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DISEASES OF THE COLON & RECTUM

ORIGINAL CONTRIBUTION

Preoperative Radiation Response Evaluated by 18-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival in Locally Advanced Rectal Cancer

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PURPOSE: This study focuses on the prognostic survival value of postirradiation metabolic activity in primary rectal cancer as measured with 18-fluorodeoxyglucose positron emission tomography.

METHODS: From July 1995 to March 2002, all 59 patients underwent two series of fluorodeoxyglucose positron emission tomography: one before preoperative radiation (standardized uptake values-1), and the other two to three weeks after radiation (standardized uptake values-2). Standardized uptake values-1 and standardized uptake values-2 correspond to before and after radiation, respectively.

RESULTS: In univariate analysis, the following emerged as significant prognostic variables: with or without residual tumor, pathologic differentiation, with or without recurrence, standardized uptake values-2, and with or without lymph node metastases. In multivariate analysis, residual tumor and standardized uptake values-2 were significant prognostic factors for survival. The median survival and the five-year overall survival rate comparing standardized uptake values-2 values <5 *vs.* >5 were 95 *vs.* 42 months and 70 *vs.* 44 percent, respectively ($P=0.042$).

CONCLUSION: A significant survival benefit was observed in patients with low fluorodeoxyglucose uptake after preoperative radiotherapy in primary tumors of rectal cancer.

KEY WORDS: Positron emission tomography; Radiotherapy; Prognostic value; Standardized uptake values; Rectal cancer; Preoperative radiation.

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A number of studies have reported that preoperative radiotherapy (RT) reduces the recurrence rate for locally advanced rectal cancer.[1–6]

Several studies have suggested that in selected patients with low rectal tumors, high-dose preoperative RT might permit the resection of the primary tumor with a high rate of preservation of sphincter function.[7–11] Such treatment results could have survival rates similar to those observed with more radical surgery without increasing the risk of pelvic or perineal recurrences.

However, except for a single European trial, definitive improvement in overall survival has not generally been demonstrated with preoperative RT alone.[3,12]

The prognosis of rectal cancer is generally related to the degree of penetration of the tumor through the bowel wall and the presence or absence of nodal involvement.[13–16] However, diagnostic accuracy of tumor penetration and nodal status is not sufficient.[17]

Many other prognostic markers have been evaluated retrospectively in determining the prognosis of patients with rectal cancer, although most, including allelic loss of chromosome 18q or thymidylate synthase expression, have not been prospectively validated.[18–20]

In those cases of rectal cancer in which preoperative RT was administered, nodal involvement and penetration of the tumor seemed to be significant for prognosis as well.[21–25] Besides nodal involvement and penetration status, no definitive prognostic markers have been reported in the preoperative radiation setting for this malignancy.

Prognostic information available before surgery is useful to select the candidates for a more aggressive surgical approach, such as extended lymphadenectomy, as well as intensive postoperative adjuvant therapy.[26–30] Also, the identification before the start of the entire treatment course of subsets of patients who are at low or high risk for recurrence can help to optimize treatment. For high-risk subsets, a more aggressive preoperative approach,

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such as combined modality preoperative treatment should be considered. Few predictors have been reported for this use.

Several studies have now been reported claiming the potential of fluorodeoxyglucose–positron emission tomography (FDG-PET) in predicting treatment outcome after preoperative RT for malignant neoplasms, including rectal cancer.[31,32] However, no consensus has been established on the usefulness of FDG-PET in predicting survival outcomes.

This study was designed to clarify the role of FDG-PET as a prognostic tool for patients with rectal cancer treated with preoperative RT.

PATIENTS AND METHODS

Study Design

From July 1995 to March 2002, the authors prospectively enrolled 59 patients with primary rectal cancer deemed eligible for preoperative RT, on the basis of a clinically bulky or tethered tumor or on imaging-based evidence of T3–4 or N1 disease by use of transrectal ultrasound. The distance from the anal edge of the tumor to the anal verge was <3 cm in 11 cases, 3 to 5 cm in 42 cases, and >5 cm in 6 cases. All patients received 50 Gy to the pelvis and were subjected to two series of FDG-PET: one before preoperative RT, and the other two to three weeks after the treatment (days after radiotherapy ranged from 11–50; mean, 17; median 16). Surgery was performed 20 to 77 (mean, 43.3; median, 41) days after the completion of preoperative RT and 3 to 63 (mean, 26.2; median, 25) days after the second FDG-PET study.

The study was a prospective trial and had institutional review board approval. Informed consent was obtained from all patients.

Treatments

For RT, a 6-MV x-ray accelerator delivered 50 Gy in 25 fractions, 5 fractions per week during five weeks. Two AP/PA opposed fields were used as a Japanese conventional radiation technique for pelvic tumors. The clinical target volume included the entire pelvic cavity, anal canal, primary tumor, mesorectal and presacral lymph nodes, nodes along the internal iliac artery, lumbar nodes up to the level of the lower border of the fifth lumbar vertebra, and nodes at the obturator foramen. No chemotherapy was added to the RT in a preoperative setting. All surgeries were performed by colorectal specialists. Abdominoperineal resection with permanent colostomy was performed mainly for low rectal cancers located <5 cm from the anal verge, and for other rectal cancers mainly intersphincteric resection with coloanal anastomosis, according to surgeons' judgment. When residual tumor cells were found in the surgical resection margin, postoperative adjuvant 5-fluorouracil–based chemotherapy was performed.

Positron Emission Tomography, Standardized Uptake Values

All patients received two series of FDG-PET: one before preoperative RT, and the other two to three weeks after the treatment (days after RT ranged from 11–50; mean days after RT, 17±7.6).[33] 18-fluorodeoxyglucose (18F) was synthesized using the Cypris Model 370 Cyclotron® (Sumitomo Heavy Industries, Shinagawa-ku, Tokyo, Japan), and FDG with an automated FDG synthesizer based on the method reported by Harms and Starling[11] radiochemical purity was >95 percent. The physical characteristics of this machine have been described in detail in a previous study.[31] Patients fasted for at least 4–1/2 hours before PET scanning so that serum glucose levels were between 80 and 110 mg/ml. All studies were performed using a Headtome IV dedicated PET scanner® (Shimadzu Corporation, Kyoto-city, Kyoto, Japan) with seven imaging planes at 13-mm intervals, each 10-mm thick. The inplane resolution was 4.5-mm full width at half maximum (FWHM). The axial resolution was 9.5-mm FWHM and the sensitivities were 14 and 24 kcps/(micro Ci/ml), respectively, for direct and cross planes. Each transmission scan was performed for eight minutes. For injections, 333 to 444 MBq of FDG were introduced via the cubital vein. A series of static acquisitions for 6 minutes each were initiated 60 minutes after the injection, and the mean time for the main tumor lesion was fixed at a constant setting of 63 minutes.

PET Data Analysis

Cross-sectional sinogram data were corrected for dead time, decay, random coincidences, and attenuation. Image reconstruction was performed by using a filtered back-projection algorithm with a Hanning filter using a cutoff frequency of 0.3 and a 128×128 matrix. Several regions of interest (ROIs) were drawn manually on the hot spots of tumors. To minimize the partial volume effect associated with decreasing tumor sizes resulting from radiotherapy, the ROIs were set to have a number of pixels between 40 and 99. FDG accumulation was measured by using standardized uptake values (SUV) obtained by the following equation:

$$\text{SUV} = (\text{decay corrected PET value})/[(\text{injected dose})/(\text{body weight})].$$[33,34]

We defined SUVs in FDG-PET before preoperative RT as SUV_1 and two to three weeks after the treatment as SUV_2.

Pathologic Analysis

Analysis of the surgical specimen included a determination of the following parameters: 1) histologic type of the tumor; 2) degree of extension of the tumor through the rectal wall; 3) nodal involvement; and 4) status of proximal and distal margins. Pathologic response criteria were

Table 1. Univariate analysis

Factor	N	Relative risk	95% confidence interval	P value
Residual tumor				
+	8	1		
−	51	0.147	0.056–0.384	<0.0001
Differentiation				
Well	41	1		0.0011
Moderate	11	3.923	1.229–12.518	0.0210
Mucinous	4	6.14	1.57–24.012	0.0091
Poorly	2	23.093	4.09–130.371	0.0004
Unknown	1			
Recurrence				
+	31	1		
−	28	0.113	0.026–0.494	0.0038
Post-SUV	59	1.306	1.073–1.591	0.0079
SUV ratio				
>100%	4	1		
<100%	55	0.239	0.067–0.854	0.0276
LN				
+	30	1		
−	29	0.341	0.121–0.958	0.0411
Astler-Coller				
B1	10	0.21	0.027–1.63	0.1354
B2	18	0.315	0.088–1.132	0.0767
C1	4	1.123	0.247–5.097	0.8808
C2	26	1		0.1643
SUV ratio	59	1.014	0.994–1.033	0.1648
Pre-SUV	59	1.088	0.962–1.232	0.1788
Pathologic effect				
Grade 0	2	0.235	0.014–4.059	0.3193
Grade 1	44	0.102	0.012–0.868	0.0366
Grade 2	12	0.121	0.012–1.182	0.0693
Grade 3	1	1		0.1877
Sex				
Male	37	1		
Female	22	0.603	0.215–1.692	0.3363
Age (yr)	59	0.986	0.941–1.032	0.5392

SUV = standardized uptake values, LN = lymph node metastases.

defined as proposed by the Japanese Society for Esophageal Disease: Grade 0, no treatment effect; Grade 1, more than one-third viable tumor cells; Grade 2, less than one-third viable tumor cells; and Grade 3, no viable tumor cells.[35]

Statistical Analysis

Statistical analyses were performed by using StatView Dataset File version 5.0 J for Windows computers. Survival periods were calculated from the start of irradiation. The survival functions were estimated with the Kaplan-Meier method estimator, and log-rank tests were used to compare the survival distributions. Both univariate and multivariate analyses for survival were performed.

RESULTS

Pathologic effect and SUV ratio (SUV_2/SUV_1) were related statistically ($P=0.047$). Pathologic effect, however, showed no significant correlation with recurrence and survival. Histologic tumor type and SUV ratio were correlated and the ratio was >100 percent when the tumor type was poorly differentiated adenocarcinoma. Although recurrence rate tended to be higher with an elevated value of SUV_2, there was no significant association between them.

SUV ratio showed a tendency to be related with recurrence, and recurrence rate was of marginally higher significance when SUV ratio was >100 percent. Survival period was significantly short when SUV ratio was >100 percent ($P=0.0121$) and/or when SUV_2 was >5 ($P=0.0378$).

In univariate analysis, residual tumor, pathologic differentiation, recurrence, SUV_2 value, and lymph node metastasis were significant prognostic factors (Table 1). In multivariate analysis, no residual tumor and SUV_2 were significant prognostic factors for survival (Table 2). The survival curves comparing patients with *vs.* without residual tumor are shown in Fig. 1. Notably, when SUV_2 value was >5, overall survival was significantly poorer (Fig. 2). The median survival time and five-year overall survival rate comparing <5 *vs.* >5 SUV_2 value was 95.4 *vs.* 41.9 months and 70.4 *vs.* 43.6 percent, respectively ($P=0.042$).

DISCUSSION

SUV before RT and Prognosis

In this study, recurrence or poor prognosis was not related to high SUV before RT, which is in agreement with previously published reports. For head and neck cancers, Greven *et al.*[36] claimed that SUV before RT did not have any correlation with local control when examined for the entire group, primary site, or T stage (n=45). Others, however, have reported studies that differed from our results. Both Allal *et al.*[37] and Rege *et al.*[38] concluded that FDG uptake followed by RT, as measured by the SUV, had potential value in predicting local control and survival in head and neck carcinomas (n=63 and n=12, respectively).

SUV after RT and Prognosis

Recurrence or poor prognosis was related to high SUV after RT in our study. This result also concurs with earlier

Table 2. Multivariate analysis

Factor	Relative risk	95% confidence interval	P value
Residual tumor	0.302	0.094–0.973	0.0449
Differentiation			
Well			0.1552
Moderate	2.774	0.734–10.482	0.1326
Mucinous	2.875	0.574–14.406	0.1990
Poorly	10.486	0.988–111.283	0.0511
Recurrence	0.155	0.019–1.297	0.0854
Post-SUV	1.502	1.128–2	0.0054
SUV ratio <100%	0.675	0.107–4.268	0.6759
LN	0.362	0.080–1.637	0.1867

SUV = standardized uptake values; LN = lymph node metastases.

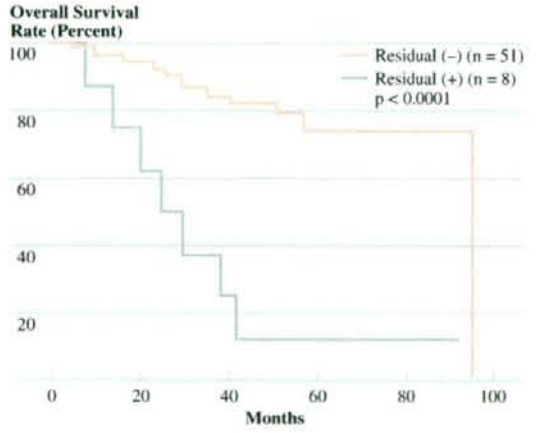


FIGURE 1. Overall survival curves comparing patients with *vs.* without residual tumor.

reports.[39,40] Higher SUV after preoperative RT predicts poor prognosis. Kunkel *et al.*[39] concluded that postirradiation FDG-uptake significantly predicted survival ($P=0.046$) and local tumor control ($P=0.0017$) in advanced oral squamous-cell carcinoma (n=35). Brun *et al.*[40] concluded that when a high initial tumor SUV was found, the reduction of SUV in the second PET examination might predict local tumor response in head and neck cancer (n=17). Swisher *et al.*[41] concluded that FDG-PET was predictive of survival in patients with esophageal carcinoma who had received preoperative chemoradiation ($P=0.01$; n=83). In our previous report,[32] only SUV_2 correlated with recurrence, although no significant correlation was observed in this study. It might be explained by the increased number of the patients involved to the study.

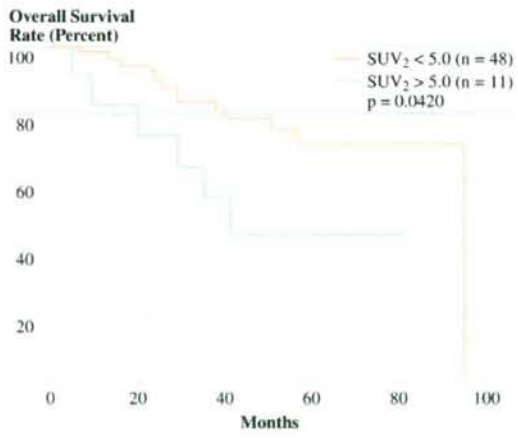
SUV before or after RT and Histologic Effects

SUV before or after RT was marginally correlated with histological effects. This finding is in agreement with previous reports. Kunkel *et al.*[42] reported a significant correlation ($P=0.045$) between post-RT FDG-uptake and histologic tumor regression was observed for mouth carcinoma (n=30). In their report, SUV>2.75 as a practical clinical threshold value for the identification of residual tumor resulted in a specificity of 88 percent, sensitivity of 68 percent, a positive predictive value of 94 percent, and a negative predictive value of 50 percent (in their report]).[41,42] In our actual follow-up data, a significant correlation could not be confirmed between post-RT SUV and patients' survivals. Brücher *et al.*[43] claimed an association for histology and survival in esophageal squamous-cell carcinoma (n=24). In responders, FDG uptake decreased by 72±11 percent; in nonresponders, it decreased by only 42±22 percent. Nonresponders to PET scanning (n=11) had a significantly poorer survival after resection than responders. Flamen *et al.*[44] also reported a correlation with histology and survival in locally advanced esophageal cancer (n=36). Response to chemoradiation as assessed by serial FDG-PET was strongly correlated with pathologic response ($P=0.002$) and survival ($P=0.087$).[44] In our study, SUV value after preoperative RT (SUV2) was significant in overall survival. In addition, the SUV ratio (SUV2/SUV1) showed an association with histopathologic effects and recurrence. These values are only available after the completion of preoperative radiation. In this respect, they may influence the surgical approach and postoperative adjuvant therapy. For example, if SUV1 was a prognostic marker, decisions could be made regarding preoperative treatment. SUV1 can control the entire treatment strategy, whereas SUV2 defines the surgical procedure and postoperative adjuvant therapy.

FDG-PET for Prediction of Survival in Rectal Cancer

The important implication of this study is that FDG-PET may be useful in assessing cytotoxic or ablative therapy. de Geus-Oei *et al.*[45] reported that a significant benefit ($P=0.017$) was observed in patients with low FDG uptake (SUV<4.26) with metastases of rectal cancer (of 152 patients, 67 were treated with resection of metastases and 85 with chemotherapy). A recent study from the Memorial Sloan-Kettering Cancer Center reported on monitoring the response to therapy with FDG-PET and the biologic basis of the change in FDG uptake of tumors in patients treated with neoadjuvant chemotherapy for hepatic colorectal metastases (13/42 evaluated patients underwent preoperative chemotherapy).[46] Fernandez *et al.*[47] concluded that post-resection screening by FDG-PET was associated with excellent five-year overall survival for patients undergoing resection of hepatic metastases from colorectal cancer (19 studies; 6,070 patients). Guillem *et al.*[48] from Memorial

FIGURE 2. Overall survival according to standardized uptake values-2 (SUV_2).



Sloan-Kettering Cancer Center suggested that FDG-PET might be useful in assessing the response of primary rectal cancer to chemoradiotherapy (n=15).

Denecke *et al.*[49] compared CT, MRI, and FDG-PET in the prediction of outcome of neoadjuvant radiochemotherapy in 23 patients with locally advanced primary T3/4 rectal cancer. The mean SUV reduction in responders (60±14 percent) was significantly higher than in nonresponders (37±31 percent; $P=0.03$). The sensitivity and specificity of FDG-PET in identifying response was 100 percent (CT 54 percent, MRI 71 percent) and 60 percent (CT 80 percent, MRT 67 percent). Positive and negative predictive values were 77 percent (CT 78 percent, MRI 83 percent) and 100 percent (CT 57 percent, MRI 50 percent) (PET $P=0.002$, CT $P=0.197$, MRI $P=0.5$). Additionally, Kalff *et al.*[50] evaluated the prognostic information obtained from the degree of change in tumor FDG-PET uptake induced by chemoradiation before radical curative surgery in 34 patients with T3/T4 rectal cancer. PET response was highly significantly associated with overall survival duration ($P<0.0001$) and time to progression ($P<0.0001$). Complete pathologic response was the only other statistically significant prognostic factor ($P<0.03$). The percentage of maximum SUV change after chemoradiation was not predictive of survival in partial metabolic response patients. Guillem *et al.*[31] tried to determine the prognostic significance of FDG-PET assessment of rectal cancer response to preoperative chemoradiation. The mean percentage decrease in SUV_{max} (ΔSUV_{max}) was 69 percent for patients free from recurrence and 37 percent for patients with recurrence ($P=0.004$). $\Delta SUV_{max} \geq 62.5$ was the best predictors of no-evidence-of-disease status and freedom from recurrence. Patients with $\Delta SUV_{max} \geq 62.5$ had significantly improved disease-specific and recurrence-free survival ($P=0.08$ and $P=0.03$, respectively).

The continued accumulation of clinical data on SUV for preoperative RT will contribute to establishing its usefulness. Studies in other malignancies, such as maxillary sinus carcinoma, are under consideration, for which preoperative RT is frequently performed.

CONCLUSION

A significant survival benefit was observed in patients with low FDG uptake (SUV<5) after preoperative radiotherapy in primary tumors of rectal cancer.

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MALT lymphoma

Radiotherapy for 41 patients with stages I and II MALT lymphoma: A retrospective study☆

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Abstract

Purpose: Mucosa-associated lymphoid tissue (MALT) lymphoma is a distinct disease with specific clinical and pathologic features that may affect diverse organs. We analyzed our recent experience with Stage I/II MALT lymphoma presenting in the stomach and other organs to assess the outcome following radiation therapy (RT) alone.

Patients and methods: Forty-one patients with Stages I (37) and II (4) disease were treated between 2000 and 2006. Patients with transformed MALT were excluded. The median age was 60 years (range, 25–86 years), male: female ratio 1:1. Presenting sites included stomach, 11; orbital adnexa, 21; thyroid, 1; other head and neck, 3; small bowel, 3; skin, 1; and rectum, 1. Thirty-five patients (85%) received RT-alone and 6 (15%) received antibiotics followed by RT. RT dose was 30 Gy in 20 fractions (fr) in all 41 patients. Mean follow-up time was 32.0 months (range, 2.1–162 months).

Results: A first complete response was achieved in all 41 patients. Only one patient died from bile duct carcinoma at 22 months from the start of irradiation for conjunctiva MALT lymphoma without recurrence of lymphoma. The other 40 patients were alive. Thirty-eight patients out of them were alive without recurrence. One patient with a duodenal lymphoma had a recurrence in non-irradiated distant sites at 1 month. Another patient with a bilateral eye lid lymphoma had a recurrence within radiation field at 41 months. The absolute local control rate with radiation was 98% (40/41 patients).

Conclusion: Localized MALT lymphomas have excellent prognosis following moderate-dose RT (30 Gy/20 fr).
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Keywords: Non-Hodgkin's lymphoma; MALT; Treatment; Radiation therapy

Mucosa-associated lymphoid tissue (MALT) type lymphoma is now incorporated into the Revised European–American Lymphoma (REAL) and the World Health Organization (WHO) classification systems [1,2] as extranodal marginal zone B-cell lymphoma, MALT type. It accounts for 4–13% of patients seen in individual cancer centers [3,4]. A recent nationwide study of malignant lymphoma among Japanese reported that it accounts for about 8% of all malignant lymphomas in Japan [5]. Although much knowledge has been gained in defining the clinical features, natural history, pathology, and molecular genetics of the disease in the last decade, the optimal treatment approach for MALT lymphomas is still evolving. The discovery of an association between *Helicobacter pylori* (*H. pylori*) infection and gastric MALT lymphoma, and tumor response with eradication of *H. pylori* [6–10], led to the novel concept that MALT lymphoma can be cured with removal of the underlying antigenic stimulus, the *H. pylori* infection. Predisposing conditions to MALT lymphoma are well recognized: Hashimoto's thyroiditis for thyroid MALT lymphoma [11] and Sjögren's syndrome for salivary gland MALT lymphoma [12].

Because 60–70% of patients with MALT lymphomas present with localized (Stage I or II) disease [3,13,14], and because there is a tendency for the disease to remain localized for a long time, local treatment, such as radiotherapy (RT), is often indicated. Previous retrospective studies demonstrated excellent local control rates and progression-free survival (PFS) after RT [15–30]. RT for orbital MALT lymphomas usually leads to late adverse events such as retinopathy, cataracts, or a dry eye [15–24]. Furthermore, there have been few published prospective trials evaluating the appropriate dose and field of RT for MALT lymphoma, except for patients with localized gastric disease [29]. Japan Radiation Oncology Group (JAROG) conducted a multicenter phase II study to evaluate moderate-dose (30.6–39.6 Gy) of RT between 2002 and 2004, depending upon the primary site and tumor bulk [31]. They concluded that moderate-dose RT was highly effective in achieving local control with acceptable morbidity in 37 patients with MALT lymphoma.

☆ Clinical investigation lymphoma

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Over the last decade and a half, works on multiple MALT lymphoma treated with RT series were published, and many of these words were specific to the organ that was treated. The radiosensitivity of MALT to radiation is also well established and the dose of 30 Gy to the stomach and even lower doses to orbital MALT lymphoma are standard of care. However, to date there are few well-documented reports of the efficacy of RT in this disease. We report the analysis of our experience of 30 Gy/20 fr involved-field RT for Stages I and II MALT lymphomas, emphasizing the excellent local control with radiation.

Methods and materials

This is a retrospective study. Forty-one consecutive patients with Stages I (37) and II (4) disease were treated between 2000 and 2006 in our institution. Patients with transformed MALT were excluded. Additionally, primary nodal marginal zone B-cell lymphoma, MALT type ($N = 2$) was also excluded. The median age was 60 years (range, 25–86 years) and male/female ratio was 1/1. Presenting sites included stomach, 11; orbital adnexa, 21; thyroid, 1; other head and neck, 3; small bowel, 3; skin, 1; and rectum, 1 (Table 1). Staging included site-specific imaging, enhanced CT or MRI in 39 patients (95%), gallium-68 scintigraphy in 7 (17%), F-18 2-deoxy-fluoro-D-glucose (FDG) positron emission tomography (PET) in 20 (49%), and bone marrow biopsy in 39 (95%). The diagnosis was made on the basis of hematoxylin and eosin-stained biopsy specimens supported by immunohistochemical analysis. Immunologic phenotyping on paraffin section was done for κ and λ light chain restriction and $CD20^+$, $CD5^-$, $CD10^-$, and cyclin $D1^-$, which in the context of the microscopic appearance, is consistent with MALT lymphoma.

Table 1
Patient and tumor characteristics

	No.	%
Anatomic location		
Stomach	11	27
Orbital adnexa	21	51
Thyroid	1	2
Other head and neck	3	7
Small bowel	3	7
Skin	1	2
Rectum	1	2
Maximum diameter of tumor		
≧5 cm	20	49
<5 cm	21	51
Sex		
Male	21	51
Female	20	49
Age		
≧60	21	51
<60	20	49
Stage		
IE	34	83
IEE	3	7
IIE	4	10
K-PS		
≧90%	39	95
<90%	2	5

Radiation method

The clinical target volume (CTV) was defined as an entire affected organ for lymohoma of the stomach or gross tumor volume (GTV) with at least 20 mm of margin for lymohoma of the small bowell, thyroid, other head and neck, skin, and rectum. Prophylactic irradiation for lymph node was not performed. The CTV was defined as the entire bulbar and palpebral conjunctiva for the orbital lymphoma with lesions confined to the conjunctiva or eyelids. The CTV was the entire orbital cavity for the retrobulbar lymphoma. A lens shield was placed unless the block compromised tumor coverage. One example of radiation dose distribution for gastric MALT lymphoma was shown in Fig. 1. RT dose was 30 Gy in 20 fr in all 41 patients regardless of the size of primary tumor. In the gastric lymphoma patients, the liver and kidneys were evaluated as the organs at risk. Of the 21 patients with orbital MALT lymphoma, 14 patients were treated with a cylindrical lens shielding (approximately 6–12 mm thick, depending on the electron beam energy). Lens shielding was placed 1 cm above the cornea.

Systemic therapy

Helicobacter pylori status was determined by the rapid urease test (Helico Check, Otsuka Co., Tokushima, Japan), serological testing (HM-CAP kit, Enteric Product, Inc., NY, USA) and ^{13}C-urea breath test before and after *H. pylori* eradication therapy. Thirty-five patients (85%) received RT alone and 6 patients (15%) that were positive of *H. pylori* infection in gastric lymphoma received antibiotics followed by RT. When patients were refractory to antibiotics or their cases were not associated with *H. pylori*, they were candidates for RT for gastric MALT lymphoma. Accordingly, cases in which *H. pylori* were completely eradicated only by antibiotic treatment were not indicated for RT. The determination of a failed response to *H. pylori* eradication therapy has so far been made at 12 months after the therapy, and RT has been applied to patients who did not achieve complete remission at that time. Patients who had simultaneous bilateral lesions were classified with Stage IEE disease according to other investigators' criteria [32–36].

Quality of follow-up

After the completion of radiotherapy, patients were followed at regular intervals. Careful clinical and ophthalmologic examinations were performed every 1–3 months for the first 2 years, every 4–6 months through year 5, and annually thereafter. For the patients with gastrointestinal MALY lymphoma, endoscopic, CT scanning and histological evaluation were performed immediately after radiotherapy and every 3–6 months thereafter. For the patients with orbital MALT lymphoma, orbital CT scanning or magnetic resonance imaging was recommended at 1 year after

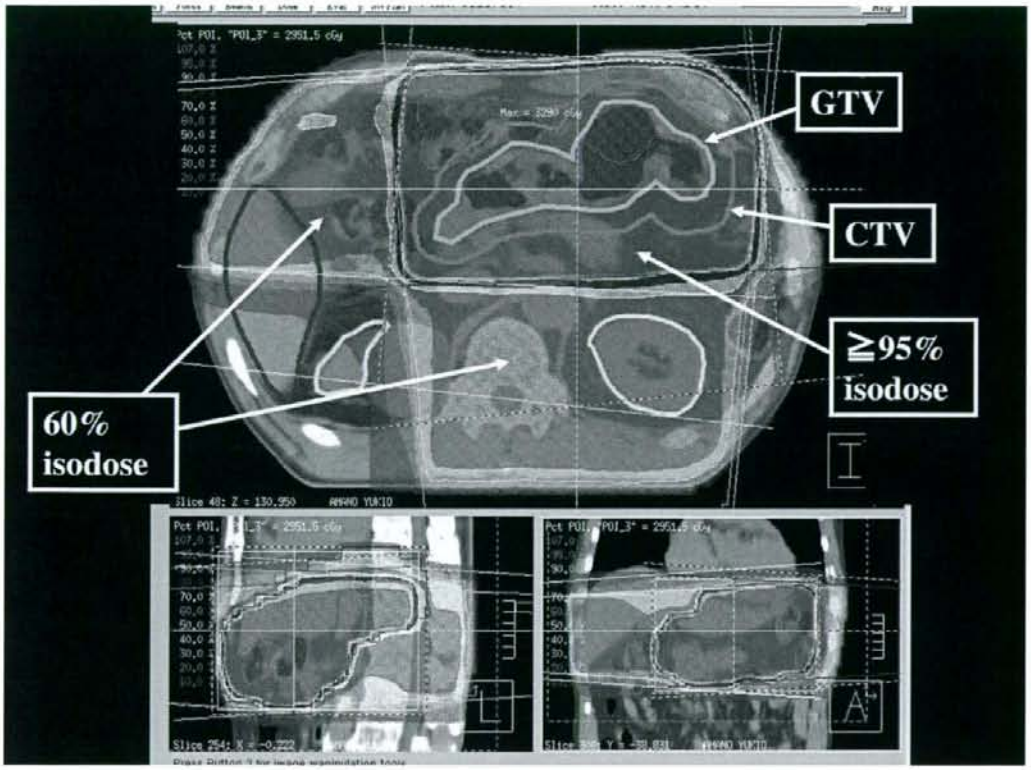

Fig. 1. Radiation dose distribution in the virtual simulation using a CT simulator of a gastric MALT lymphoma. The radiation portal consisted of a combination of the anterior–posterior direction and the lateral direction.

radiotherapy but was not required and other radiographic studies were performed as indicated clinically.

Statistical methods

The progression-free survival (PFS) was assessed using the method of Kaplan and Meier. Acute toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). Late effects were graded according to the Radiation Therapy Oncology/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.

Results

A first complete response was achieved in all 41 patients. Only one patient died from bile duct carcinoma at 22 months from the start of irradiation for conjunctiva MALT lymphoma without recurrence of lymphoma. The other 40 patients were alive. The 5-year overall survival rate was 96.7%. Thirty-eight patients out of them were alive without recurrence. The absolute local control rate with radiation was 98% (40/41 patients). Progression-free survival (PFS) curve of the 41 patients is shown in Fig. 2. The 5-year PFS rate for the entire group was 90.6%. Mean follow-up time was 3.3 years (range, 0.2–12.2 years).

The PFS took into account not only local relapses but also distant relapses. One relapse (the primary site: duodenum) was observed in non-irradiated distant sites at 1 month. The

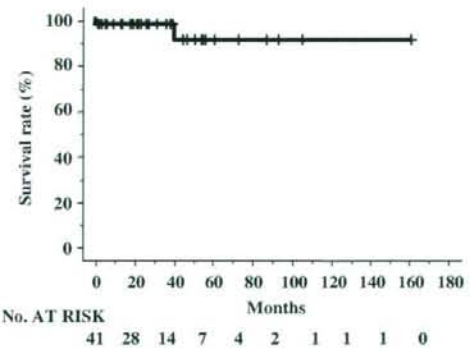

Fig. 2. Progression-free survival of the 41 patients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue.

patient with a duodenal lymphoma had a recurrence in the abdominal para-aortic lymph node showing transformation into diffuse large B-cell lymphoma. After the recurrence, the patient was given systemic chemotherapy consisting of 6 cycles of R-CHOP regimen. It involved the monoclonal antibody rituximab, and the drugs: cyclophosphamide, doxorubicin, vincristine and prednisolone. After the salvage therapy, no recurrence has been detected until now for 71 months.

Another relapse (originated from bilateral eye lid) was within electron irradiation field at 41 months. The relapse lesion in the left lower eyelid was resected completely. The pathology remained unchanged. After the resection, no recurrence has been detected till now for 53 months (Table 2).

Acute toxicity and late complications

Radiation-induced side effects were negligible in the majority of the patients. No life-threatening toxicity (≧grade 4) occurred. Although acute radiation-induced conjunctivitis developed in 5 patients, none of them had severe later complications. The incidence of any later complications is listed in Tables 3 and 4. Cataract did not develop in any of the 14 patients who were treated with lens shielding. We observed three Grade 3 cataracts during this study period at 36, 46, and 162 months after the completion of RT.

Discussion

Because MALT lymphoma has been considered to be less responsive to standard chemotherapy than other aggressive lymphomas, RT has been used as the first line local treatment. Only for limited-stage gastric MALT lymphoma linking to *H. pylori* infection, *H. pylori* eradication therapy today has become recognized as a first-line treatment [50]. RT has been applied to patients who did not achieve complete remission after *H. pylori* eradication therapy.

This report on the RT treatment of MALT lymphoma in a variety of sites with involved-field RT of 30 Gy shows good clinical results. We have demonstrated that the PFS was 90.6% at 5 years. Our findings demonstrated that RT-alone was highly effective in achieving local control for localized MALT lymphoma. These favorable outcomes after RT are consistent with previous retrospective studies, which administered various doses of RT with a median of 25–40.5 Gy [15–24,26–30]. Many researchers concluded that 30 Gy of RT could achieve excellent local control.

Although several groups treating solely MALT lymphoma mentioned that 25–30 Gy is enough to control the disease [26,28], we also suggest that 30 Gy in 20 fr was appropriate for controlling MALT lymphoma without severe detrimental effects. Shu et al. [51] reported that the 10-year actuarial relapse-free survival, cause-specific survival, and overall survival rates were 93.1%, 97.9%, and 86.9%, respectively, for 48 orbital MALT lymphomas by RT of median 30.6 Gy (range; 5.4–30.6 Gy). Le et al. [52] reported 100% of the local control and recommended using a radiation dose of 30–30.6 Gy in 1.5–1.8 Gy fr for localized orbital MALT lymphoma. Zhou et al. [53] also reported 100% of the local control rate for orbital indolent lymphoma and concluded that a dose of 30 Gy was sufficient.

Table 2
Treatment and outcome characteristics

	No.	%
Radiation dose		
30 Gy/20 fr	41	100
Outcome		
Dead	1	2
Alive with recurrence	2	5
Alive without disease	38	93
The site of recurrence		
Within radiation field	1	2
Outside radiation field	1	2
Modality		
Electron	19	46
Photon	22	54
Energy		
6 MV	16	41
10 MV	6	15
6 MeV	18	44
12 MeV	1	2

Table 3
Acute and late toxicities in 21 orbital adnexa MALT lymphoma

	No. of patients (%)		
	Grade 0	Grades 1–2	Grade 3
Acute toxicities			
Dermatitis	18 (86%)	3 (14%)	0
Conjunctivitis/Corneitis	16 (76%)	5 (24%)	0
Total	13 (62%)	8 (38%)	0
Late toxicities			
Eyesight decline	19 (90%)	2 (10%)	0
Conjunctivitis/Corneitis	13 (62%)	8 (38%)	0
Cataract	16 (76%)	2 (10%)	3 (14%)
Total	7 (34%)	11 (52%)	3 (14%)

Table 4
Acute and late toxicities in 15 gastrointestinal MALT lymphoma

	No. of patients (%)		
	Grade 0	Grades 1–2	Grade 3
Acute toxicities			
Dermatitis	14 (93%)	1 (7%)	0
Mucotitis	8 (53%)	7 (47%)	0
Total	7 (47%)	8 (53%)	0
Late toxicities			
Edema	14 (93%)	1 (7%)	0
Intestinal obstruction	13 (87%)	2 (13%)	0
Pancreatitis	14 (93%)	1 (7%)	0
Ulcer	14 (93%)	1 (7%)	0
Total	11 (73%)	4 (27%)	0

Several phase II studies demonstrated antitumor activity of the purine analogs fludarabine and cladribine [37,38]. Chemotherapy alone (such as alkylating agent) series reported the significantly higher recurrence rate and cannot be the standard therapy for local advanced gastric MALT lymphoma [39–41]. Other groups have also shown that the anti-CD20 monoclonal antibody rituximab was effective for MALT lymphoma [42,43]. These findings also will be further elucidated in large-scale clinical trials.

According to Hellenic Cooperative Oncology Group's study [46], their patients received various commonly used chemotherapy regimens. Anthracycline-based treatments or rituximab did not offer any survival advantages. As rituximab therapy was started only recently, the follow-up, however, may have been too short to reveal any benefit. Other retrospective studies also observed no difference in efficacy between specific regimens [44,45], and several prospective phase II trials reported similar results [41,42,47,48].

The most frequent sites in this study were the stomach, the orbital adnexa, the head and neck, and the small bowel. Despite the low number of patients in our study, this observation is in agreement with other studies reporting the salivary glands, the orbit, the lung, the intestine and the skin as the most common nongastric lymphoma sites [13,43–46].

The next problem that should be resolved is the optimal target volume for MALT lymphoma. There are only a few studies that clearly demonstrate the target volume in the literature [16,21–23,25,27–29,31]. For gastric MALT lymphomas, the entire stomach and perigastric nodes are considered to be the target volume [28,29]. Olivier et al. [22] also delivered RT to the affected parotid gland with or without the first-echelon node for parotid lymphoma. On the one hand, Pfeffer et al. [49] showed that 4 of 12 patients with orbital lymphoma who received partial orbital irradiation experienced recurrence. Thus it seems reasonable that the target volume for MALT lymphoma should include the entire affected organ.

Conclusion

In conclusion, the results from this retrospective study confirm that RT was highly effective in achieving local control for localized MALT lymphoma, and 30 Gy in 20 fr was appropriate for controlling MALT lymphoma without severe detrimental effects.

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Three-dimensional Conformal Radiotherapy for Hepatocellular Carcinoma with Inferior Vena Cava Invasion

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Background: Hepatocellular carcinoma with inferior vena cava invasion is a rare but fatal condition of disease progression. The aim of this study was to analyze the results of treatment for hepatocellular carcinoma with inferior vena cava invasion by three-dimensional conformal radiation therapy.

Methods: From 1990 to 2006, 18 histopathologically confirmed hepatocellular carcinoma patients with inferior vena cava invasion who were unsuitable for surgery were treated by three-dimensional conformal radiation therapy at our hospital with two to four static or dynamic conformal arc fields.

Results: A median total tumor dose of 50 Gy (range 30–60 Gy) was delivered. The progression-free rate was 91.6% among the patients in whom follow-up computed tomography was obtained. Actuarial survival at 1 year was 33.3%, and the median survival period was 5.6 months.

Conclusions: Three-dimensional conformal radiation therapy might offer a chance of long survival for a part of the hepatocellular carcinoma patients with inferior vena cava invasion, since a third of such patients survived more than a year. Additional treatments should be considered to prevent distant metastases and hepatic functional deterioration after three-dimensional conformal radiation therapy.

Key words: hepatocellular carcinoma – inferior vena cava – three-dimensional conformal radiation therapy – hepatic functional reserve – liver cirrhosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the eighth major cause of cancer death in the United States and the third in Japan (1,2). Local ablative therapies such as hepatectomy, radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI) should be administered, if possible, to patients with limited extension of HCC. But when the tumor invades the inferior vena cava (IVC), these treatments are indicated only for very few patients. In some reports, a part of these patients can survive long by hepatic resection combined with IVC resection (3–5). But such aggressive surgeries are not suitable for most patients, and other treatment modalities are also restricted not only by poor hepatic function, but also frequently by extensive disease progression. Transcatheter arterial chemoembolization (TACE) is often tried in HCC patients with IVC invasion for whom ablative treatment is unsuitable. However, TACE rarely achieves local tumor control to prolong survival periods sufficiently in such a critical condition, although the efficacy of this treatment has been proven in meta-analyses (6,7).

A few decades ago, liver was assumed to be a highly radiosensitive organ that was unsuitable for high-dose radiotherapy. But recent progress in radiation oncology has enabled us to concentrate high-dose radiation on liver tumors while preserving hepatic function after treatment (8–15). In addition, some institutions apply stereotactic radiotherapy to solitary small liver tumors. Consequently, radiotherapy has come to play an important role in multidisciplinary treatment of HCC.

At our institution, three-dimensional conformal radiation therapy (3D-CRT) has been the primary treatment strategy for HCC with portal vein invasion, and has achieved good clinical results (9). As with the treatment of HCC patients

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with portal vein invasion, radiotherapy is considered for HCC patients with IVC invasion at our institution if they are unsuitable for surgery. But there are few reports on radiotherapy for such patients (16), and the natural course of such conditions is not well known. In the present study, we retrospectively reviewed the medical records of HCC patients with IVC invasion and analyzed the efficacy of radiotherapy in these patients.

METHODS

From 1990 to 2006, 18 HCC patients with IVC invasion were treated by radiotherapy at our hospital. Their clinical courses and treatment results were retrospectively reviewed. HCC was diagnosed by using ultrasonography, computed tomography (CT), angiography and liver biopsy. In each patient, the diagnosis was confirmed histopathologically. IVC invasion was defined by a low-attenuation mass that protruded into the intraluminal space of IVC on enhanced CT and/or detection of pulsatile flow in IVC thrombi by Doppler ultrasonography. The patients' characteristics are shown in Table 1.

Patients with liver cirrhosis of Child–Pugh class C were not indicated for the treatment. CT-based radiotherapy treatment planning was made for all patients by the following treatment planning systems, RPS700U(3D) (Mitsubishi Electric Co., Tokyo, Japan) or Pinnacle[3] (Philips/ADAC, Milpitas, CA, USA). Clinical target volume was contoured on serial CT images with a 0.5–1-cm margin around the gross tumor volume, covering IVC-protruding tumor as well as the primary tumor invading to the IVC. Other co-existing intrahepatic tumors which had no continuity to the IVC-invading tumor were not included in the clinical target volume, and managed by other treatment modalities. Planning target volume was determined by a 0.5–2.0-cm margin around the clinical target volume. A dynamic conformal arc or two to four static ports were used for irradiation. In earlier periods, dynamic conformal arc therapy or multiport (mainly four ports) treatment plans were used, and we could not obtain dose-volume histograms in the treatment-planning machine. In recent years, treatment plans using two opposed fields have been preferred, because such treatment enables the maximization of the non-irradiated volume of the normal liver tissue. This treatment planning strategy is based on the fact that the normal liver tissue tolerance is lower in patients with viral hepatitis and liver cirrhosis than

Table 1. Patient characteristics

Case no.	Age and sex	Previous treatment				Etiology	Child–Pugh class	Pre-treatment AFP (ng/mL)[1]	Pre-treatment PIVKAII (mAu/mL)[2]
		Surgery	TACE	PEI	RFA				
1	48M	Information not available				HBV	A	38	1
2	67M	Information not available				HBV	B	60	8
3	63M	○		○		Unknown	A	9	N/A
4	67M			○		HCV	A	2385	125
5	80F	Information not available				HCV	A	3	1134
6	58M		○			Alcohol	B	9	26622
7	45M	○	○			HBV	B	136260	10784
8	71M		○		○	HCV	B	4	3242
9	74M		○			HCV	B	10	88
10	70M		○			HCV	B	13	7207
11	61M		○			HCV	B	21	3639
12	72M	○	○	○	○	HCV	A	6175	28
13	70M		○			HCV	B	126	39
14	76M		○			HCV	B	20	3572
15	71M	○	○			HCV	A	11	538
16	74M		○	○	○	HCV	A	38	681
17	69F		○		○	HCV	B	8	1119
18	81M	○	○	○	○	HCV	A	1	12008

Open circles indicate that the patient has received the specific treatment(s). M, male; F, female; TACE, transcatheter arterial chemoembolization; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; HBV, hepatitis B virus; HCV, hepatitis C virus; N/A, not available; PIVKAII, protein induced by Vitamin K absence-II.
[1]Normal range of serum concentration of AFP is <9 ng/mL.
[2]Normal range of serum concentration of PIVKAII is <40 mAu/mL.

in healthy patients (8). The general principle of treatment planning was to keep V_{30}, which was defined as the percent volume of the liver exceeding 30 Gy, lower than 30% of the whole liver volume minus tumor volume. We aimed for a total tumor dose of 50–60 Gy in conventional fractionation, but allowed smaller doses according to the dose-volume histogram of the normal liver at the physician's discretion. X-rays were delivered by linear accelerators ML15-MDX (Mitsubishi Electric Co., Tokyo, Japan) or CRS-6000 (Mitsubishi Electric Co., Tokyo, Japan). Written informed consent was obtained from the patients before treatment.

Follow-up and survival periods were calculated from the first day of radiation therapy. Actuarial survival rates were calculated by the Kaplan–Meier method. The statistical significance between groups was assessed with the log-rank test. Differences were considered statistically significant when $P < 0.05$.

RESULTS

All patients tolerated the treatment well. No severe complications were observed during the treatment period. The total tumor dose ranged from 30 to 60 Gy, with a median dose of 50 Gy (Table 2). All patients were followed until death except for the three patients who were alive at the time of analysis. Other treatment variables and results are summarized in Table 2.

Treatment response was defined as the tumor status at the last follow-up CT (Table 2). The response rate (complete response + partial response) and progression-free rate (complete response + partial response + stable disease) were 33.3% (95% confidential interval: 6.7–60.0%) and 91.6% (95% confidential interval: 75.9–100%), respectively, among the 12 patients for whom follow-up CTs were obtained. Only one patient developed local progression of the IVC-invading tumor within 6 months after 3D-CRT, and this was determined to be a progressive disease. This patient started systemic chemotherapy with 5-fluorouracil and interferon after diagnosis of a progressive disease, and was alive at the time of this analysis with no further progression of the tumor after introduction of this chemotherapy, 26.2 months after treatment. In the remaining 11 patients, no tumor regrowth was observed within the irradiated volume at the last follow-up.

At the time of the last follow-up, three patients were alive and the others were dead. Actuarial survival rate was 33.3% at 1 year, with a median survival period of 5.6 months (Fig. 1). The causes of death are shown in Table 2. The Child–Pugh class A group tended to survive longer than the class B group, but the difference did not reach statistical significance level (7.8 months versus 3.3 months, $P = 0.136$, Fig. 2 and Table 3). The survival period did not differ between responders (complete response + partial response) and non-responders (stable disease + progressive disease) (Fig. 3 and Table 3). Older patients (70 years or older) and

Table 2. Treatment-related variables and results

Case no.	Total dose (Gy)	Equivalent dose (Gy)[1]	Irradiation technique	Treatment response	Follow-up period (months)	Cause of death
1	48	52	Opposed two fields	N/A	5.6	Unknown
2	48	52	Dynamic conformal	N/A	3.0	Unknown
3	30	37.5	Dynamic conformal	N/A	7.2	Unknown
4	42	42	Dynamic conformal	N/A	1.3	Pulmonary metastasis
5	60	60	Dynamic conformal	CR	7.8	Non-tumoral Liver failure
6	50	50	Dynamic conformal	N/A	3.7	Rupture of esophageal varix
7	50	50	Four fields	SD	3.3	Tumor-related Liver failure
8	46	46	Four fields	SD	2.6	Non-tumoral Liver failure
9	50	50	Four fields	PR	7.2	Pulmonary metastasis
10	50	50	Dynamic conformal	PR	16.3	Non-tumoral Liver failure
11	40	40	Four fields	SD	1.8	Pulmonary metastasis
12	50	50	Dynamic conformal	CR	13.7	Tumor-related Liver failure
13	52	52	Four fields	N/A	1.6	Pulmonary embolization
14	46	46	Opposed two fields	SD	4.7	Tumor-related Liver failure
15	50	50	Four fields	SD	14.5	Brain metastasis
16	50	50	Non-coplanar	PD	26.2	(Alive)
17	40	40	Opposed two fields	SD	12.6	(Alive)
18	50	50	Opposed two fields	SD	10.2	(Alive)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
[1]Equivalent dose in conventional fractionation of 2.0 Gy per fraction was calculated based on a linear quadratic model assuming $\alpha/\beta = 10$ (32).

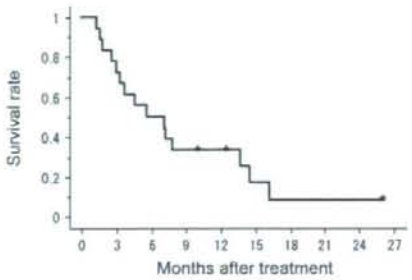

Figure 1. Overall survival of the whole group of 18 patients.

patients with hepatitis C virus tended to survive longer than the other patients, but the differences were also not statistically significant (Fig. 4). The median survival periods were 7.8 and 3.3 months for the groups 70 years or older and under 70 years, respectively ($P = 0.064$). The median survival periods of the patients with HCV carriers and other etiologies were 7.8 and 3.7 months, respectively ($P = 0.111$). A representative case is shown in Fig. 5.

Table 3. Univariate analysis of potential prognostic factors

Factor	*n*	Median survival (months)	*P* value
Etiology			
HCV	13	7.8	0.111
Others	5	3.7	
Treatment response			
Responders	4	7.8	0.894
Non-responders	8	4.6	
Age at treatment			
≥ 70	10	7.8	0.064
< 70	8	3.3	
Child–Pugh class			
A	8	7.8	0.136
B	10	3.3	
Pre-treatment AFP			
≤ 20 ng/mL	10	7.2	0.305
> 20 ng/mL	8	3.0	
Pre-treatment PIVKA II			
≤ 1000 mAu/mL	9	5.6	0.987
> 1000 mAu/mL	9	4.7	

DISCUSSION

HCC with IVC invasion is difficult to treat and associated with poor prognosis, because of its inherent nature of serious condition of the disease and the limited availability of treatment strategies. We have treated such patients by 3D-CRT, and here reviewed their treatment results retrospectively.

The literature offers no detailed data on the natural history of HCC with IVC invasion. But vascular invasion from HCC has been associated with miserable prognoses (16–18) and a limited life expectancy of 2–3 months, if untreated. However, Mizumoto et al. (19) reported good clinical results of proton beam therapy in patients with HCC invading to the IVC. All three of the patients they treated lived more than a year after this therapy.

The prognosis of patients with HCC is known to be dependent on the hepatic functional reserve (20,21). Our results are consistent with this knowledge, because the median survival of Child–Pugh class A patients was slightly longer than that of class B patients (Fig. 2). On the other hand, treatment response did not influence patients' survival periods (Fig. 3). But the treatment response after radiotherapy is predictive of survival in the curative treatment settings in many primary cancer sites (22–24). There are three possible explanations for this: (i) a relatively long period (typically several months) is required for tumor shrinkage after radiotherapy, considering the median survival periods of these patients; (ii) fatal deterioration of hepatic function can be seen, owing to the damage to normal liver tissue as a result of radiotherapy; (iii) it is sometimes difficult to distinguish the tumor thrombus from blood clots adhering to the IVC-invading tumor on follow-up CT images; and (iv) the group in this analysis was too small for statistical differences. Older age was a marginally significant prognostic factor in our results (Fig. 4). Age as a prognostic factor,

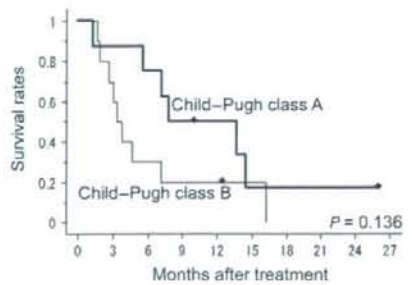

Figure 2. Overall survival by pre-treatment hepatic functional reserve.

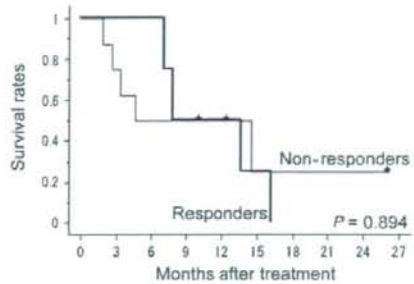

Figure 3. Overall survival by treatment response.

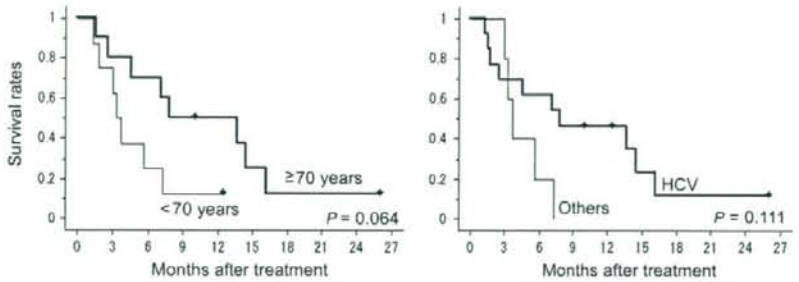

Figure 4. Overall survival by age (left panel) or etiology (right panel).

however, is controversial in the literature, because older age might sometimes be a favorable prognostic factor in some conditions but an unfavorable one in others (25–27).

In our experience, six patients died of liver failure. Of these six, three were assumed to be owing to the intrahepatic tumor growth from their clinical courses, and the other three were brought by undetermined causes. We could not differentiate the natural course of cirrhosis from treatment-related liver failure exactly. In this respect, we could not exclude the possibility of the treatment-related morbidities in Cases 5, 8 and 10 in Tables 1 and 2 with liver failures, although there had been no case with clinically apparent radiation-induced liver disease (RILD). In addition, there is no denying that the rupture of esophageal varix and the pulmonary embolization have occurred irrelevant to 3D-CRT or other treatments in Cases 6 and 13. But after 3D-CRT, 33.3% of our patients survived more than a year. In this respect, our 3D-CRT appeared to offer a chance to survive more than a year for a third of the patients with such critical conditions, although the median survival period was not satisfactory. The reason for such unsatisfactory results included the high incidence of deaths due to metastatic disease or liver failure despite the good progression-free rate of 91.6% for the irradiated IVC-invading tumor.

To minimize the probability of radiotherapy-related liver failure, treatment strategies have been improved (28,29). Despite these efforts, RILD can sometimes occur typically 2 weeks to 4 months after hepatic irradiation, and the threshold for RILD is reported to be 31 Gy of mean liver dose (29). Moreover, 50–76% of the patients who developed RILD died of this complication (30,31). Considering these situations, 3D-CRT has a potential benefit over the conventional two-dimensional radiotherapy in the viewpoint of normal liver protection. This point, however, has not been demonstrated in the previous literature to the best of our knowledge.

Some institutions adopt stereotactic body radiotherapy by multi-port irradiation technique. But the volume of low-dose-irradiated normal liver tissue is increased by the multi-port irradiation, especially when the clinical target volume is large. Radiation tolerance of the non-cancerous liver with chronic viral hepatitis or cirrhosis is known to be lower than that of healthy liver (29). We have a hypothesis that two opposed fields radiotherapy might be more protective than multiple-port radiotherapy for the cirrhotic liver. This is why we changed the 3D-CRT strategy from multiple-port irradiation to two opposed fields irradiation. We are now under investigation of the effect of treatment strategy on the survival or on the risk of RILD.

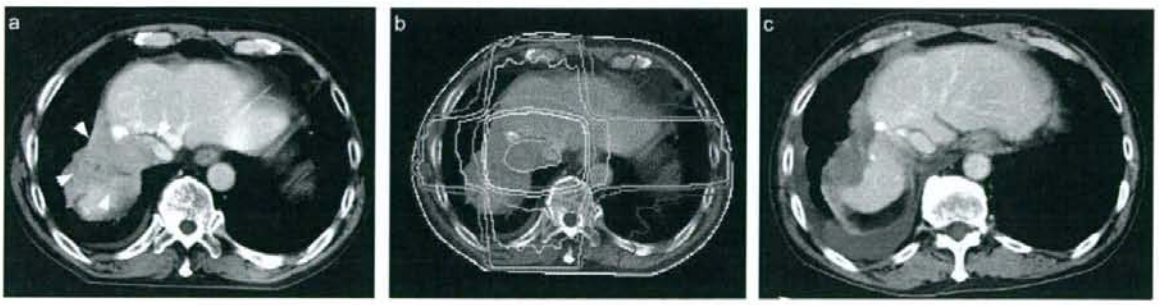

Figure 5. A representative case of a 72-year-old male with Child–Pugh class A hepatic function (case 12 in the Tables 1 and 2). (a) Before radiotherapy, the tumor located in S7 extended to IVC and the intraluminal space was narrow in the CT images. The tumor was indicated by the red arrowhead. (b) Dose distribution of the treatment plan. A total tumor dose of 50 Gy was delivered in 25 fractions by a dynamic conformal arc with four static fields. (c) Three months after radiotherapy. S7 tumor disappeared and no enhancement defect was observed within IVC, and the treatment response was judged as a complete response. The patient died of hepatic failure 13.7 months after irradiation. The irradiated tumor had no sign of regrowth at the time of death. (A colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.)

Follow-up CT could not be obtained for six patients. This might be attributable in part to early deterioration in performance status, since all six died within 8 months after treatment. It is possible that disease control was not achieved in these patients and that the progression-free rate of 91.6% was thus overestimated. In this respect, additional treatments should be considered as many patients developed distant metastases or hepatic functional deterioration shortly after 3D-CRT.

CONCLUSIONS

A part of the HCC patients with IVC invasion might have benefited from 3D-CRT and a third of such patients had had a chance of surviving more than a year; otherwise they could not have survived long with this progressive fatal disease. However, further treatment should be considered to prevent distant metastasis and to protect post-treatment hepatic function, because the majority of the patients died from metastatic diseases or liver failure in spite of good local tumor control by 3D-CRT.

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Conflict of interest statement

None declared.

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