducible factor 1α expression as an intrinsic marker of hypoxia: correlation with tumor oxygen, pimonidazole measurements, and outcome in locally advanced carcinoma of the cervix. Clin Cancer Res 2004;10:8405–12.
15. Koukourakis MI, Giatromanolaki A, Sivridis E, et al. Hypoxia-regulated carbonic anhydrase-9 (CA9) relates to poor vascularization and resistance of squamous cell head and neck cancer to chemoradiotherapy. Clin Cancer Res 2001;7:3399–403.
16. Kaanders JH, Wijffels KI, Marres HA, et al. Pimonidazole binding and tumor vascularity predict for treatment outcome in head and neck cancer. Cancer Res 2002;62:7066–74.
17. Eschmann SM, Paulsen F, Reimold M, et al.

Prognostic impact of hypoxia imaging with F-misonidazole PET in non-small cell lung cancer and head and neck cancer before radiotherapy. J Nucl Med 2005;46:253–60.

18. Haugen H, Magnusson B, Svensson M, et al. Preradiotherapy hemoglobin level but not microvessel density predicts locoregional control and survival in laryngeal cancer treated with primary radical radiotherapy. Clin Cancer Res 2004;10:7941–9.
19. Foote RL, Weidner N, Harris J, et al. Evaluation of tumor angiogenesis measured with microvessel density (MVD) as a prognostic indicator in nasopharyngeal carcinoma: results of RTOG 9505. Int J Radiat Oncol Biol Phys 2005;61:745–53.
20. Cooper RA, Wilks DP, Logue JP, et al. High tumor angiogenesis is associated with poorer survival in carcinoma of the cervix treated with radiotherapy. Clin Cancer Res 1998;4:2795–800.
21. Aebersold DM, Beer KT, Laissue J, et al. Intratumoral microvessel density predicts local treatment failure of radically irradiated squamous cell cancer of the oropharynx. Int J Radiat Oncol Biol Phys 2000; 48:17–25.
22. Weidner N, Semple JP, Welch WR, et al. Tumor angiogenesis and metastasis-correlation in invasive breast carcinoma. N Engl J Med 1991;324:1–8.
23. Barbareschi M, Weidner N, Gasparini G, et al. Microvessel density quantification in breast carcinomas. Appl Immunohistochem 1995;3:75–84.
24. Fox SB, Leek RD, Weekes MP, et al. Quantification and prognostic value of breast cancer angiogenesis: Comparison of microvessel density, Chalkley count and computer image analysis. J Pathol 1995;177: 275–83.
25. Canete A, Navarro S, Bermudez J, et al. Angiogenesis in neuroblastoma: relationship to survival and other prognostic factors in a cohort of neuroblastoma patients. J Clin Oncol 2000;18:27–34.
26. Chantrain CF, Declerck YA, Groshen S, et al. Computerized quantification of tissue vascularization using high-resolution slide scanning of whole tumor sections. J Histochem Cytochem 2003;51: 151–8.
27. Laterza E, de' Manzoni G, Tedesco P, et al. Induction chemo-radiotherapy for squamous cell carcinoma of the thoracic esophagus: long-term results of a phase II study. Ann Surg Oncol 1999; 6:777–84.
28. Raoul JL, Le Prise E, Meunier B, et al. Neoadjuvant chemotherapy and hyperfractionated radiotherapy with concurrent low-dose chemotherapy for squamous cell esophageal carcinoma. Int J Radiat Oncol Biol Phys 1998;42:29–34.
29. Ando N, Ozawa S, Kitagawa Y, et al. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. Ann Surg 2000;232:225–32.
30. Devesa SS, Blot WJ, Fraumeni JF, Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998;83: 2049–53.
31. Hansen S, Grabau DA, Sorensen FB, et al. The prognostic value of angiogenesis by Chalkley counting in a confirmatory study design on 836 breast cancer patients. Clin Cancer Res 2000;6:139–46.
32. Fontanini G, Lucchi M, Vignati S, et al. Angiogenesis as a prognostic indicator of survival in non-small-cell lung carcinoma: a prospective study. J Natl Cancer Inst 1997;89:881–6.

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頭頸部がん領域の粒子線治療

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論文要旨

粒子線治療は世界の25カ所以上で実施されているが，兵庫県立粒子線医療センターは，1台の装置で陽子線治療と炭素イオン線治療のできる世界唯一の施設である。陽子線は，2001年臨床試験（治験），2003年4月一般診療開始。炭素イオン線は，2002年治験，2005年3月一般診療開始。頭頸部領域では，2006年3月末で，陽子線治療と炭素イオン線をあわせて，950例以上の治療を行っている。粒子線治療装置は高額だが，シンプルで高精度な治療が容易に行われ，また，抗がん剤を併用しないでも局所制御が得られ，頭頸部領域のがん治療としては，QOLの面，治療効果から，期待できる治療法である。

キーワード：頭頸部癌，粒子線治療，陽子，炭素イオン

1. はじめに

放射線は大きく電磁波と粒子線に大別される。電磁波の代表は，X線やγ線で，光子線と総称され従来から放射線治療に利用されている。一方，粒子線は電子，中性子や水素，炭素の原子核などの粒子を利用した放射線である。陽子は水素原子の原子核で正の電荷を持つイオンで，重イオンはヘリウムや炭素など陽子より重い原子の原子核を示し，これらを高エネルギーに加速したものが陽子線と重イオン線である。それらによって行われる治療を，粒子線治療と総称する。この粒子線をがんの治療に用いることを米国のRobert Wilsonが，1946年に初めて提案[1]してから60年経過した現在，粒子線治療は世界の25を超える施設で実施されている。なかでも兵庫県立粒子線医療センターは，陽子線治療と炭素イオン線による治療の行える世界で初めての施設として誕生した。2001年，陽子線による臨床試験（治験）を終了し，医療用具の製造承認を得て，2003年4月から陽子線の一般診療を開始した。また，炭素イオン線は，2002年に治験を行い，2005年に承認を受け，2005年3月から一般診療を開始している。

粒子線治療の物理的特性としては，従来の放射線である光子線（X線やγ線）と比べ線量分布に優れる[2,3]。即ち，従来の放射線治療では，身体の表面ほど放射線の線量が多く，体内に進んでいくほど線量が少なくなるのに，粒子線治療では，身体の表面や途中にある正常な組織にはそれ程強く作用せず，ある一定の場所で最も強く作用（ブラッグピーク）し，その直後より先には進まなくなる。しかも装置を調整することで，このブラッグピークを重ねて，連続したブラッグピーク（拡大ブラッグピーク）を作り出せるので，厚みを持ったがんに対しても一様に照射できる（図1）。基礎研究の結果では，陽子線での生物的特性は，従来の放射線と余り違いはない。炭素イオン線は，陽子線と比べると12倍の質量の粒子を加速してできるので，特に生物的特性に違いが生じる。その結果，従来の放射線治療で使われていた光子線に抵抗性の低酸素のがん細胞に対して，炭素イオン線は治療効果が高いと考えられ，臨床面でも良好な結果であった[4]。陽子線使用施設では，基礎研究の結果から，放射線線抵抗性腫瘍に対して積極的に治療がされておらず，一般的には，基礎＝臨床と考えられ，放射線抵抗性腫瘍は，陽子線治療の適応外と思われていた。前述のように，当センターでは，2003年4月から2005年3月まで陽子線のみでの一般診療を行ってきた。この間，頭頸部領域の放射線抵抗性腫瘍の患者さんも多数来院され，炭素イオン線施設への紹介などもしてきたが，治療開始に時間がかかることや，どうしても当センターでの治療を希望するなどの事情が生じ，患者さんとも良く話し合いをして，放射線抵抗性腫瘍に対しても陽子線治療を行った。結果は，炭素イオン線治療での結果と同様局所に対しては非常に良好であった。

粒子線治療の魅力はやはり患者さんのQOL（生活の質）を最も高く得られることである。手術では，出血や創部の治癒遷延などで退院が延びることがあり，また，化学療法や放射線治療では，反応が強く出た場合，退院を延ばすことがある。粒子線治療では，治療スケジュールの変更がなく，今日入院した方でも退院日までの完全なスケジュール管理ができ，したがって，患者さんにとって最も楽ながん治療といえる。

当センターは，照射治療施設を行う照射治療棟と入院機能（50床）を有する病院棟からなる。照射治療棟には，直径30mのシンクロトロンを中心とした，粒子線治療装

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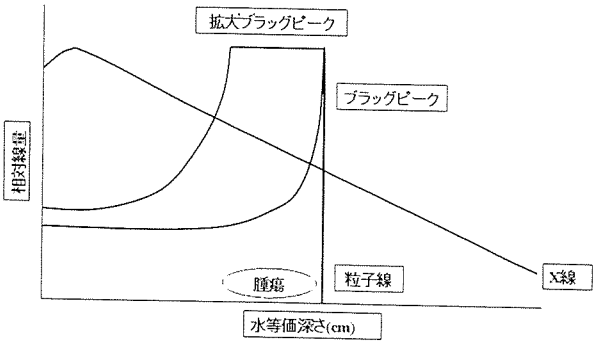

図 1　粒子線とX線の線量分布。粒子線は，ブラッグピークを重ねる拡大ブラッグピークで腫瘍に一様に照射できるのに，X線は，腫瘍に一様に照射できず，また腫瘍の後方にも照射される。

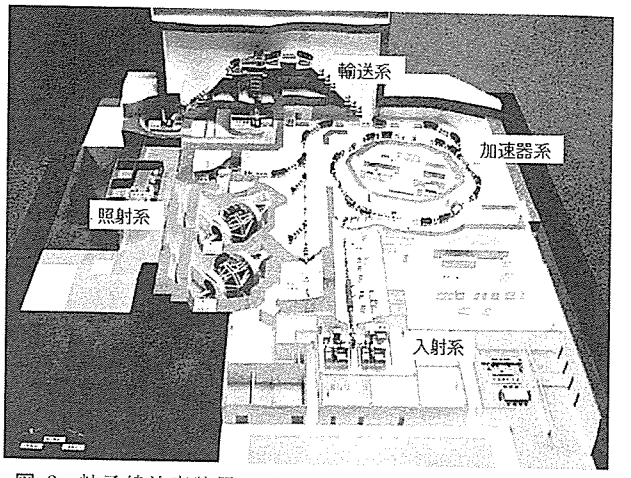

図 2　粒子線治療装置。巨大な装置だが，仕組みは，入射系，加速器系，輸送系，照射系とシンプル。

置が存在し，病院棟は，アメニティーに十分配慮した病棟（50床）と診療部門からなる。このような施設でのがん治療での治療成果をあげるためには，精度の高いがん治療システムが必要になる。

2. 粒子線医療センターの総合的システム

粒子線医療センターで行われる粒子線治療は，粒子線治療システム，治療計画システムと治療確認システムからなる総合的システムで行われる。粒子線治療システムは新しい医療装置で，医療用具としての国からの承認を必要とする。そのため，医療用具製造承認のための臨床試験を装置メーカーである三菱電機株式会社の依頼で行った。治療計画システムは，すでに医療用具として使われている種々の放射線診断装置と治療計画装置の組み合わせで，治療確認システムは，PETカメラである。

1）粒子線治療システム

粒子線治療装置とは，体内深い腫瘍に粒子を集中させて照射する医療用具であるが，体内深くまで粒子が届くように加速し，なおかつ可能な限り正常細胞には影響しないようにする機能が必要である。加速器が大きいため，従来の医療用具の概念を超えた巨大な装置で，入射系（イオンビームを入射），加速器系（治療に適合したエネルギーまでビームを加速），輸送系（加速したビームを指定された照射室に効率良く輸送），照射室にある照射系（供給されたビームを腫瘍に適正に照射）から構成される（図2）。

2）治療計画システム

治療計画システムは，CT，MRI，治療計画装置からなる。治療計画装置は，CMS製の治療計画装置FOCUSに，ペンシルビーム法による粒子線治療計算コードを載せたもので，治療情報管理サーバ（WS）と治療計画端末（WS）からなる。

3）治療確認システム

荷電粒子は，高速で物質を通過すると，物質を構成している原子と粒子との衝突が繰り返され，このときにポジトロンを放射する。そこで，治療直後にPETカメラ（SET-2300W；島津，京都）で治療患者を撮れば，治療部位の確認ができ記録できる[5]。

4）その他の治療支援システム

肝がんや肺がんの治療をする時に腫瘍は呼吸で移動する。呼気の状態で腫瘍の動きが安定するので呼気時に照射するが，重イオン線治療に開発された呼吸同期照射法を，当センターでも用いている。

3. 粒子線治療の流れ

1）固定具作成とCT，MRI撮影

放射線診療技師が，CT装置上で，熱可塑性プラスチックを使って患者の固定用具を作る。その固定用具をつけたまま，治療部位のCTを撮る。CT撮影後固定具ははずしてMRIを撮る。CT画像，MRI画像は，院内画像用サーバに送られる。

2）治療計画

治療計画は，治療計画装置で行われるが，次の手順で行われる。まず，治療計画装置にCTとMRIの画像が取り込まれ画像がフュージョンされCT-MRI画像となる。そのCT-MRI画像に医師が治療部位を書き込んでいく。治療部位が決まるとコンピュータ処理がされて，治療計画が作成される。

3）治療討議

治療計画をもとに，医師，技師，医学物理士，看護師の複数のスタッフによる治療討議が行われる。治療討議は，病院情報システムが自由に使われるカンファレンス室で行われる。問題があれば再治療計画が命じられるが，問題がなければ承認される。承認は，病院情報システム上で行われ，責任者がボタンを押すことで，その承認データ（治療計画のすべてで，粒子線の種類，治療で使われるエネルギー，拡大ブラッグピークを作るリッジフイルター，一日の治療線量や総線量など）が，粒子線治療システムに送られる。

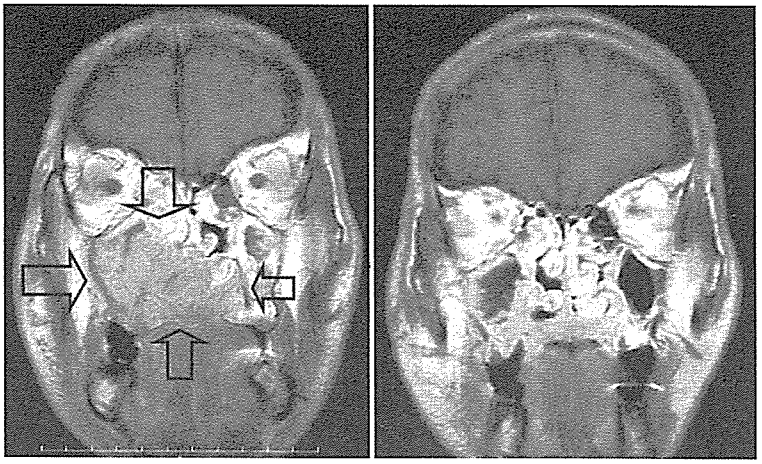

図 3　治療例。顔の MRI 像で，左の画像の矢印で囲まれたのが癌。治療後癌は消失。5 年後の現在，普通の日常生活をされている。

4）新患測定

治療討議で承認された新患の治療線量は，加速器技術者によって水ファントムで測定し，照射線量の測定値を決定している。そして，その測定値を放射線技師がチェックしている。このような測定は，治療終了後の夜間に行っている。

5）リハーサル

治療の前日に患者さんによる治療のリハーサルが行われる。当センターでは，治療時の位置あわせの精度基準を 1 mm 以内としているので，その精度を維持するための準備である。具体的には，患者さんをまず治療台に寝かせ固定具をつけ，レーザポインタで位置あわせをし，治療計画で作成した DRR 画像を基準として，正側面の基準 X 線画像（参照画像）を作成する。この作業は，約 30 分，長い時は 1 時間を要する。治療精度の最大のポイントで，患者さんと技師の共同作業である。

6）標準測定，補正

治療開始前の早朝 6 時に加速器を立ち上げ，装置が安定すると，当日の加速器の出力値を加速器技術者が測定（標準測定）し，新患測定値の補正を行い，当日の治療線量を決定している。これも放射線技師が再チェックしている。また，大気圧などにより，微妙に線量を補正する必要があり，全例治療直前に放射線技師が修正している。

7）治療

リハーサルで作成した参照画像に，その日に撮る画像を重ね合わせる方法で，患者さんの寝台を動かすことにより位置あわせをする。1 mm 以内の基準に対して，現在平均 0.5mm 以内の精度での位置あわせが行われている。ただ，この位置あわせに約 15 分近くかかっており，自動化などの方法が望まれる。具体的には，コンピュータ画面の左側に参照画像示され，当日の患者位置を示す右の X 線像と一致した時点で，治療が行われる。治療は約 1 ～ 2 分である。

4. 医　療

1）適応

粒子線治療が卓越した効果を上げるのは，深部の実質臓器のがんで，限局したものが対象となる。当センターでは，先行する施設の成績[6]などから考えて，頭頸部がん，肺がん，肝がん，前立腺がん，骨軟部肉腫を第一のターゲットとしている。各々のがん治療のための治療基準は，外科や泌尿器科などの専門家とともに専門部会を構築し，その中で検討している。自治体の病院であることから，研究的な試みはしないで，先行する施設で有効かつ安全であった治療法をまず取り入れている。治療が困難なのは，胃がんや大腸がんなどの消化管のがんで，治療後にがんが治っても穴が開く可能性が高いからである。また，子宮頸がん等のように周囲に腸管のある臓器では，照射野に腸管が入らなければ治療が可能だが，そのような事は少なく，治療のできない事が多い。したがって，現時点では，肝臓を除く腹腔内のがんにはあまり向いていない。ただ，膵がんの術前照射を神戸大学医学部との連携で開始しており，今後慎重に検討していく。

2）粒子線医療センターでの臨床試験[7]

陽子線治療は，2001 年 5 ～ 11 月の 30 例で，終了後，医療用具の承認のための申請を行った。炭素イオン線は，2002 年 1 ～ 7 月の 30 例で行われ，2003 年 2 月に申請をした。

陽子線治療

陽子線治療では，頭頸部がん 4，肺がん 5，肝がん 5 と前立腺がん 16 で，男性 26，女性 4 だった。照射線量は，頭頸部がん；65GyE/26 回/7 週，肺がん；80GyE/20 回/5 週，肝がん；76GyE/20 回/5 週，前立腺がん；74GyE/37 回/8 週だった。急性反応は，全例一過性で問題はなく，照射されたがんで制御できなかったのは，治療前の腫瘍サイズが 10cm を超える頭頸部がんの 1 例のみで，全例での

1年局所制御率は，96.7%であった。頭頸部の著効例を図3に示す。

炭素イオン線治療

放射線抵抗性腫瘍を対象とし，頭頸部がん19（悪性黒色腫8），肺がん3，肝がん6と骨軟部腫瘍2で，男性17，女性13だった。照射線量は，頭頸部がん；57.6GyE/16回/4週，肺がん；68.4GyE/9回/3週，肝がん；52.8GyE/8回/2週，骨軟部腫瘍；70.4GyE/32回/8週だった。急性反応は，全例一過性で問題なく，1年局所制御率90%であった。局所再発3例は全例頭頸部がんで，頭頸部領域での進行した放射線抵抗性腫瘍に対する治療経験不足も要因と考えている。

3）粒子線医療センターでの一般診療

陽子線治療の承認は，2002年10月に受けることができ，2003年4月から陽子線治療の一般診療を開始した。治療の対象部位としては，臨床試験の実績に基づき，頭頸部がん，肺がん，肝がん，前立腺がんを第一のターゲットとしている。陽子線治療の臨床試験では，前立腺がん以外週4回の照射だったが，一般診療ではすべて週5回の照射で行っている。したがって，照射期間が短くなった。また，先行する施設の実績から，肺がん，肝がんに対する陽子線での60GyE/10回/2週や炭素イオン線での52.8GyE/4回/1週の新しい短期照射法も始めている。治療患者数は，2006年3月末までで，904例（陽子：862例　炭素：42例）である。

陽子線，炭素イオン線とも高度先進医療としての治療となるが，粒子線治療費（288.3万円）は，患者負担である。

5. 頭頸部がんの中間報告

2001年4月から2006年3月までに粒子線治療を行った頭頸部領域の悪性腫瘍患者125例を対象にした。101例は陽子線，24例は炭素イオン線で治療した。病理組織は，陽子で粘膜悪性黒色腫（MMM），扁平上皮癌（SCC），腺様嚢胞癌（ACC），腺癌（Ad），嗅神経芽腫（ONB）の順に多く，炭素でも扁平上皮癌を除く4つの組織型が同じ順で多かった。陽子，炭素ともT3-T4の進行癌が70%を占め，残り10%はN2-N3またはM1の姑息照射例であった。姑息照射例と2例未満の病理組織を除いた陽子86例と炭素17例の2年局所制御率（LC）は79%と85%，2年全生存率（OS）は68%と68%でいずれも2つの粒子線の間に有意差を認めなかった。ACC，Ad，MMM，ONB，SCCの2年LCは，陽子で90%，100%，73%，100%，70%，炭素で75%，0%，100%，100%，評価不能であった。同様に2年OSは，陽子で93%，38%，70%，100%，45%，炭素で75%，0%，50%，100%，評価不能であった。陽子，炭素ともAd次いでMMMで遠隔再発による原病死が多かった。LCについては陽子，炭素とも術後再発の有無により差を認めなかったが，OSについては陽子で術後再発例の方が有意に予後不良であり，炭素でも術後再発例に死亡率が高かった。T3-T4の進行例が大半であったにもかかわらず，陽子，炭素ともほとんどの病理組織で粒子線照射単独により2年で70%以上の局所制御が得られた。一方，Ad，MMMは早期に遠隔再発により原病死する例が多く，特に術後再発例では血行性播種のリスクが高いと考えられた。

6. おわりに

粒子線治療は導入に多額の費用が必要だが，年間症例数では，IMRTなどと比べると約5-10倍以上の治療が可能になるので，当センターのような多数の患者さんの治療を期待される自治体の病院には向いている。

神戸や大阪などの大都市から離れて立地する当センターでも患者にとって楽な粒子線治療では，約25%は通院治療で，2時間半かけて車で来られる人もいる。また，治療のない週末には，在院2名のみで他はすべて外泊という日もあり，しかもその外泊者の中には九州から治療を受けに来られている方数名も含まれていた。このようなことは，従来の放射線治療を行ってきた我々の経験からはまったく異質な医療である。

粒子線治療装置は，装置そのものが研究であった時代から医療に広く活用できる時代になってきた。医療を行うものにとって最重要なことは，どのような治療を行うかであって，装置そのものではない。当センターのような自治体で行う診療は，安全に多くの患者さんに提供する医療である。一方，大学や研究機関で行う医療は，治療適応疾患の拡大や新しい治療法を研究する使命があり，チャレンジが要求される。一般の病院で行う医療と大学・研究機関で行う医療の役割分担は，先端医療では特に重要である。役割分担が明白になる事で，粒子線治療を受けたいと希望される患者さんの理解が得られ，それが将来の粒子線治療の適応拡大につながると考える。

文　献

1）Wilson R.R.: Radiological use of fast protons. Radiology 47：487-491, 1946
2）Tsujii H., Tsuji H., Inada T., et al: Clinical results of fractionated proton therapy. Int. J. Radiat. Oncol. Biol. Phys. 25：49-60, 1992
3）Slater J.M, Archambeau J.O, Miller D.W.: The proton treatment center at Loma Linda University Medical Center: Rationale for and description of its development. Int. J. Radiat. Oncol. Biol. Phys. 22：383-389, 1992
4）Tsujii H., Morita S., Miyamoto T., et al: Preliminary results of phase I/II carbon-ion therapy at the National Institute of Radiological Sciences. J. Brachyther Int. 13：1-8, 1997
5）Hishikawa Y., Kagawa K., Murakami M., et al: Usefulness of Positron-Emission Tomographic Images After Proton Therapy. Int. J. Radiat. Oncol. Biol. Phys. 53：1388-1391, 2002
6）Ogino T.: National Cancer Center has started proton therapy. Jpn. J. Clin. Oncol. 29：179, 1999
7）村上昌雄，香川一史，菱川良夫他：兵庫県立粒子線医療センターでの臨床試験報告：陽子線治療　日医放会誌　62：79-85，2002

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Ion Beam Treatment for Head and Neck Cancer

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The ion beam treatment in the Hyogo Ion Beam Medical Center (HIBMC) is carried out with a comprehensive system that consists of an irradiation system, a treatment planning system and a treatment verification system. The treatment verification system consists of a positron emission tomography (PET) camera. As charged particles produce short-lived positron-emitting isotopes in tissues, the treated site can be verified by images taken immediately after irradiation using a PET camera.

A technician sets up an immobilizing device fitted to an individual patient using plastic materials, and takes CT and MRI images of the treatment target site. Treatment planning is carried out using the 3-D treatment planning system. At this time CT and MRI fusion images are used for treatment planning. Before treatment, a rehearsal is done and on the day of treatment, the positioning is performed in the same way as the rehearsal. After positioning, ion beam therapy is started. A respiratory gating system is used for patients with lung or liver cancer.

On April 1, 2001, HIBMC was opened as the world's first facility to provide both proton and carbon-ion radiotherapy. We have treated more than 950 patients with a variety of malignant tumors including skull base, head and neck, lung, liver and prostate tumors. Excellent local control for these tumors has been obtained with minimum side effects. Experience of clinical trial and general practice, showed that radio-resistant tumors in the head and neck region like mucosal malignant melanoma and adenoid cystic carcinoma could be locally controlled with proton beam therapy. In the future we will analyze the difference between two beams for the patient with head and neck cancer.

Key words : head and neck cancer, ion beam radiotherapy, proton, carbon ion