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Prognostic value of pretreatment ^{18}F-FDG PET-CT in radiotherapy for patients with hepatocellular carcinoma

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Purpose: The purpose of this study was to investigate the predictable value of pretreatment ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) in radiotherapy (RT) for patients with hepatocellular carcinoma (HCC) or portal vein tumor thrombosis (PVTT).

Materials and Methods: We conducted a retrospective analysis of 36 stage I–IV HCC patients treated with RT. ^{18}F-FDG PET-CT was performed before RT. Treatment target was determined HCC or PVTT lesions by treatment aim. They were irradiated at a median prescription dose of 50 Gy. The response was evaluated within 3 months after completion of RT using the Response Evaluation Criteria in Solid Tumors (RECIST). Response rate, overall survival (OS), and the pattern of failure (POF) were analyzed.

Results: The response rate was 61.1%. The statistically significant prognostic factor affecting response in RT field was maximal standardized uptake value (maxSUV) only. The high SUV group (maxSUV ≥ 5.1) showed the better radiologic response than the low SUV group (maxSUV < 5.1). The median OS were 996.0 days in definitive group and 144.0 days in palliative group. Factors affecting OS were the %reduction of alpha-fetoprotein (AFP) level in the definitive group and Child-Pugh class in the palliative group. To predict the POF, maxSUV based on the cutoff value of 5.1 was the only significant factor in distant metastasis group.

Conclusion: The results of this study suggest that the maxSUV of ^{18}F-FDG PET-CT may be a prognostic factor for treatment outcome and the POF after RT. A %reduction of AFP level and Child-Pugh class could be used to predict OS in HCC.

Keywords: Radiotherapy, Positron emission tomography, Hepatocellular carcinoma

Introduction

Liver cancer is the fifth most common cancer in males and the ninth most common cancer in females worldwide. Hepatocellular carcinoma (HCC) accounts for most (70%–90%) of all primary liver cancers [1]. The incidence of HCC has been steadily on the rise, and in men HCC is the second leading cause of death worldwide. The ratio of male to female HCC patients is 2.43:1. HCC occurs most frequently in the fifth decade of life (28.6%), followed the sixth decade (26.0%) and the seventh decade (22.3%) [2]. The treatment options of HCC include surgery, liver transplantation, radiofrequency ablation (RFA), percutaneous ethanol injection, transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy, and systemic chemotherapy [3,4]. In addition, a combination of TACE and radiotherapy (RT) showed a favorable

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treatment outcome in locally advanced HCC [5]. With great advances in RT, external RT becomes an effective treatment method for HCC. However, there is insufficient data to predict RT response. For this reason, some studies made an effort to determine what factor is most powerful and predictable, including standardized uptake value (SUV). Kim et al. [6] reported that in HCC patients, the higher SUV (≥2.5) group showed better treatment outcome than the lower SUV (<2.5) group, although there was no significant difference (p = 0.56) in overall survival (OS) between the two groups. Shiomi et al. [7] showed that the higher SUV (≥1.5) group had a lower survival rate than the lower SUV (<1.5) group in HCC patients with larger than 20 mm in tumor size. Therefore, we retrospectively reviewed the medical records of HCC patients who were treated with RT to determine the associations between SUV ratio, RT response, OS, and the pattern of failure (POF).

Materials and Methods

We treated 125 HCC patients with RT to primary tumor or portal vein tumor thrombosis (PVTT) only from February 2006 to March 2012. Forty of these patients had undergone ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) before RT. Four patients were excluded due to receiving a dose of <30 Gy. Therefore, 36 (29 men and 7 women) with stage I–IV HCC patients were included in the study. RT was delivered to primary HCC (n = 8) for the purpose of definitive treatment and 12 for the purpose of palliative treatment, PVTT only (n = 9), primary HCC with PVTT (n = 6) or primary HCC with inferior vena cava (IVC) thrombosis (n = 1) according to the purpose of treatment. The median age of the patients was 56 years (range, 41 to 78 years).

HCC was diagnosed pathologically using invasive hepatic biopsy (n = 1) or clinically using noninvasive imaging studies with or without tumor marker levels (n = 35). According to the National Cancer Information Center of Korea, chronic hepatitis and liver cirrhosis caused by hepatitis B virus (HBV), hepatitis C virus (HCV), and alcohol were the main causes of HCC in South Korea. Therefore, in these high-risk patients (including HBV positivity, HCV positivity, and liver cirrhosis), liver ultrasonography and serum alpha-fetoprotein (AFP) levels were performed. In addition, if any suspected findings were observed in these test results, liver dynamic CT or liver magnetic resonance imaging (MRI) was performed.

In this study, a total of 36 patients underwent liver CT scan, of whom 6 also underwent liver MRI. HCC was diagnosed using typical findings on CT scans of hypervascularization in the arterial phase with washout in the portal (=delay) phase [8], with or without elevation of AFP levels [9].

1. Patients and characteristics

In this study, the male to female rate was 4.14:1. The number of patients under 60 years of age was 25, and that over 60 years of age was 13. The Eastern Cooperative Oncology Group (ECOG) performance status scores were measured before RT in all patients. Sixteen patients had ECOG performance status score 0, 13 patients had 1, and 7 patients had 2. Thirty patients had Child-Pugh (CP) class A, and 5 patients had CP class B. CP class was not determined in 1 patient because the patient did not undergo serum albumin tests immediately before RT. The patient had CP-B (CP score = 7) HCC 5 months before RT and CP-B (CP score = 8) HCC after completion of RT. Thirty patients had chronic HBV infection, 2 patients had chronic HCV infection, and the remaining 4 patients had non-B, non-C hepatitis. According to the American Joint Committee on Cancer TNM staging (seventh edition) for HCC, 3 patients were at stage I, 1 patient at stage II, 15 patients at stage III (4 at stage IIIA and 11 at stage IIIB), and 17 patients at stage IV (15 at stage IVA and 2 at stage IVB). In addition, other stage classifications such as Japan Integrated Staging (JIS) system, Cancer of the Liver Italian Program (CLIP) score, Okuda stage were described in Table 1.

Seventeen patients were delivered conventional RT and 19 patients were delivered hypofractionated RT. Patients receiving prescription dose over 50 Gy were 21 and less than 50 Gy were 15. Twenty-eight patients had elevated serum AFP level before RT and 7 had not. One patient had no data on serum AFP levels before RT. Treatments before RT were TACE alone in 27 patients, both TACE and RFA in 1 patient, both TACE and systemic chemotherapy in 4 patients, and no treatment in 4 patients (Table 1).

Patients underwent ^{18}F-FDG PET-CT before RT, and the SUV was obtained from each patient. The SUV was calculated using the following formula:

$$SUV\,(\mathrm{t}) = \frac{Liver\ tissue\ radioactivity\ concentration\ (\mathrm{MBq/kg})\ at\ time\ (\mathrm{t})}{Injected\ radioactivity\ (\mathrm{MBq})\ /\ Patient's\ body\ weight\ (\mathrm{kg})}$$

The maximal uptake of the HCC lesions in each patient was presented as maxSUV.

2. Radiotherapy

All patients underwent simulation CT by a LightSpeed RT16 CT scanner (GE Healthcare, Waukesha, WI, USA). Each simulation delineated planning target volume (PTV) and dose

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Table 1. Clinical characteristics of entire 36 patients

Characteristic	No. (%)	Definitive group (n = 8)	Palliative group (n = 28)
Sex			
Male	29 (80.6)	6	23
Female	7 (19.4)	2	5
Age (yr)			
<60	23 (63.9)	4	19
≥60	13 (36.1)	4	9
ECOG PS			
0	16 (44.5)	3	13
1	13 (36.1)	3	10
2	7 (19.4)	2	5
Etiology			
B	30 (83.3)	6	24
Non-B	6 (16.7)	2	4
CP class[a]			
A (5/6)	30 (85.7)	7	23
B (7/8/9)	5 (14.3)	0	5
TNM stage			
I–II	4 (11.1)	4	0
III–IV	32 (88.9)	4	28
JIS system[b]			
0–2	17 (48.6)	7	10
3–4	18 (51.4)	0	18
CLIP score[c]			
0–2	18 (52.9)	7	11
3–5	16 (47.1)	0	16
Okuda stage[d]			
I	15 (44.1)	7	8
II–III	19 (55.9)	0	19
RT type			
Conventional	17 (47.2)	2	15
Hypofractionated	19 (52.8)	6	13
Prescription dose (Gy)			
≥50	21 (58.3)	7	14
<50	15 (41.7)	1	14
Serum AFP level before RT[e]			
Elevated	28 (80.0)	5	23
Not elevated	7 (20.0)	3	4
Previous treatment			
TACE	27 (75)	6	21
TACE + RFA	1 (2.8)	1	0
TACE + CTx	4 (11.1)	0	4
No treatment	4 (11.1)	1	3
maxSUV			
≥5.1	18 (50.0)	0	18
<5.1	18 (50.0)	8	10

ECOG PS, Eastern Cooperative Oncology Group performance status; CP class, Child-Pugh class; JIS, Japan Integrated Staging; CLIP, Cancer of the Liver Italian Program; RT, radiotherapy; AFP, alpha-fetoprotein; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; CTx, systemic chemotherapy; maxSUV, maximal standardized uptake value.
[a]One patient in definitive group had no albumin data shortly before RT. Complementally, The CP class of 5 months before RT was B (CP score = 7) and post RT CP class was B (CP score = 8). [b]One patient in definitive group had no CP score. [c]One patient in definitive group had no CP score and one patient in palliative group had no AFP values. [d]One patient in definitive group and palliative group each had no albumin and bilirubin values. [e]One patient in palliative group had missing value.

prescriptions by Eclipse ver. 8.9 (Varian Medical Systems, Palo Alto, CA, USA) or the tomotherapy planning system (Accuray Inc., Sunnyvale, CA, USA). Each treatment was conducted using a Clinac iX Linear Accelerator (Varian Medical Systems) or the TomoTherapy Hi-Art system (Accuray Inc.).

Gross tumor volume (GTV) was defined as a primary HCC mass or a PVTT lesion depending on the purpose of treatment aim. In cases of definitive group, GTV was defined as a HCC mass; in cases of palliative group, GTV was defined as a PVTT lesion with or without the HCC mass. In patients who had large HCC mass with PVTT, we treated PVTT alone using TACE followed by RT. Because PVTT has limited applicability in TACE, it need to be treated with different modalities for better prognosis [10]. However, when the primary HCC was single, localized, close to PVTT, both HCC and PVTT lesions were included in GTV. In designing PTV, margins were individualized in accordance with liver mobility and the treatment purpose of each patient.

Twenty patients received conventional RT, and 16 patients received hypofractionated RT. The median dose of conventional RT was 50 Gy in 25 fractions, and that of hypofractionated RT was 50 Gy in 10 fractions. Conventional RT and hypofractionated RT were prescribed in 1.8–3.0 Gy in 20–30 fractions and 3.0–6.0 Gy in 10–15 fractions, respectively.

3. Response evaluation and statistical analysis

Treatment outcome was evaluated with liver CT 2–3 months after completion of RT. The Response Evaluation Criteria in Solid Tumors (RECIST) were used to determine radiological treatment outcome. We analyzed treatment outcome of tumor masses only within the RT filed, not beyond the RT field using the RECIST. Complete response was defined as disappearance of all target lesions, partial response defined as an at least 30% decrease in maximum diameter of the target lesion on CT scan. Progressive disease was defined as an at least 20% increase in maximum diameter of the target lesion. Stable disease was defined as the absence of complete response, partial response, or progressive disease. We defined complete response and partial response as objective response on CT scans. The primary endpoint was treatment outcome, and secondary endpoints were OS and treatment failure. OS time was defined as the interval from the date of completion of RT to a patient's expiration date. Treatment failure was categorized into three groups according to the POF: in-field failure, out-field failure, and distant metastasis. In-field failure was defined as disease progression in the RT field, and out-field failure as intrahepatic disease progression beyond the RT field. Distant metastasis

was defined as disease progression at any sites outside the liver.

We analyzed OS curves using Kaplan-Meier survival analysis with the log-rank test. Cox regression analysis was used to assess prognostic factors, and logistic regression analysis was used to evaluate what factor would be related to treatment response. If patients had missing data, they were excluded from the analysis. Each analysis was statistically significant when p-value was less than 0.05.

Table 2. Factors affecting objective tumor response by RECIST (CR + PR, n = 22/36)

Characteristic	No. of patients with OTR	p-value
Etiology		0.544
B	19	
Non-B	3	
CP class		0.707
A (5/6)	18	
B (7/8/9)	4	
TNM stage		0.631
I–II	2	
III–IV	20	
JIS system		0.066
0–2	8	
3–4	14	
CLIP score[a]		0.140
0–2	9	
3–5	12	
Okuda stage[a]		0.113
I	7	
II–III	14	
RT type		0.790
Conventional	10	
Hypofractionated	12	
Prescription dose (Gy)		0.564
≥50	12	
<50	10	
%reduction in AFP levels		0.697
≥50	8	
<50	14	
Previous treatment		0.552
Yes	19	
No	3	
maxSUV		0.046
≥5.1	14	
<5.1	8	

RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; OTR, objective tumor response; CP class, Child-Pugh class; JIS, Japan Integrated Staging; CLIP, Cancer of the Liver Italian Program; RT, radiotherapy; AFP, alpha-fetoprotein; maxSUV, maximal standardized uptake value.
[a]If the patient does not have values, they were excluded and then calculated.

Results

Patients were divided into two groups according to maxSUV of ^{18}F-FDG PET-CT. The cutoff point of maxSUV in the receiver operation characteristic (ROC) curve was 5.1 (area under curve [AUC], 0.669). Therefore, patients with a maxSUV of ≥5.1 were classified as the high SUV group (n = 18), and those with <5.1 as the low SUV group (n = 18). After that, we analyzed what factor would affect treatment outcome.

Objective tumor responses were noted in 61.1% of the patients (complete response 2.8% and partial response 58.3%). Tumor responses were evaluated only within the RT filed. We determined clinical factors associated with tumor response including etiology (HBV vs. non-HBV), CP class (A vs. B), TNM stage (I–II vs. III–IV), JIS system (0–2 vs. 3–4), CLIP score (0–2 vs. 3–5), Okuda stage (I vs. II–III), RT type (conventional vs. hypofractionated), prescribed dose (≥50 Gy vs. <50 Gy), %reduction in AFP levels (≥50% vs. <50%), Previous treatment (yes vs. no) and maxSUV (≥5.1 vs. <5.1) (Table 2).

Among them, the only statistically significant factor affecting tumor response was maxSUV. The high SUV group showed a better objective tumor response than the low SUV group (63.6% vs. 36.4%, p = 0.046).

However, despite the better treatment outcome, the high SUV group showed a significantly worse OS (p = 0.006) (Fig. 1). Thus, the characteristics of the patients were analyzed between the two groups according to maxSUV 5.1, and patient heterogeneity was found in the two groups with the purpose

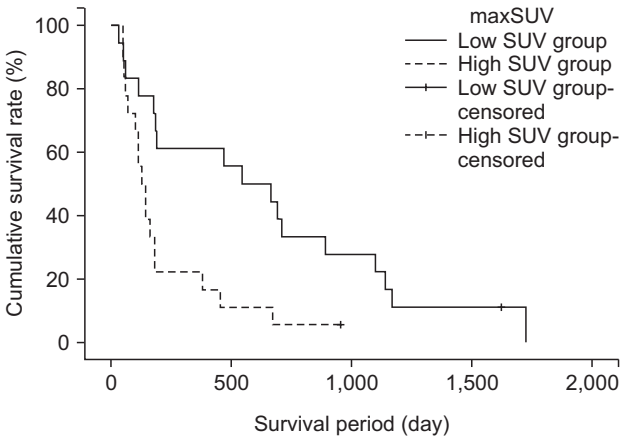

Fig. 1. The maximal standardized uptake value (maxSUV) affecting overall survival with no subgroups (p = 0.006).

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Table 3. Thirty-six patients' characteristics according to maxSUV value

Characteristic	High SUV group (maxSUV ≥ 5.1)	Low SUV group (maxSUV < 5.1)	p-value
No. of patients	18	18	
Age (yr), median (range)	51.5 (41–77)	59.5 (45–78)	
Sex			1.000
Male	14	15	
Female	4	3	
ECOG PS			0.372
0	8	8	
1	5	8	
2	5	2	
Etiology			0.177
B	17	13	
Non-B	1	5	
CP class[a]			1.000
A (5/6)	15	15	
B (7/8/9)	3	2	
TNM stage			0.104
I–II	0	4	
III–IV	18	14	
JIS system[a]			0.002
0–2	4	13	
3–4	14	4	
CLIP score[a]			0.303
0–2	7	11	
3–5	10	6	
Okuda stage[a]			0.037
I	4	11	
II–III	13	6	
RT type			0.505
Conventional	10	7	
Hypofractionated	8	11	
Prescription dose (Gy)			0.695
≥50	8	13	
<50	10	5	
%reduction in AFP levels			0.086
≥50	4	10	
<50	14	8	
Previous treatment			0.603
Yes	15	17	
No	3	1	
Treatment aim			0.003
Definitive	0	8	
Palliative	18	10	

SUV, standardized uptake value; ECOG PS, Eastern Cooperative Oncology Group performance status; CP class, Child-Pugh class; JIS, Japan Integrated Staging; CLIP, Cancer of the Liver Italian Program; RT, radiotherapy; AFP, alpha-fetoprotein.
[a]If the patient does not have values, they were excluded and then calculated.

Table 4. Factors affecting overall survival according to treatment aim except initial TNM stage IVB (n = 34)

Characteristic	Definitive group (n = 8)		Palliative group (n = 26)	
	No. of patients[a]	p-value	No. of patients[b]	p-value
Etiology		0.448		0.847
B	6		22	
Non-B	2		4	
CP class[c]		-		0.008
A (5/6)	7		21	
B (7/8/9)	0		5	
TNM stage		0.179		-
I–II	4		0	
III–IV	4		26	
JIS system[c]		-		0.616
0–2	7		10	
3–4	0		16	
CLIP score[c]		-		0.786
0–2	7		9	
3–5	0		16	
Okuda stage[c]		-		0.349
I	7		8	
II–III	0		17	
RT type		0.734		0.775
Conventional	2		13	
Hypofractionated	6		13	
RT dose (Gy)		0.353		0.584
≥50	7		14	
<50	1		12	
%reduction in AFP levels		0.046		0.447
≥50	5		9	
<50	3		17	
Previous treatment		0.209		0.654
Yes	7		23	
No	1		3	
maxSUV		-		0.383
≥5.1	0		17	
<5.1	8		9	

CP class, Child-Pugh class; JIS, Japan Integrated Staging; CLIP, Cancer of the Liver Italian Program; RT, radiotherapy; AFP, alpha-fetoprotein; maxSUV, maximal standardized uptake value.
[a]Among 8 patients, 7 patients were expired. [b]Among 26 patients, 25 patients were expired. [c]If the patient does not have values, they were excluded and then calculated.

of treatment (p = 0.003) (Table 3). Therefore we analyzed OS according to the purpose of treatment in 34 patients except stage IVB patients in initial TNM staging.

Median survival times were 996.0 days in the definitive group and 144.0 days in the palliative group. In each group, we evaluated factors affecting OS, including etiology (HBV

vs. non-HBV), CP class (A vs. B), TNM stage (I–II vs. III–IV), JIS system (0–2 vs. 3–4), CLIP score (0–2 vs. 3–5), Okuda stage (I vs. II–III), RT type (conventional vs. hypofractionated), prescribed dose (≥50 Gy vs. <50 Gy), %reduction in AFP levels (≥50% vs. <50%), Previous treatment (yes vs. no) and maxSUV (≥5.1 vs. <5.1) (Table 4). If patients had missing data, they were excluded from the analysis. Among these factors, %reduction in AFP levels was a significant factor for OS in the definitive group (p = 0.046), and CP class in the palliative group (p = 0.008) (Figs. 2 and 3).

We also analyzed patterns of disease progression. Five patients who underwent RT at our hospital and showed disease progression during the follow-ups at other hospitals were excluded from the study because they had insufficient data on disease progression. Stage IVB patients at initial TNM staging were also excluded. Of the 29 patients, 4 showed in-field failure, 14 showed out-field failure, and 11 showed distant metastasis. The only significant factor was maxSUV in the distant metastasis group (p = 0.008) (Table 5).

Discussion and Conclusion

HCC is one of the major health problems all over the world, and the incidence of HCC has gradually increased. The management of HCC is extremely important in Korea having a high incidence of HBV infections.

The major treatment options for HCC include TACE, RFA, surgical resection, systemic chemotherapy, and RT. Among them, RT shows a good treatment outcome compared to other local treatment options, such as TACE or RFA. Huang et al. [11] reported, in a study of HCC patients with PVTT, that patients irradiated at ≥50 Gy showed better survival than those who was not (p < 0.001). Park et al. [12] showed an objective response of 66.1% (complete response 8.5% and partial response 57.6%) in irradiated patients (RT dose ≥50 Gy; α/β = 10) with unresectable HCC masses, without grade 3 or 4 toxicity. Seong et al. [13] demonstrated results similar to those of the two aforementioned studies. The main eligibility criterion for those studies involving the treatment outcome of HCC was unresectable HCC that failed TACE, and their objective response rate was 66.7% (complete response 0.6% and partial response 66.5%), which is similar to ours (61.1%; complete response 2.8% and partial response 58.3%).

There are several laboratory tools to predict treatment outcome and OS. According to Park et al. [14], a combination of AFP and protein induced by vitamin K absence/antagonist-II (PIVKA-II) is useful predictor in locally advanced HCC patients. Daniele et al. [15] demonstrated that serum matrix metalloproteinase-2 (MMP-2) level of >1,500 ng/mL, and the ratio of MMP-2/tissue inhibitor of metalloproteinase-2 (TIMP-2) predict treatment outcome in HCC patients. Additionally, Jun et al. [16] indicated that some clinical factors, such as patient age, CLIP score, serum alkaline phosphatase, lactate dehydrogenase, C-reactive protein, tumor size, and distant metastasis status, are predictors of survival and tumor recurrence after treatment, including RT.

Previous studies evaluated the relation between SUV of ^{18}F-FDG PET-CT and RT response. Kim et al. [6] proposed that ^{18}F-FDG PET-CT is a useful predicting factor for RT response. They analyzed factors, such as viral status, CP class, tumor size, TNM stage, PVTT status, treatment method (CCRT vs. TACE + RT), RT dose, and SUV, and demonstrated that tumor response

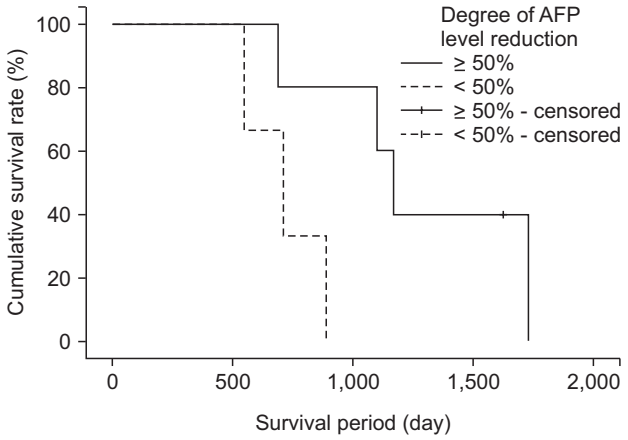

Fig. 2. The degree of alpha-fetoprotein (AFP) level reduction affecting overall survival in definitive group (p = 0.046).

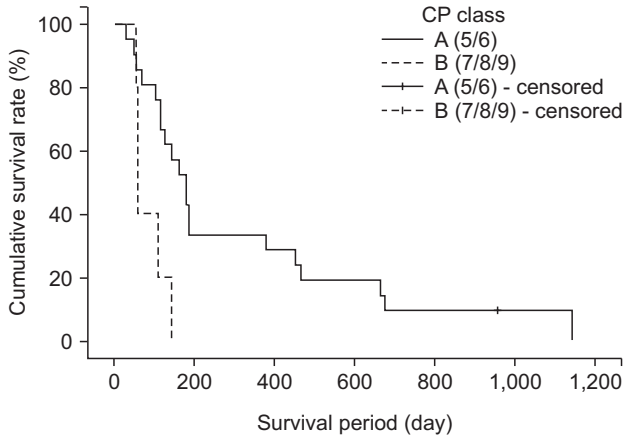

Fig. 3. The degree of alpha-fetoprotein (AFP) level reduction affecting overall survival in palliative group (p = 0.008). CP, Child-Pugh.

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Table 5. Factors affecting pattern of failure except initial TNM stage IVB (n = 29)

Characteristic	In-field (n = 4)		Out-field (n = 14)		Distant metastasis (n = 11)	
	No. (%)	p-value	No. (%)	p-value	No. (%)	p-value
Etiology		0.838		0.645		0.332
B	3		12		10	
Non-B	1		2		1	
CP class[a]		-		0.391		0.277
A (5/6)	3		13		10	
B (7/8/9)	0		1		1	
TNM stage		0.633		0.101		-
I–II	2		2		0	
III–IV	2		12		11	
JIS system[a]		-		0.371		0.100
0–2	3		8		4	
3–4	0		6		7	
CLIP score[a]		0.623		0.262		0.860
0–2	2		6		6	
3–5	1		7		5	
Okuda stage[a]		-		0.326		0.113
I	3		7		3	
II–III	0		7		7	
RT type		0.569		0.801		0.136
Conventional	2		5		6	
Hypofractionated	2		9		5	
RT dose (Gy)		0.066		0.949		0.375
≥50	2		10		5	
<50	2		4		6	
%reduction in AFP levels		0.964		0.097		0.139
≥50	3		6		4	
<50	1		8		7	
Previous treatment		0.921		0.252		0.758
Yes	3		13		9	
No	1		1		2	
maxSUV		-		0.380		0.008
≥5.1	0		6		10	
<5.1	4		8		1	

CP class, Child-Pugh class; JIS, Japan Integrated Staging; CLIP, Cancer of the Liver Italian Program; RT, radiotherapy; AFP, alpha-fetoprotein; maxSUV, maximal standardized uptake value.
[a]If the patient does not have values, they were excluded and then calculated.

was better in the higher SUV group (≥2.5) than in the lower SUV group (<2.5).

In our study, patients were divided to two groups according to the cutoff point of maxSUV of 5.1 based on the ROC curve. The high and low SUV groups were treated at median doses of 45.9 and 50.0 Gy, respectively. Within the RT field, the high SUV group achieved a better treatment outcome than the low SUV group, as assessed by the RECIST criteria (p = 0.046).

Glucose is required during cell proliferation [17]. In clinical oncology, ^{18}F-FDG is widely used as a glucose analog, and ^{18}F-FDG PET-CT revealed a high glucose uptake region like malignant tumors, especially poorly differentiated tumors, and a region with a high SUV [18,19]. In other words, cell division occurs more actively when tumors have a higher maxSUV on PET-CT. This means that RT exposure time during cell division is longer in the high SUV group than in the low SUV group. Therefore, the high SUV group has significantly better treatment outcome than the low SUV group.

The OS rate was higher in the low SUV group, although treatment outcome was even better in the high SUV group. The reason for this may be that there were differences in patient characteristics between the two groups. Treatment

aim according to disease status was statistically significant between the high and low SUV groups (p = 0.003). The two groups were subdivided into the definitive and palliative groups according to the purpose of treatment to analyze factors affecting OS. In the high SUV group, the number of patients for the purpose of palliative treatment was 18 and that for the purpose of definitive treatment was 0; in the low SUV group, that for the purpose of palliative treatment was 10 and that for the purpose of definitive treatment was 8.

Based on these subgroups, a %reduction in AFP levels was the only factor affecting OS in the definitive group, and CP class was in the palliative group (Figs. 2 and 3). Patients in the definitive group were limited to early stage, and their average serum AFP level measured directly before RT was 74.1 ng/mL (range, 2.75 to 245.0 ng/mL). The average reduction in AFP levels was 54.6 ng/mL (range, 6.2 to 92.7 ng/mL) except 1 patient who showed an increased serum AFP level after RT. Gomaa et al. [20] documented that the pretreatment serum AFP level predicts OS in patients HCC at early and intermediate stages. They treated the patients using various treatment modalities according to the Barcelona Clinic Liver Cancer recommendation. They also analyzed serum AFP levels according to the cutoff value of 200 ng/mL and reported that patients with a serum AFP level of <200 ng/mL had a higher median survival rate than those with a serum AFP level of ≥200 ng/mL. Although their study did not include RT, it employed all other treatment modalities for local control.

In our study, %reduction of the serum AFP level was a predictor of OS in patients with HCC at definitive group: early stage patients. Patients with a ≥50% reduction in serum AFP levels showed a longer survival time (p = 0.046) (Fig. 2). However, our study included patients whose initial serum AFP level was not elevated. If patients with a normal serum AFP level were excluded, the number of the patients analyzed was too small to interpret results. This is a limitation of our study.

CP class was a significant predicting factor for OS in the patients with HCC at palliative group: advanced stage patients (Fig. 3). Pressiani et al. [21] showed that the OS rate is higher in CP-A HCC patients than in CP-B HCC patients for locally advanced HCC when they were treated with sorafenib (Nexavar), a kinase inhibitor (p < 0.001), which is consistent with our result except that patients were treated with systemic therapy in previous studies.

The POF was also analyzed, and the only statistically significant factor was maxSUV with the cutoff value of 5.1 in the distant metastasis group (p = 0.008) (Table 5). In patients with progressive disease in the form of metastatic disease who were treated for the purpose of palliative treatment, the number of patients with a maxSUV of ≥5.1 was 10, and that with a maxSUV of <5.1 was 1. Their treatment targets were variable, including PVTT only (n = 2), primary HCC (n = 6), primary HCC with PVTT (n = 2), and primary HCC with IVC thrombosis (n = 1).

Pant et al. [22] suggested that ^{18}F-FDG-avid primary tumors carry higher risk for metastasis than non-^{18}F-FDG-avid primary tumors and HCC at higher stages was found more commonly in ^{18}F-FDG-avid primary tumors. Tumors with a high SUV have a short doubling time. Thus, RT response is better in the high SUV group than in the low SUV group. However, if there were any residual lesions after RT, tumor cells can spread more frequently and rapidly in the high SUV group than in the low SUV group. Koom et al. [23] divided tumors outside the RT field into four groups: group 1 (single tumors within the RT field), group 2 (multiple tumors within the RT field), group 3 (multiple tumors outside the RT field but controlled), and group 4 (multiple tumors outside the RT field, viable tumors). In their study, if any viable intrahepatic tumors are outside the RT field, OS was poorer (p = 0.004). In our study, because all patients in the distant metastasis group were treated for the purpose of palliative treatment, out-field tumors remained after RT. Therefore, it is apparent that the frequency of distant metastasis is high in the high SUV group than in the low SUV group.

In conclusion, the results of this study suggest that the cutoff value of 5.1 in ^{18}F-FDG PET CT can be useful for predicting RT response and the trend of distant metastasis. And the serum AFP level may be a significant predictor of OS in patients with HCC at early to intermediate stages and in CP-A advanced HCC patients. However, the small number of patients is thought to be limitation of this study. Additional future prospective studies with a larger number of patients are needed to confirm our results.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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