estimated by subtracting the period of hospitalization by any causes from the overall survival time. We checked the number of and reasons for attendance at outpatient clinics and recorded all treatments, including supportive care, performed at each attendance. We also assessed the number of times patients were hospitalized, the reasons for hospitalization and medical conditions at discharge. We accumulated early death observed within 30 days after the last administration of chemotherapy to investigate the cause of death. Survival analysis was performed using the methods of Kaplan and Meier, by adopting all deaths from any cause as events.

RESULTS

Patient Characteristics

One hundred and ninety-nine patients received chemotherapy during the study period, of whom 135 patients were excluded from analysis and 64 patients fulfilled the eligibility criteria and were entered into the study. The reasons for exclusion were prior chemotherapy (70 patients), no visible tumor (13 patients), older than 76 years (13 patients), severe peritoneal dissemination (10 patients), inadequate oral intake (nine patients), other active malignancy (eight patients), serious medical complication (seven patients), PS 3 or 4 (four patients), and symptomatic brain metastasis (one patient). Table 1 shows the characteristics of the patients. The median age was 64 years (range 32–75 years); 30 patients were PS 0, 27 patients were PS 1, and seven patients were PS 2. One patient had no metastatic sites, 34 patients had one metastatic site, 22 patients had two metastatic sites, eight patients had three or more metastatic sites.

Treatment

Table 2 lists the chemotherapy regimens received over the entire clinical courses of the patients. The median number of regimens was two (range, 1–6), 72% of patients received second-line chemotherapy, and 39% of patients had three or more chemotherapy regimens. In 31 patients (48%), the first-line chemotherapy was started at the outpatient clinic. Oral administration of S-1 was the most frequently used in first-line chemotherapy (35 patients, 55%), and 21 (33%) patients who were given CDDP-containing regimens or continuous infusion of 5-FU required hospitalization. The most frequently used forms of second-line chemotherapy were w-PTX (26 patients, 57%) and a combination of CPT-11 and CDDP (11 patients, 24%).

Table 1. Patient characteristics

Age (years)		
	Median	64
	Range	(32–75)
Gender		
	Male	46
	Female	18
PS	0/1/2	30/27/7
Number of metastatic sites	0/1/2/3/4	1/34/21/6/2

PS, performance status.

Attendance at the Outpatient Clinic

Table 3 lists the number of and reasons for attendance at the outpatient clinic. The median number of visits to outpatient clinics was 29 visits per patient (range, 0–84). The total number of visits was 1917, of which 145 (8%) were unplanned, which were caused by accidental disease (50 visits), disease progression (46 visits), toxicity (45 visits), or for prescription (four visits). Supportive care was performed in outpatient clinics at 142 visits (7%) such as hydration (88 visits), transfusion (28 visits), abdominal paracentesis (eight visits), insertion of a central venous line (seven visits), and administration of granulocyte colony-stimulating factor (two visits).

Survival and Hospitalization

Although some patients were referred to other hospitals, we obtained the information concerning the reason and period

Table 2. Treatment

	1st line	2nd line	3rd line	≥4th line
	$n = 64$	$n = 46$	$n = 25$	$n = 10$*
S-1	35	5	–	3
S-1/CDDP	10	1	–	–
MTX/5-FU	7	–	–	3
CPT11 + CDDP	6	11	2	–
5-FUci	5	–	–	–
Weekly PTX	1	26	12	2
CPT11 + MMC	–	3	4	–
5-FU/l-LV	–	–	2	3
5-FU + CDDP	–	–	–	1
CDDPip	–	–	2	–
CPT-11	–	1	2	–
CDDP + VP-16	–	–	–	1
Hepatic arterial infusion	–	–	1	2
MMC	–	–	–	1

*Repetition (+).
S-1, tegafur-gimeracil-oteracil-potassium; CDDP, cisplatin; MTX, methotrexate; 5-FU, 5-fluorouracil; CPT11, irinotecan; ci, continuous infusion; PTX, paclitaxel; MMC, mitomycin; l-LV, l-leucovorin; ip, intra peritoneum; VP-16, etoposide.

Table 3. Attendance to outpatient clinic and providing supportive care

	Number	Median	(Range)
Total	1917	29	(0–84)
Planned	1772	25	(0–79)
Emergent	145	2	(0–10)
Accidental disease	50		
Disease progression	46		
Side effect	45		
Prescription	4		
Supportive treatment	142		
Hydration	88		
Transfusion	28		
Abdominal paracentesis	8		
Insertion of CV line	7		
Exchange of drainage	5		
G-CSF	2		
Wound care	2		
Enema	1		
Withdrawing of urine	1		

CV, central venous; G-CSF, granulocyte colony-stimulating factor.

of hospitalization, and the date and cause of death by making inquiries directly to these hospitals.

The median follow-up was 520 days (range, 309–871 days), and the median overall survival time was 353 days. The 1-year survival rate was 49%, while the 2-year survival rate was 26% (Fig. 1). The median non-hospitalized survival time was 282 days (range, 0–786 days) and the median total period of hospitalization for each patient was 59 days (range, 0–138 days) (Fig. 2). The median number of hospitalizations was four (range, 0–15) per patient and the median period of each hospitalization was six days (range, 1–96 days). The total number of hospitalizations was 291, of which 110 (38%) were unplanned and reasons for unplanned hospitalization were related to disease progression (85 hospitalizations), toxicity (14 hospitalizations), accidental disease (nine hospitalizations), or examination (two hospitalizations) (Table 4).

Medical Condition at Discharge

Patients were discharged 290 times (Table 5), 56 (19%) of which were associated with an unresolved medical problem needing intensive care or follow-up to be managed at the outpatient clinic. These included toxicity (14 discharges), total parenteral nutrition (14 discharges), symptoms of cancer (17 discharges), percutaneous endoscopic gastrostomy (seven discharges), and other problems (four discharges).

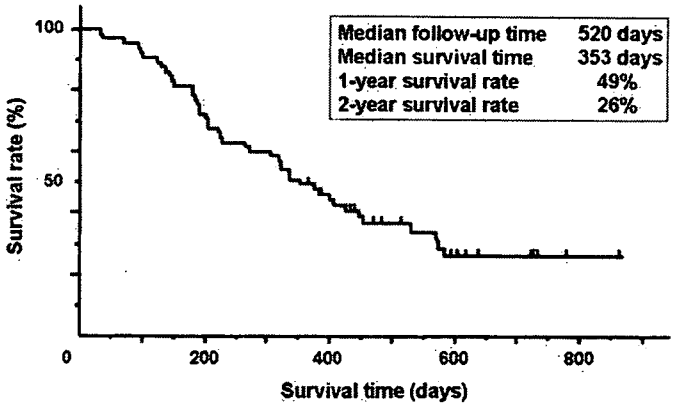

Figure 1. Overall survival.

Treatment-related Death

Fifteen patients (23%) died within 30 days after the last administration of chemotherapy. Of these 15 patients, three died of treatment-related death (TRD), and the other 12 early deaths within 30 days after last administration of chemotherapy occurred after confirming tumor progression. Two of three TRDs were treated at the outpatient clinic. One patient with PS 2 and massive ascites caused by peritoneal dissemination received w-PTX regimen as the second line setting. Vomiting appeared on day four after the sixth administration of chemotherapy and he entered the hospital for septic shock on the same day. Despite intensive supportive care he died on day five. Another patient with PS 1 and chronic renal failure received w-PTX regime as the third line setting. Although the only complication he had was grade 1 (NCI-CTC ver.2) nausea till day four, he entered hospital for grade 4 leucopenia on day five after the eighth administration of chemotherapy agent. While he recovered from leucopenia on day 11, grade 3 thrombocytopenia persisted. Bleeding from primary tumor occurred after confirming disease progression and he died of hypovolemic shock on day 26. The last patient died of pneumocystis carini

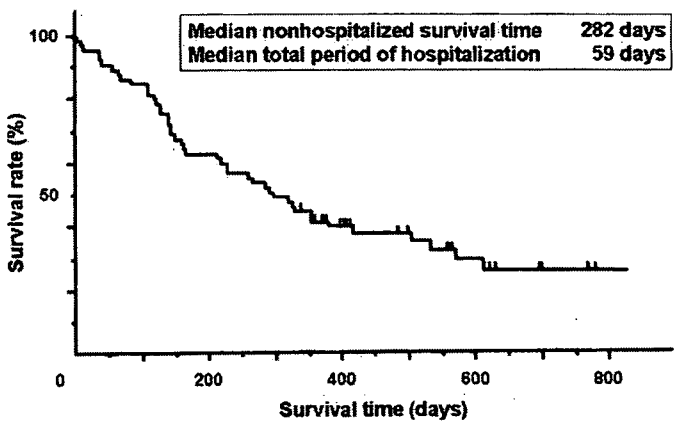

Figure 2. Non-hospitalized survival.

Table 4. Number and period of hospitalization

	Number	Median number	(Range)	Median period (days)	(Range)
Total	291	4	(0–15)	6	(1–96)
Planned	181	–		5	(1–65)
Emergent	110	–		16	(1–96)
Disease progression	85	–		21	(2–96)
Toxicity	14	–		9	(1–22)
Accidental disease	9	–		8	(2–22)
Examination	2	–		4	(3–5)

Table 5. Medical condition at discharge

	Number
Total	290
No problem	193
Death	41
Problems unresolved	56
Toxicity	14
TPN	14
Symptoms of cancer	17
PEG	7
Mental	3
PTBD	2
HOT	1
Stent in bile duct	1
Unresolved accidental disease	1

TPN, total parenteral nutrition; PEG, percutaneous endoscopic gastronomy; PTBD, percutaneous transhepatic bile duct drainage; HOT, home oxygen therapy.

pneumonia caused by grade 4 leucopenia after 1st administration of CDDP and VP-16 initiated during hospitalization.

DISCUSSION

In the recent randomized studies investigating the effects of single agent 5-FU therapy or the combination therapy of 5-FU plus CDDP, docetaxel and 5-FU plus CDDP, 5-FU and doxorubicin plus MMC or etoposide and leucovorin plus 5FU, it was reported that the median survival time was 7–9 months, the 1-year survival rate was 28–40% and 2-year survival rate was 7–18% (7,16–19).

For the single agent therapy of S-1, a novel oral derivative of 5-FU, the median survival time of 207 days, and 1- and 2-year survival rates of 36 and 14%, respectively, were reported in a Japanese phase II study (2,3). Furthermore a Japanese phase I/II study of S-1 combined with CDDP reported a median survival time of 383 days, and 1- and 2-year survival rates of 52 and 10%, respectively (4). However, a Japanese phase II study on CPT-11 combined with CDDP showed a median survival time of 322 days (6). In our study, the median survival time was 353 days, and 1- and 2-year survival rates were 49 and 26%, respectively. Although our survival data were obtained by retrospective analysis, our clinical outcomes seem to be equal or exceed those reported in previous studies.

In our study, the median non-hospitalized survival time was 282 days and median overall survival time was 352 days. We found no reports referring to non-hospitalized survival of patients with gastric cancer and it is difficult to compare our results with those of other researchers. In our hospital, we use various supportive systems to help patients remain at home and to care for patients from the initiation of chemotherapy to the terminal stage.

The incidence of TRD is 1–5% in some phase III studies (7,16). Three TRDs caused by leucopenia and thrombocytopenia occurred in our study (5%). Of two patients who were treated at the outpatient clinic, one patient entered hospital quickly after symptoms appeared. Another patient recovered from the leucopenia immediately after hospitalization so we do not consider that chemotherapy at the outpatient clinic caused delay of supportive care and that TRD might have been avoided if the patients had been treated in hospital. The number of early deaths within 30 days after the last administration of chemotherapy in our series seems high. The median number of chemotherapy regimens was two, and many patients received three or more chemotherapy regimens. Some of them were initiated despite poor medical conditions. We thus hypothesize that the risk of TRD increases according to the number of regimens received. Moreover, the indications for chemotherapy, especially in the subsequent treatment lines, should be decided more carefully to promote the safety of chemotherapy.

Most patients undergoing chemotherapy visit the hospital usually once every week or two. The median number of visits to the outpatient clinic was 29 and the median survival time was about 1 year. However, because of toxicity or disease progression, the patients' medical conditions sometimes changed between planned visits. We found that 8% of the total number of visits to the outpatient clinic were unplanned and that 7% of all visits required supportive care. We made an effort to prolong non-hospitalized survival by providing home nutrition and other supporting systems. This situation might make the incidence of unplanned attendance at the outpatient clinic look high, but we believe these are important in providing chemotherapy for patients with gastric cancer.

The incidence of unplanned or emergency hospitalization was 38% of the total number of hospitalizations. The main reason for hospitalization was worsening of patient's medical conditions caused by disease progression. Gastric cancer sometimes causes impaired oral intake, ileus, ascites, hydronephrosis and other severe complications. These serious complications can not be managed at an outpatient

clinic, and therefore the median duration of emergency hospitalization (16 days) was longer than that of planned hospitalization (five days). These data suggest the importance of establishing a system by which patients are accepted quickly for unplanned or emergency hospitalization in order to ensure safety of chemotherapy.

As mentioned above, we made an effort to prolong non-hospitalized survival by providing various support systems and 19% of the total number of discharges had associated problems such as toxicity, total parenteral nutrition at home, symptoms of cancer and percutaneous endoscopic gastrostomy. Although we helped patients adapt to these problems before discharge, our data suggest that these problems could also be managed or resolved at an outpatient clinic.

In conclusion, chemotherapy for patients with unresectable recurrent gastric cancer can be performed safely with support in hospitals. Japanese hospitals should not only establish outpatient chemotherapy centers but also a system to quickly provide emergency care during chemotherapy. We expect that the support system for providing chemotherapy safely will become more popular in Japan, and contribute to patients' QOL in the near future.

Conflict of interest statement

None declared.

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Efficacy and Safety of an Irinotecan plus Bolus 5-Fluorouracil and L-Leucovorin Regimen for Metastatic Colorectal Cancer in Japanese Patients: Experience in a Single Institution in Japan

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Background: Short-term infusion of 5-fluorouracil with leucovorin in combination with irinotecan or oxaliplatin has been considered as standard treatment for metastatic colorectal cancer. However, until infusion of 5-fluorouracil regimens and oxaliplatin was approved for the treatment of metastatic colorectal cancer in Japan early in 2005, combination of irinotecan with bolus 5-fluorouracil/leucovorin had been the standard treatment. This retrospective study evaluates the efficacy and safety of a modified irinotecan with bolus 5-fluorouracil/leucovorin regimen in Japanese colorectal cancer patients.
Methods: Forty-six patients untreated with chemotherapy for metastatic colorectal cancer received a modified form of the irinotecan with bolus 5-fluorouracil/leucovorin regimen, consisting of intravenous irinotecan (100 mg/m^2) and L-leucovorin (10 mg/m^2), and then 5-fluorouracil 500 mg/m^2 as an intravenous bolus infusion, weekly for 4 weeks, repeated every 6 weeks until progression or unacceptable toxicity.
Results: The overall response rate was 48% (95% confidence interval, 34–62%), and 48% of patients had stable disease. Median progression-free survival was 8.3 months and overall survival was 20.3 months. The incidence of grade 3 or 4 toxicity was as follows: neutropenia, 50%; diarrhea, 4%; fatigue, 13%; nausea, 7%; and vomiting, 7%. Neither treatment-related nor all-cause mortality occurred within 60 days of chemotherapy initiation. Despite the limited availability of oxaliplatin, 29 patients received an oxaliplatin-based regimen after progression.
Conclusion: A modified irinotecan plus bolus 5-fluorouracil/L-leucovorin regimen was an active and well-tolerated regimen in Japanese patients with advanced colorectal cancer, showing a different toxicity profile from Western patients.

Key words: colorectal cancer – 5-fluorouracil – irinotecan – L-leucovorin – IFL regimen

INTRODUCTION

Approximately 92 000 new cases of colorectal cancer (CRC) are diagnosed each year in Japan, of which 61 000 are colon and the remainder rectal cancers. In 2004, more than 40 000 Japanese died of CRC (1).

Irinotecan, a potent inhibitor of topoisomerase I, extends survival significantly as compared with the best supportive care or 5-fluorouracil (5-FU) infusion as second-line therapy for colorectal cancer. Three pivotal phase III trials demonstrated combined irinotecan plus 5-FU/leucovorin (LV) compared with 5-FU/LV alone in the first-line treatment provided a survival benefit, with a median overall survival time of 12.6–16.9 to 14.8–20.1 months (2–4). At that point, irinotecan in combination with either bolus or infusion of 5-FU/LV had been considered the standard of care as first-line treatment.

Despite favorable initial reports, randomized trials have suggested that the irinotecan plus bolus 5-FU/LV (IFL) regimen may be more toxic than originally suspected. In two United States Cooperative Group trials (one for metastatic CRC, the other in the adjuvant setting), unacceptably high incidences of early treatment-related death were noted, leading to suspension of accrual in both studies (5,6). The

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patients who died had shown similar clinical course (dehydration, neutropenia, and sepsis), with the majority of the deaths occurring during the first 6 weeks of therapy or shortly thereafter (7). Subsequently, a reduced-dose IFL regimen consisting of irinotecan 100 mg/m^2 and bolus 5-FU 400 mg/m^2 plus L-leucovorin 20 mg/m^2, was developed, showing a lower incidence of severe toxicity as compared with original IFL regimen in treatment-related or 60-day all-cause death. The reduced-dose IFL was associated with a significantly worse response rate, progression-free survival, and overall survival, compared with FOLFOX4 (oxaliplatin plus infusion of 5-FU/LV) (8). Moreover, a recent randomized phase III study has shown that infusion of 5-FU regimens (FOLFIRI) may be a safer option and superior to bolus 5-FU regimens in terms of progression-free and overall survival (9). As a result, either the original IFL or the reduced-dose IFL regimen should no longer be considered as an appropriate choice for irinotecan/5-FU/LV therapy.

Despite publication of these data, neither infusion of 5-FU regimens nor oxaliplatin were approved for metastatic CRC in Japan until early 2005, so the IFL regimen had been considered as the standard treatment for metastatic CRC, instead of FOLFIRI or FOLFOX. A previously reported single phase I and single phase I/II trial of a modified form of the IFL regimen in Japanese patients with metastatic colorectal cancer demonstrated that this modified regimen, whose recommended doses were irinotecan 100 mg/m^2, 5-FU 500 mg/m^2, and L-LV 10 mg/m^2 or 25 mg/body, was highly active, with a response rate of 44–69% and median time to progression of 7.8 months (10,11). However, the efficacy and toxicity profile of this modified IFL regimen in Japanese patients has remained unclear because of the low numbers of patients included in these studies. The aim of the retrospective analysis is to evaluate efficacy and toxicity of the modified IFL regimen as a first-line treatment against metastatic CRC in Japanese patients.

PATIENTS AND METHODS

Patient Selection

The selection criteria for inclusion in this retrospective analysis were: histologically or cytologically proven metastatic and unresectable colorectal adenocarcinoma; no prior chemotherapy or receiving adjuvant chemotherapy completed at least 6 months before; an age of $\geq$20 to $\leq$75; an Eastern Cooperative Oncology Group performance status (ECOG PS) of $\leq$2; a leukocyte count of 3000–12 000 cells/μl; a hemoglobin level of $\geq$8 g/dl; $>$100 000 platelets/μl; a serum bilirubin level of $\leq$1.1 mg/dl; serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level of $\leq$100 U/l; a serum creatinine level of $<$1.1 mg/dl (for men) or 0.8 mg/dl (for women). Patients who had an active extracolonic malignancy or had received prior radiotherapy were also excluded.

Treatment Plan

The treatment schedule consisted of irinotecan 100 mg/m^2 given intravenously as a 90-min infusion, L-leucovorin 10 mg/m^2 as an intravenous (i.v.) bolus, and then 5-FU 500 mg/m^2 as an i.v. bolus infusion, given once every week for 4 weeks, and repeated every 6 weeks (modified IFL regimen). All patients routinely received 3 mg of granisetron plus 8 mg dexamethasone in a 30 min intravenous infusion before administration of irinotecan. Treatment continued until disease progression, unacceptable toxicity, or patient refusal. Whenever severe adverse events occurred, the doses were adjusted to accommodate individual levels of tolerance based on the physician's assessment. Any grade 3 or 4 adverse events resulted in an approximately 20% dose reduction of irinotecan and bolus 5-FU for subsequent cycles. Persistent grade 2 or worse adverse events delayed therapy until recovery.

The use of colony-stimulating factors was allowed if medically justified. Intensive treatment with loperamide, if needed, was used for diarrhea. Other supportive treatments were given if required.

Evaluation of Patients

We retrospectively reviewed clinical records of patients including characteristics (age, gender, ECOG PS, primary site, number of organs involved, metastatic site, history of primary tumor resection, carcinoembryonic antigen (CEA), and prior adjuvant chemotherapy), dosage, schedule of irinotecan, L-leucovorin and 5-FU, and observed toxicities after the initial treatment. We also evaluated the confirmed response rate, progression-free survival, and overall survival.

All patients underwent physical examination, chest X-ray, and computed tomographic scans of the abdomen, pelvis, and chest before starting treatment at baseline. All patients were included in safety and efficacy analyses. Safety assessment and laboratory tests were performed weekly. The severity of adverse effects was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. Tumors were measured at 6- to 8-week intervals, and response was evaluated according to the response evaluation criteria for solid tumors (RECIST). Relative dose intensities of irinotecan and 5-FU were calculated by dividing the actual delivered dose by the planned dose.

The evaluation of response and progression was based on radiologist-reported measurements. Complete and partial response required subsequent confirmation of response after an interval of at least 4 weeks. All clinical courses including subsequent chemotherapy were surveyed until death or last contact. The Kaplan–Meier method was used to evaluate median duration of treatment, progression-free survival, and overall survival. The median duration of treatment was calculated from the date of starting treatment to

the date of disease progression or cessation of treatment for any reason, whichever date occurred first. Progression-free survival was calculated from the date of starting treatment to the earlier date of disease progression or death. Without contradictory dates, patients who were lost to follow-up were assumed to have progressed at the last date of confirmation to be progression free. For patients whose treatments were ceased without progression who had received subsequent surgery or another treatment, progression-free survival was defined as the time from the date of starting treatment to the date of its cessation. Overall survival was calculated from the date of starting treatment to death or last contact. Patients who were lost to follow-up were assumed to have been dead at the last contact. The cutoff dates were October 31, 2006 for progression-free survival and overall survival.

RESULTS

Patient Characteristics

From September 2002 to December 2004, when neither infusion of 5-FU nor oxaliplatin was available in Japan, we administered a modified form an IFL regimen to 57 patients with metastatic CRC in a first-line treatment setting. Eleven patients (19%) were excluded according to the selection criteria. The excluded patients consisted of two patients with neuroendocrine carcinoma, one patient over 75 years old, a patient with an ECOG PS >2, five patients who had inadequate hematological, renal, and liver function, and two patients having extracolonic malignancy.

Characteristics of the 46 selected patients included in this study are shown in Table 1. Their median age was 59 years. Sixty-five percent of the patients had an ECOG PS of 0 at baseline. Seventy-six percent of the patients had at least two organs involved, with the liver being the most common site of metastasis. Because most patients had synchronous metastatic disease at diagnosis, only two of them had received adjuvant therapy.

Table 1. Patient Characteristics

No. of patients	46		
Age, years		No. of organs involved	
Median	59	1	11
Range	41–71	2	17
		≥3	18
Sex		Metastatic site	
Male	29	Liver	30
Female	17	Lung	25
		Lymph nodes	24
ECOG performance status		Abdominal mass	2
0	30	Others	15
1	12	Existence of primary site	
2	4	Yes	14
Primary site		No	32
Colon	28		
Rectum	17	Adjuvant chemotherapy	
Multiple	1	Yes	2
		No	44
Metastases		CEA	
Synchronous	34	<10ng/ml	14
Metachronous	12	≥10ng/ml	32

Treatment

The median duration of treatment with the modified IFL regimen was 7.9 months. The total number of administrations was 1137 for the 46 patients with a median of 23.5 times per patient (range 4–63).

Dose reduction was required in 11 out of the 46 patients (24%), in three of whom dose reduction was performed at the beginning of the treatment, in four during the first course, in three during the second, and in one during the third. The reasons for dose reduction at initiation were age over 70 years old (two patients out of 11, 18%) and starting treatment immediately after surgery (one of 11, 9%). The main reasons for dose reduction during all treatment periods was toxicity including grade 4 leukopenia (two of 11, 18%), grade 3 fatigue (one of 11, 9%), grade 3 leukopenia (one of 11, 9%), grade 3 diarrhea plus vomiting (one of 11, 9%), grade 2 prolonged nausea (one of 11, 9%), grade 2 weight loss (one of 11, 9%), and grade 4 anemia (one of 11, 9%).

Forty patients (87%) required delayed administration, with the median number being three times, during all treatment periods. The total number of delayed administrations was 162 out of 1299 planned administrations (12%). The reasons for delayed administration were patient preference without toxicity (75 out of 162, 46%), grade 2 leukopenia (37 of 162, 23%), grade 2 nausea (nine of 162, 6%), grade 1 infection without neutropenia (nine of 162, 6%), grade 2 vomiting (five of 162, 3%), grade 3 fatigue (four of 162, 4%), grade 2 diarrhea (two of 162, 1%), grade 2 anemia (two of 162, 1%), grade 2 fatigue (two of 162, 1%), and other reasons (17 of 162, 10%).

Hospitalization due to toxicities was required in six out of the 46 patients (13%). The reasons for hospitalization were grade 3 nausea plus vomiting in two patients (33%), grade 3 diarrhea plus vomiting in one (17%), grade 3 diarrhea in one (17%), grade 4 anemia in one (17%), and grade 3 fatigue in one (17%).

During all treatment periods, the mean doses of irinotecan and 5-FU were 55 mg/m^2/week and 290 mg/m^2/week, respectively. The mean relative doses of irinotecan and 5-FU were 82 and 87%, respectively.

Table 2. Confirmed response rate

Event rate	No. of patients (%)
Complete response	1 (2)
Partial response	21 (46)
Stable disease	22 (48)
Progressive disease	1 (2)
Not evaluated	1 (2)
Overall response rate	22 (48)
95% confidential interval	34–62%

Efficacy

The confirmed response rate was 48 percent (95% confidence interval, 34–62%) (Table 2). All patients ceased treatment. Forty-two (91%) ceased treatment because of disease progression; the remaining four patients (9%) did so because of complete response in one patient and subsequent rescue surgeries after tumor shrinkage in three patients. Thirty-six patients (78%) were dead. Median progression-free survival was 8.3 months and median overall survival was 20.3 months, with a median follow-up time among survivors of approximately 30 months. Progression-free survival and overall survival curves are shown in Figure 1.

Adverse Events

The worst grade of toxicity per patient is shown in Table 3. Grade 3 or 4 fatigue occurred in six patients (13%), and grade 3 or 4 nausea and vomiting in three patients (7%), respectively. Two patients (4%) had grade 3 or 4 diarrhea. Moreover, the incidence of grade 4 neutropenia was 22%, while febrile neutropenia did not occur. Neither treatment-related nor 60-day all-cause mortality was seen in this study.

Second-Line Therapy

Among patients with follow-up data, 39 patients (85%) received subsequent chemotherapy after first-line treatment.

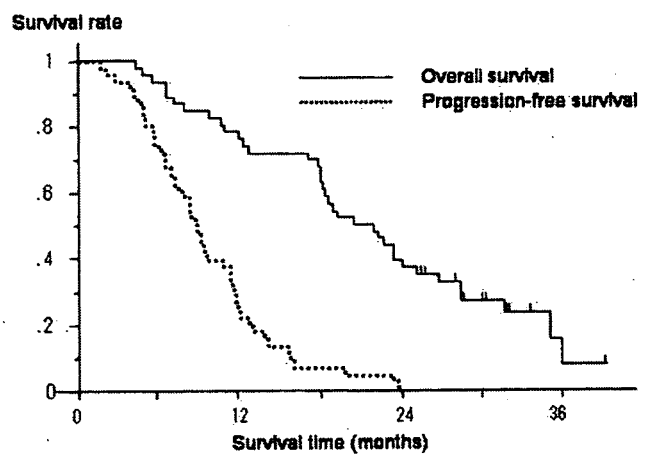

Figure 1. Overall and progression-free survivals.

Table 3. Toxicity per patient during receiving modified IFL

	1	2	3	4	% ≥ Grade3
Anemia	15	18	4	1	11
Leukopenia	5	22	7	3	22
Neutropenia	8	9	13	10	50
Thrombocytopenia	10	4	1	0	2
Diarrhea	10	7	2	0	4
Fatigue	8	6	6	0	13
Nausea	11	11	3	0	7
Vomiting	8	6	3	0	7
Febrile neutropenia	—	—	0	0	0
Mucocitis	2	1	0	0	0
Hand-foot syndrome	1	0	0	0	0
Rash	0	1	0	0	0
Hyperbilirubinemia	7	8	0	0	0
Elevation of AST/ALT	21	4	3	0	7

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Twenty-nine patients (63%) received an oxaliplatin-based regimen, in spite of the limited availability of that agent in Japan until April 2005, because efficacy and safety data of oxaliplatin with bolus 5-FU plus L-leucovorin in Japanese patients had been reported and we treated the patients with this regimen who had failed to the IFL regimen since May 2003, after informed consent from each patient and approval of the compassionate use of oxaliplatin by the clinical practice committee in our institution had been obtained.

DISCUSSION

Our retrospective study assessed the efficacy and safety of a modified IFL regimen in Japanese patients with previously untreated metastatic colorectal cancer. The patient baseline characteristics in this study were similar compared with Western studies except for the incidence of prior adjuvant chemotherapy. The incidence of adjuvant chemotherapy was lower, not only in this study, but also in another Japanese study (4–5%), as compared with an incidence of 11–28% in Western countries (3,8–13). This difference might influence the clinical outcome, because the overall response rate (48%) was higher than originally reported in the United States (39%), but similar to those reported in Japan (44–69%) (3,10,11).

The toxicity profile for the regimen, especially the lower incidence of diarrhea, might be notable in comparison with either original or reduced-dose IFL regimens. Although there are limitations in comparing the results of different studies and our findings were based on a retrospective analysis in the single institution, one of the potential reasons for the difference in the incidence of diarrhea of this regimen is

5-FU tolerability. A bridging study of uracil/tegafur (UFT) plus an oral LV regimen in Japanese and American patients demonstrated that the incidence of diarrhea of grade 3 or higher in the Japanese was lower than that in the Americans (9 vs 22%, respectively) (14). Other reasons for the lower incidence of diarrhea in the Japanese patients receiving the modified IFL regimen might be associated with the lower dose of irinotecan at 100 mg/m^2 weekly. The incidence of diarrhea of grade 3 or higher was 16.4% in patients receiving reduced-dose IFL treatment with weekly irinotecan 100 mg/m^2, compared with 19–28% in patients with original IFL treatment in Western countries involving weekly irinotecan at 125 mg/m^2 (3,8,9,12,13). Weekly irinotecan at 125 mg/m^2 in the original IFL regimen would probably lead to early treatment discontinuation due to severe adverse events. On the other hand, grade 3 or higher neutropenia was observed in 50% of the patients in this study, in whom the incidence was considered to be higher than the incidence of 26.7% in the reduced-dose IFL regimen in the United States (8). Recently, a regional safety comparison between the United States and East Asia in a phase III trial of adjuvant stage III colon cancer, comparing a XELOX regimen (combined oxaliplatin plus capecitabine) with a 5-FU/LV regimen, demonstrated that the relative risk of grade 3 or 4 neutropenia in the United States is slightly lower than that in East Asia (0.96 vs 1.00, respectively) (15). That finding is consistent with this study. However, febrile neutropenia during the treatment did not occur in this study, perhaps because careful safety assessment and laboratory tests were performed weekly before the treatment. Thus, neutropenia of grade 3 or higher was manageable under careful clinical management. As a result, we achieved a longer treatment duration of 7.9 months as compared with 5.5 months originally reported in the United States. Moreover, the reduced-dose IFL regimen showed a similar survival benefit to the original IFL regime as a historical comparison, with a median overall survival time of 16.6 months to 14.8–17.6 months. Therefore, it is suggested that weekly irinotecan at 100 mg/m^2 as examined in this study might be appropriate for Japanese patients.

The most impressive finding from this study is an overall survival in excess of 20 months, probably because of the longer progression-free survival of 8.3 months as compared with 7.0 months as originally reported. Additionally, overall survival of patients with advanced colorectal cancer was reported to be strongly correlated with the percentage of patients who received the three drugs, fluorouracil, irinotecan, and oxaliplatin, in the treatment of their disease (16,17). The predicted overall survival was calculated using a mathematical regression model: overall survival (months) = 13.2 + (% patients receiving three drugs × 0.1). In our study, 63% of patients received all three drugs, and the predicted overall survival was calculated as 19.5 months (13.2 + 63 × 0.1). Moreover, six arms of four published phase III trials included more than 60% of the patients receiving all three drugs in the course of their treatment, and showed a median overall survival time of 19.3–21.5 months, which was comparable with the overall survival time of 20.3 months shown in our study (13,18–20).

A recent randomized phase III study comparing irinotecan in combination with bolus 5-FU (IFL) to infusion of 5-FU (FOLFIRI) as first-line treatment for metastatic colorectal cancer demonstrated that FOLFIRI was significantly better in terms of progression-free survival, and showed a trend to superior overall survival and a more favorable toxicity profile, as compared with an IFL regimen (9). N9741 randomized phase III studies demonstrated that FOLFOX4 led to superior response rate, time to progression, and overall survival compared with either original or reduced-dose IFL (13). At present, first-line FOLFIRI or FOLFOX have become standards of care for metastatic colorectal cancer patients worldwide. In time, neither original nor reduced-dose IFL regimes should be considered as appropriate treatments.

In conclusion, our results suggest that a modified IFL regimen was an active and well-tolerated treatment for Japanese patients with advanced colorectal cancer, and might show different toxicity profiles than in Western patients, such as a lower incidence of severe diarrhea and a higher incidence of neutropenia without fever.

Conflict of interest statement

None declared.

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脳外科領域の粒子線治療

Ion beam treatment of brain surgery domain

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抄　録

目的：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．粒子線治療の特徴や適応を示し，脳外科領域の粒子線治療の経験を提示する．

対象，方法：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，2007年3月末で，陽子線治療と炭素イオン線をあわせて，1,400例以上の治療を行い，脊索腫や髄膜腫の頭蓋底腫瘍を経験した．

結果：線量分布が，従来の放射線治療と比べ優れる粒子線治療では，頭蓋底腫瘍でも有効であった．

結論：粒子線治療は，脳外科領域の腫瘍の治療法として，QOLの面，治療効果から，期待できる新しい治療法である．

Abstract

On April 1, 2001, the Hyogo Ion Beam Medical Center (HIBMC) was opened as the first facility in the world to provide ion beam therapy using 2 types of beams, protons and carbon-ions. To investigate the effect and safety of the treatment of proton and carbon-ion beams in the HIBMC, we have made a clinical phase I/II study from 2001 to 2002. After clinical study, we started general practice of proton therapy on April 1, 2003 and that of carbon-ion therapy on March 15, 2005. Until the end of March 2007, more than 1400 patients were treated in our center involving some patients with skull- base tumor. In the present article, we will report the treatment systems of ion-beam thearapy and the clinical results, especialy in the brain surgery domain.

Key words: skull-base tumor, ion-beam radiotherapy, proton, carbon ion

序　文

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

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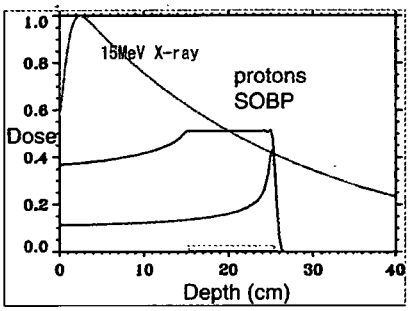

Fig. 1　Percentage depth dose curve of radiation.

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50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]．すなわち，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（Fig. 1）．基礎研究では，陽子線での生物的特性は，従来の放射線とあまり違いはない．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]．陽子線では，放射線抵抗性腫瘍にあまり有効でないと考えられていたが，当センターでの頭頸部領域の放射線抵抗性腫瘍の治療結果から，臨床面では，炭素イオン線治療と同様，局所に対しては非常に有効であった[5]．

対象・方法

1. 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，体内深い腫瘍まで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よく輸送），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（Fig. 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

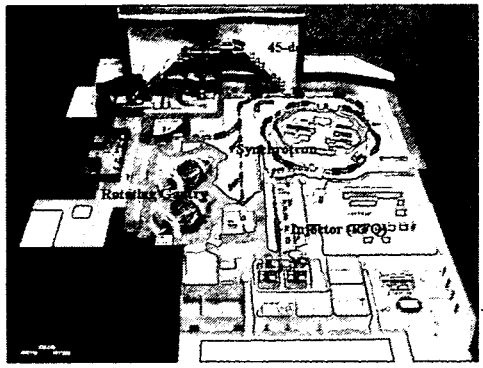

Fig. 2 Irradiation system.

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; 島津製作所，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[6]．

(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．

2. 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．

(1) 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．

(2) 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. 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，2007年3月末までで，1,400例を超えている．

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．2006年12月の時点で，頭蓋底腫瘍は，陽子線12例，炭素イオン線3例であった．

結　果

頭蓋底腫瘍症例は，2006年12月の時点ですべて生存中（最長4年）であった．陽子線治療で

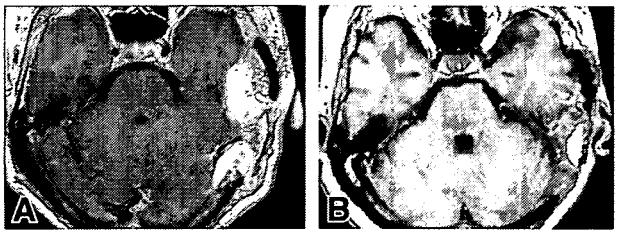

Fig. 3 Chondrosarcoma of the temporal bone (post-ope. recurrence).
A: Before treatment.
B: 12 months after proton treatment (65GyE/26fr/5.2weeks).

は，脊索腫5例，軟骨肉腫1例（Fig. 3），髄膜腫3例，神経鞘腫3例であった．炭素イオン線では，神経鞘腫2例，脊索腫1例であった．

考　察

昨今，放射線治療装置の高精度化が進み，多くの新しい装置が提供されてきている．粒子線治療は，究極の高精度な放射線治療装置で，システム化が進んでいる装置である．導入に多額の費用が必要だが，年間症例数では，他の高精度の装置と比べ，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の治療を期待される自治体の病院には向いている．

当センターのような山奥にある病院でも，頭蓋底腫瘍の治療は特に問題なくできた．粒子線治療の特性である線量分布の良さが患者に負担をかけないことで，このことを可能としてきた．

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る．当センターのような自治体で行う診療は，安全に多くの患者に提供する医療である．また，脳外科を専門とする病院への粒子線治療装置の導入は，当センターでできないような，より専門性を必要とする，脳腫瘍への治療の可能性が期待される．当センターは，粒子線治療装置を稼動するための経験を先行する施設として持っており，今後導入する施設への研修・教育を，普及の使命として行って行きたい．

結　論

粒子線治療は，頭蓋底腫瘍の治療に有効であり，今後の脳外科領域腫瘍の治療に可能性を示した．

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粒子線治療
—乳癌に対する適応—

村上昌雄[*1]・菱川良夫[*2]

abstract

乳癌に対する放射線治療は長期にわたる晩期有害事象の検討結果，さらなる線量分布の改善が期待される．陽子線治療はブラッグピークという物理学的特性があるため，通常の放射線による標準的な接線対向2門照射や最も進歩したIMRT（強度変調放射線治療）と比べてもターゲットに十分な線量を与えられると同時に同側肺，対側乳房，心臓に対する照射線量が低く抑えられるという治療計画上のメリットは大きい．陽子線治療は腋窩や鎖骨上窩など領域リンパ節照射も含めた乳房照射時にも有用である．今後発展が期待される短期乳房部分照射において，その真価が発揮できると思われる．

I 粒子線治療とは

X線あるいは電子線は広く使われるので通常の放射線（conventional radiation）とよばれ，これより重い原子核あるいは原子構成粒子を加速して得られる放射線を重粒子線（heavy particle radiation）とよぶ．陽子（proton）は水素（hydrogen）の原子核で，その質量は電子の1,836倍であり最も軽い原子核である．陽子より重たい粒子線を重イオン線（heavy-ion radiation）とよび陽子線と区別する．

現在，重粒子線のなかでは陽子線と炭素イオン線が世界中で最も多く使用されている．粒子線治療施設は世界的に見てもまだ少なく，2005年7月の集計では25施設（陽子線：22施設，炭素イオン線：2施設，陽子線＋炭素イオン線：1施設）にすぎない．現在までに世界で陽子線治療は約42,000名，重イオン線（He，C，Neなど）治療は4,500名が受けている．日本においては陽子線治療が国立がんセンター東病院，筑波大学陽子線医学利用研究センター，兵庫県立粒子線医療センター（HIBMC），静岡県立静岡がんセンターおよび若狭湾エネルギー研究センターにおいて臨床試験あるいは高度先進医療として行われており，炭素イオン線は放射線医学総合研究所とHIBMCにおいて臨床試験あるいは高度先進医療として行われている．今後世界で20施設の建設計画があり，その内訳は陽子線15施設，陽子線と重イオン線併用5施設となっている[1]．

荷電重粒子線は飛程（range）終端に急峻に増加するブラッグピーク（bragg peak）とよばれる物理学的な特徴があり，加速エネルギーに応じて体内のある一定の深さでピークを形成する．ビーム軸方向でブラッグピークを超えた領域への被曝は皆無であり，皮膚面近くの入射部領域の比較的低線量域（plateau）においては，腫瘍線量より低い線量に抑えることができる．これは従来のエックス線，ガンマ線，電子線にはない特徴である（**図1**）．

実際の照射では腫瘍の大きさに合わせてビームを形成する必要があり，施設によりその方法が異なる．横方向への拡大には散乱体システムや直列直交に配

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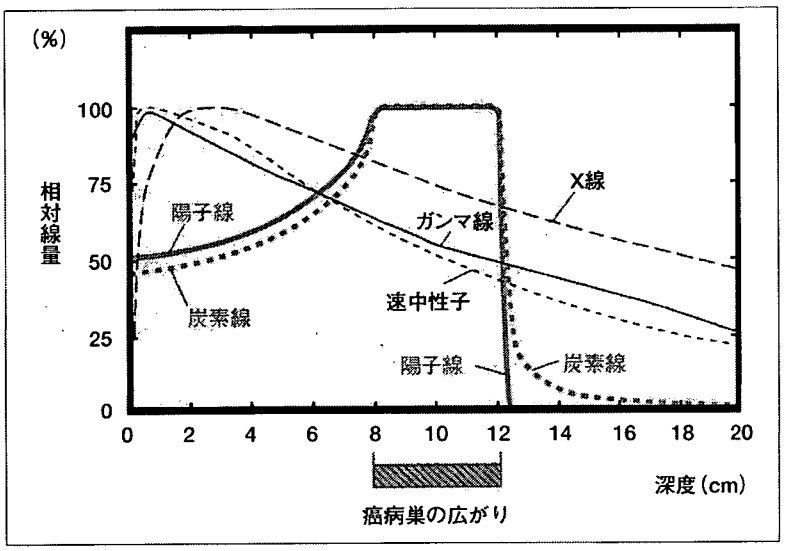

図1
荷電重粒子線の特徴

置した2対の電磁石からなるワブラーシステムを用いて行い，腫瘍の側方形状はコリメータで調整する．ビーム軸方向は腫瘍の最も厚い部分に合わせてブラッグピークを拡大（spread-out bragg peak：SOBP）させ，腫瘍の皮膚面からの距離に見合った場所でビームが停止するようにエネルギーを調整（レンジシフタなどで）したうえで，ボーラスを用いて腫瘍の遠位端の形状に合わせてビームを停止させる静的な方法がとられることが多い（静的ビームモデュレーション）．しかしこの場合，大きな腫瘍では線量のピーク・プラトー比は減少し，腫瘍の最も厚い部分に合わせてブラッグピークを拡大させるため腫瘍より手前にある皮膚などの正常組織の障害が問題になる場合もある．標的の形状に合わせたレンジモジュレーションとビームスポットを走査する動的ビームモデュレーションは線量集中性からみて理想であるが，呼吸性移動など動きのある体幹部の治療には不向きとなる．現在，ビームスキャンニングで治療を行っているのはスイスのPSI（Paul Scherrer Institute）の陽子線治療と，ドイツのGSIにおける炭素イオン線治療であり，日本の6施設はすべて静的ビームモデュレーションを使用している．

II 乳癌に対する粒子線治療

通常の放射線を用いた乳癌治療は，乳房温存療法における全乳房照射，局所進行・進行再発乳癌に対する局所制御をめざした根治照射，あるいは転移性腫瘍に対する対症・姑息的照射など適用範囲が広い．一方，粒子線治療は乳癌に対してほとんど行われていない．その理由は，前述のように粒子線治療施設はわが国でも6カ所しかないという治療施設のキャパシティーの問題があること，多くの粒子線治療施設は静的ビームモデュレーションを用いており，使用する最大照射野は10～22cm（国内6施設）であるため，乳房全体を照射するには大きさからみて不十分であるという装置側の制限があること，がまず挙げられる．また乳房温存療法における全乳房照射は長年にわたる膨大な臨床研究の末，美容効果を維持しながら副作用も少ない治療法として確立されてきた優れた方法であり，全乳房照射に使用するX線を用いた乳房接線照射を粒子線治療に置き換える必要性が少ないという臨床的側面もある．さらに，進行期乳癌や転移の治療は，通常，広範囲な病巣の広がりを示すことが多く，粒子線治療の適応になることは少ないことなどが考えられる．

一方，通常の放射線治療による接線対向2門を用いた全乳房照射では，対側乳房への小線量被曝，肺や心臓（左乳房の場合）に対する無用な照射が問題となっている．急性期には特発性器質化肺炎，晩期有害事象として対側乳癌の発症が増え，肺癌などの2次発癌，心疾患による死亡割合の増加が指摘されている[2), 3)]．

領域リンパ節と乳房を含めた複雑なターゲットを

対象として，X線による強度変調放射線治療（IMRT），スポットスキャンニングによる陽子線治療の治療計画の比較を行った報告[4]では，ターゲットへの線量集中性はIMRTと陽子線に大きな差はみられなかったが，IMRTの場合，同側肺への被曝線量（平均15Gy）はX線と電子線を用いた標準的プラン（17Gy）と大きな差はなく陽子線（13Gy）より劣った．さらに心臓への被曝線量に関して，IMRTでは肺野への被曝を抑える結果としてむしろ標準的プラン（15Gy）より高く（平均16Gy），陽子線治療（6Gy）の優位性が証明された．しかしこの陽子線はPSIのスポットスキャンニング法を用いた動的ビームモデュレーションであるため，現有のわが国のシステムでは使用困難である．同様に所属リンパ節転移陽性例における通常の放射線，IMRT，および陽子線治療（静的ビームモデュレーション；1門照射）の比較を行ったスウェーデンからの報告においても，陽子線治療の優位性が得られている．またNTCP（normal tissue complication probability）を用いた放射線治療の晩期有害事象として生じる心疾患の検討では，通常の放射線を用いた接線2門照射の6.7%から陽子線の0.5%へと死亡率の低下が見込まれている[5]．所属リンパ節領域を含まない，もう少し単純な乳房全体照射における各種X線と陽子線を用いた治療計画の比較検討においても，陽子線治療の優位性は明らかであった[6]．

このように，リンパ節領域に照射する場合には光子線と電子線の混合照射となる場合が多く，ターゲットの線量の均一性は悪くなる．最も進化したX線治療法であるIMRTを用いればターゲットの不均一性の問題は解消できるが，陽子線治療を用いれば1～2門照射という単純な照射法においても，優れた線量集中性のためターゲットへ十分な線量を照射できると同時に，対側乳房，肺，心臓などの隣接臓器への被曝が少ない点がメリットとなる．

III 陽子線を用いた短期乳房部分照射（Accelerated Partial Breast Irradiation：APBI）

最近，APBIという新たな試みが行われつつあり，乳癌に対する粒子線治療の幕開けとなる可能性がある．APBIの詳細は本号の他稿に委ねるが，ひと言でいえば乳房温存療法において短期間で乳房（腫瘍床を中心に）を部分照射する方法である．乳房内多発病巣の頻度が少ない症例に適応を限定すれば，早期乳癌に対する乳房温存療法に使用される全乳房照射に取って代わる治療法として容認できる可能性がある[7]．また従来の乳房温存療法後の乳房内再発における根治的乳房切除術に取って代わる可能性も指摘されている[8]．通常のX線を用いた全乳房照射の場合，接線照射で総線量50Gy，1回2Gy，照射回数25回，5週間を要し，断端陽性の場合は10Gy/5回くらいのブースト電子線照射が行われることが多い．APBIなら低線量率組織内照射では45～60Gy/4～6日，高線量率組織内照射では32～37Gy/4～5日，マンモサイト（MammoSite®）を使用した高線量率腔内照射では34Gy/5～7日，慣用電圧X線を用いた術中照射では15～20Gy/1日，3次元原体照射やIMRTなどのX線を用いた体外照射では30Gy/5回/10日など，いずれも短期間の治療が行われている．

陽子線を用いたAPBIも単純乳房照射と同様，十分に可能である．MGH（Massachusetts General Hospital）では乳癌切除（lumpectomy）を行った腔から20mmのマージンを付けた領域に照射している．2004～2005年に治療された25名の乳癌（2cm以下で腋窩リンパ節陰性）の報告[9]では，32 Cobalt Gray Equivalents（CGE）/4日（2回/日）を1～3門の陽子線で治療した．ターゲットに対する線量分布は十分であり，同側肺の被曝線量も低く抑えられ，また，対側肺や心臓に対して全く照射されなかった．これらの結果から，APBIにおける陽子線治療は今後大いに期待できると報じている．

MGHにおける12名のI期乳癌に対する陽子線を用いたAPBIの初期臨床報告では，観察期間中央値12カ月で再発は認めていない．美容上の評価も良好であるが，急性反応として3～4週間後に79%に中—高度の発赤を認め，6～8週間後に中—高度の湿性皮膚炎を認めたと報告している．また晩期有害事象では3例に毛細血管拡張，1例に肋骨骨折を認め，皮膚障害の程度を減じる工夫も必要と報告している[10]．経済効率の観点からすると放射線による心疾患の発症が最も重要であり，左乳癌など心臓への被曝が予想される症例では陽子線の費用対効果がよい結果となる[11]．

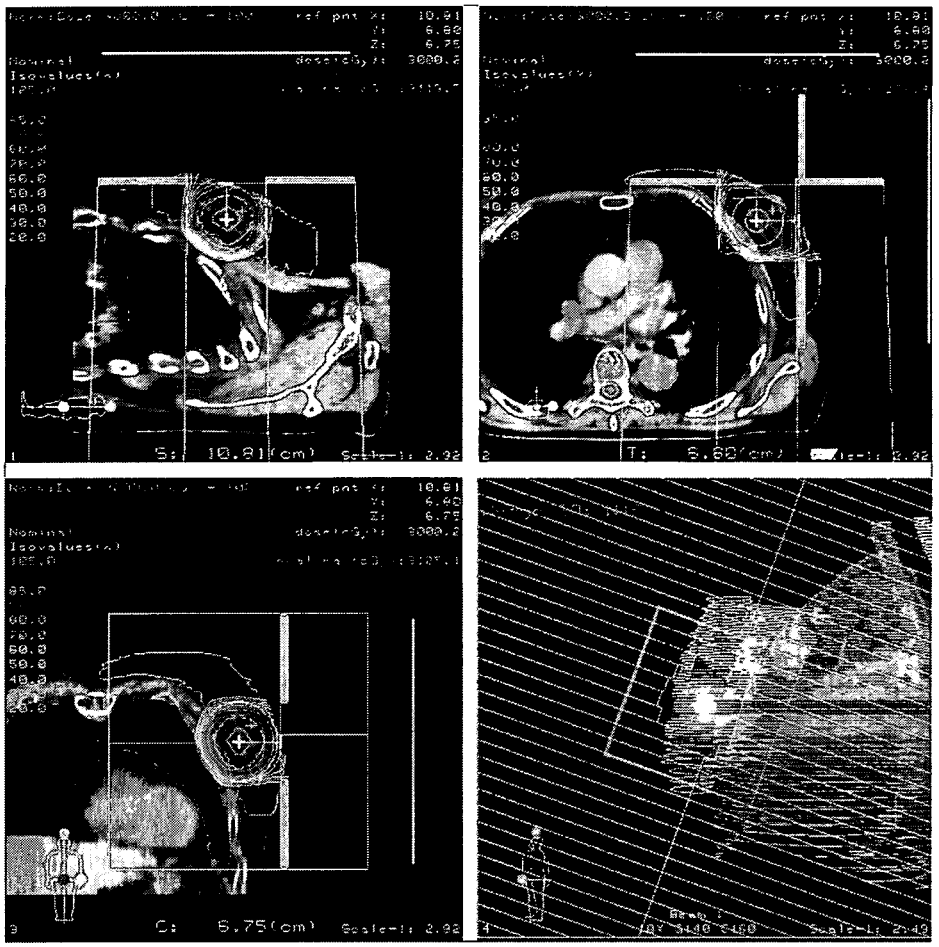

図2
APBIを想定した陽子線2門照射の腫瘍中心部における線量分布図

APBIがはたして全乳房照射の代わりになるかどうかは，Freedman[12] らの報告の通り長期の観察を経なければ結論は出ない．現在RTOGなどで比較試験が行われており，その結果が待たれるところである．HIBMCではまだ乳癌に対する粒子線治療は行っていない．しかし，上記結果を踏まえ今後，乳癌外科，腫瘍内科と共同して実施する予定である．参考までに，当センターにおけるAPBIを想定した陽子線2門照射の腫瘍中心部における線量分布図を示す（図2）．

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治療計画画像作成にあたり，当センター放射線技術科諸氏，特に矢能稔啓氏に大変お世話になった．

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肺癌低線量CT検診

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はじめに●

肺癌の予防には禁煙が最も重要であるが，禁煙しても過去の喫煙や受動喫煙の影響もあるので，肺癌患者の増加はしばらく続くと思われる．

肺癌は末期になるまで自覚症状がでにくく，進行癌の治療成績は依然として不良である．したがって，早期に発見し確実な治療を行うことが，肺癌の治療成績向上のためには重要であり，そのために間接X線写真と喀痰細胞診による検診が一般的に行われており，最近はX線写真に代わってCTを導入する施設も増加しつつある．

現在の肺癌検診および低線量CTによる検診の現状と問題点および今後の展望について解説する．

現行の肺癌検診●

国は胃，子宮，肺，乳房，大腸の癌検診を推奨しており，老人保健法の下で，肺癌検診は1987年から結核検診で撮影したフィルムを再読影するとともに，喫煙指数が600以上および半年以内に血痰を有する受診者には喀痰細胞診を追加することで行われていた．

X線撮影に関しては，100 mmの間接フィルムと希土類増感紙の使用，高圧撮影，呼吸器専門医を含む複数の医師による二重読影，有所見例の過去画像との比較，喀痰細胞診は3日間以上の蓄痰法で行うことなどの規制が加えられていた．

受診者は1998年には全国で700万人を超え，毎年増加傾向にあった．しかし，1998年に癌検診が一般財源化するに伴い伸び悩み，2003年の780万人をピークに減少に転じつつある．加えて2006年の結核予防法の改正により結核検診の対象者が大幅に絞り込まれたことなどにより，更なる受診者の減少が危惧されている．

現行の肺癌検診の有効性●

一方，肺癌検診の有効性についてはメイヨークリニックで行われた大規模なRCT（無作為化比較対照試験）で両群の肺癌死亡数に差がなかったことから，X線と細胞診での検診は無効とされているが，対照群も実際にはかなり検診を受けていたことなどから見直しの動きも出ている．

本邦では肺癌による死亡者群と性，年齢，喫煙量をそろえた健常者群の検診受診歴をさかのぼって調査する症例対照研究で有効性が統計学的に証明できた．また，自治体別の検診受診率の高さと肺癌死亡率との逆相関の証明や，検診発見の無治療臨床病期I期肺癌例がほぼ5年以内に死亡することの証明などから，祖父江班が行った「有効性評価に基づく肺癌検診ガイドライン」において，市町村が行う対策型の検診でも，個人が受診する任意型の検診でも，推奨度は「B：実施することを勧める」，と判定されている[1)]．

低線量CT検診の導入と成績●

前述のように現行の検診の効果は証明されたが，その程度は他臓器の癌検診に比べると低く，また今回の症例対照研究は，最も検診に熱心な地区で行われていることを考慮すると，検診の成績をあげ，肺癌死亡率を減少させるためには，全国どこでも高画質の画像が得られ，高精度で診断可能な検査方法の開発が模索されていた．

一方，CTは微小な陰影の検出に優れていたが，当初は撮影時間や被曝の多さ，費用の高さからあくまでも精密検査の機器と考えられていた．しかし，1980年代の末からCTは急速に進歩し，撮影時間も短縮し，また被曝を下げても異常の検出は可能であることも明らかになり，撮影条件や検出能に関する読影実験が行われるようになった．これらのデータをもとに1993年から「東京から肺

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