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FDG-PET after radiotherapy is a good prognostic indicator of rectal cancer

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In the management of rectal cancer after the combined therapy of the radiation and surgical operation, the evaluation of the prognosis is important. Although fluoro-18-deoxyglucose positron emission tomography (FDG-PET) is considered as a useful tool for evaluation of therapeutic effect of this cancer as well as the other cancers, however, there are few articles that clearly describe the appropriate procedure of the FDG-PET in order to obtain the best prognostic value. The purpose of the present study is to compare several variations of a semi-quantification method, the Standardized Uptake Values (SUV) and to determine the most appropriate parameter for the prognostic prediction and to propose the quantitative guideline of the FDG-PET. Especially, the authors focused on the SUV after radiotherapy, which had not been considered as a key quantitative value, as it was rather taken as a mere indicator of the therapeutic (radiotherapeutic) effect, not a direct indicator of the prognosis for the cancer itself. ***Methods:*** Forty patients with rectal cancer in the lower rectal region underwent two series of FDG-PET study before and after pre-operative radiotherapy. Their SUVs were calculated from FDG-PET data and compared with the results of the long-term follow-up of the patients as well as with histopathological outcomes. ***Results:*** All 40 patients had high FDG uptake before radiotherapy. The mean value of SUV before radiotherapy (SUV1) was 7.6. After radiotherapy, the mean value of SUV (SUV2) decreased to 4.2. There was a significant difference in SUV2 between the groups with and without recurrence ($p < 0.05$), however, SUV1 or SUV ratio (SUV2/SUV1) displayed no significant difference with the incidence of recurrence. ***Conclusion:*** SUV2 was considered to be a good prognostic indicator for long-term prognosis of rectal cancer patients. SUV1 nor SUV ratio SUV2/SUV1 did not have the equivalent prognostic usefulness. Subsets of patients with SUV2 greater than 3.2 should be observed closely.

Key words: FDG-PET, Standardized Uptake Value, rectal cancer, prognostic indicator

INTRODUCTION

IN THE PAST TWO DECADES, the incidence of rectal cancer has greatly increased in number and has reached 37,000 new cases annually in the United States.[1] In Japan, the same alarming tendency has appeared because of the Westernization of nutrition and life patterns. The treatment regimen for this cancer is mainly a surgical procedure, Miles' operation, or low anterior resection (LAR), but adjuvant radiotherapy and/or chemotherapy is widely performed. Although many factors have been reported as possible factors to predict the recurrence of rectal cancer, none of these appear established.

At the same time, fluoro-18-deoxyglucose positron emission computed tomography (FDG-PET) is practiced more and more often as a supplementary method for CT and MRI.[2,3] This provides physiological information that is indispensable for the determination of the treatment efficacy. Thus far, several articles describing the usefulness of FDG-PET have been published, but its role is, at

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present, limited to the evaluation of the initial status of the lesions before therapy[4,5] or early therapeutic effects.[6–9] Semi-quantification using the Standardized Uptake Value (SUV) is a potential candidate for evaluation of the therapeutic effect, but there is a lack of supporting evidence with a larger study population. This is partly because of the relatively short follow-up periods noted in previous studies. The purpose of the present study is to compare several quantification methods using the SUV and to determine the most appropriate parameter for the prognostic prediction and to propose the quantitative guideline of the FDG-PET. Especially, the authors focused on the SUV after radiotherapy (SUV2), which has not been considered as a key quantitative value, as it was rather taken as a mere indicator of the therapeutic (radiotherapeutic) effect, not a direct indicator of the prognosis for the cancer itself. When the treatment efficacy or the prognosis after the treatment is assessed, the SUVs before (SUV1) and after radiotherapy should be considered. The authors made a hypothesis that SUV after radiotherapy is

Table 1 PET data, plasma CEA levels, radiographical measurement, histological data, and follow up status of the patients

No.	Age (y)	Sex	SUV1	SUV2	CEA1	CEA2	Shrinkage rate (%)	Histology	Penetration	LN	ly	v	mr	initial size	Prognosis
1	64	M	5.13	4.06	1.3	1.2	37.5	well	pm	+	−	−	−	L	dist
2	59	M	6.15	4.22	75.0	5.0	10.0	well	ss	−	−	+	−	M	(−)
3	41	M	8.19	5.2	7.1	2.3	26.7	well	a2	+	+	+	−	L	dist
4	71	M	7.39	2.76	4.6	2.2	20.0	mucinous	a2	+	−	+	+	L	local
5	70	F	6.71	4.74	5.4	1.2	50.0	moderate	a1	+	−	+	−	L	(−)
6	55	M	7.59	4.27	11.8	2.4	43.0	moderate	a2	+	+	+	+	L	local
7	52	M	8.84	3.72	167.4	4.3	40.0	moderate	a2	+	+	+	+	L	dist
8	63	M	6.51	3.99	28.3	3.8	30.0	well	pm	−	−	+	−	L	(−)
9	48	F	5.63	3.65	1.9	1.2	54.5	well	a2	+	+	+	+	L	dist
10	54	M	6.18	3.11	10.8	7.6	40.0	NA	a1	−	−	−	−	L	(−)
11	67	M	7.32	4.13	8.6	3.6	33.4	well	mp	−	−	−	−	L	(−)
12	65	F	6.08	1.98	55.4	6.9	31.0	NA	NA	−	−	−	−	L	dist
13	57	M	8.48	5.33	5.9	6.3	20.0	well	a2	−	−	−	−	M	(−)
14	47	M	13.60	2.6	2.1	2.1	76.0	well	a1	−	−	+	−	L	(−)
15	64	M	19.60	13.2	12.1	5.5	20.0	well	mp	+	−	+	−	L	local
16	67	M	12.40	6.5	21.4	4.0	10.0	well	a2	−	−	−	+	M	dist
17	53	F	14.60	4.4	33.6	1.7	33.0	well	a1	+	−	−	−	L	(−)
18	40	F	17.70	5.64	2.6	1.3	15.0	mucinous	a1	−	−	−	−	L	(−)
19	57	M	7.41	2.43	1.8	1.7	50.0	well	mp	+	−	−	−	L	(−)
20	47	M	8.10	3.1	2.4	1.9	60.0	well	mp	−	−	−	−	L	(−)
21	76	F	6.20	3.1	3.3	3.3	36.0	well	a1	−	−	−	−	L	(−)
22	77	M	6.68	2.55	4.0	3.7	53.0	well	a2	−	−	−	−	L	(−)
23	42	M	4.89	2.87	29.4	3.5	40.0	well	a1	−	−	+	−	L	dist
24	66	M	7.05	3.02	15.3	7.7	33.0	moderate	a1	+	−	−	−	L	(−)
25	62	M	4.67	2.3	2.4	2.8	30.0	well	a2	+	−	+	−	L	(−)
26	73	F	4.78	3.2	188.0	33.0	10.0	well	ai	−	−	−	−	M	dist
27	73	F	2.97	3.16	7.1	4.9	44.0	well	mp	+	+	+	−	L	dist
28	49	F	6.78	4.44	39.2	20.2	50.0	well	a2	+	−	+	−	L	dist
29	68	M	7.45	2.56	2.5	1.8	33.0	well	ss	+	−	+	−	L	(−)
30	65	F	8.23	3.95	9.8	2.0	50.0	well	a1	−	−	+	−	L	dist
31	59	M	5.45	3.04	4.7	2.3	20.0	well	a1	+	−	−	−	L	(−)
32	62	F	5.15	3.06	8.3	15.7	10.0	well	a2	+	−	−	−	L	(−)
33	58	M	4.63	4.51	1.8	1.5	42.0	well	mp	−	−	−	−	L	(−)
34	62	M	7.08	4.34	7.9	6.6	30.0	moderate	a1	+	−	+	−	L	dist
35	67	M	8.79	7.71	28.4	36.1	10.0	well	a1	+	−	+	−	L	dist
36	65	M	6.69	6.19	192.2	16.6	9.0	well	a1	+	−	+	−	L	(−)
37	63	M	3.34	4.55	9.9	5.7	10.0	poorly	a2	+	+	+	+	M	(−)
38	50	M	6.17	3.72	5.1	3.5	20.0	moderate	a2	+	−	+	−	M	(−)
39	64	F	11.50	10.4	3.2	3.2	10.0	well	a2	−	−	−	−	M	local
40	64	F	3.48	1.29	38.2	4.6	30.0	well	a1	+	−	+	−	L	(−)

LN, lymph node metastasis; ly, lymphatic infiltration; v, infiltration of vessels; mr, local microscopic residual; well, well differentiated carcinoma; moderete, moderately differentiated carcinoma; pm, proper muscle; ss, subserosa; mp, muscularis propria; a1, slight infiltration beyond proper muscle; a2, extensive infiltration beyond proper muscle; ai, invasion to adjacent organ(s); L, axial diameter exceeded 4 slices; M, axlial diameter was 4 slices; dist, distant metastasis, local, local recurrence; (−), no metastasis/recurrence; M, male; F, female; NA, data not available

more important rather than that before radiotherapy, as it represents how the tumor has changed its nature after radiotherapy and it would not be modified by the surgical procedure afterwards. In this article, SUV1 was assessed in comparison to SUV2 and the SUV1/SUV2 ratio as well as CT measurement and histological outcomes.

MATERIALS AND METHODS

Patients

Forty patients with rectal cancer in the lower rectal region (27 men and 13 women; age range 40–77 years, mean age of 60.0 y, and median age of 63.0 y) were included in the study. All of the patients gave written informed consent. Patient information is summarized in Table 1. The pathological diagnosis of the lesions was adenocarcinoma for 36 of the cases: 29 well differentiated, 6 moderately differentiated, one poorly differentiated, two mucinous, and two unknown.

Radiotherapy and Surgery

All but two patients received pre-operative whole pelvis external radiotherapy of a total of 50 Gy with 25 fractions of 2 Gy employing anteroposterior/posteroanterior opposite fields. Patient no. 12 received 60 Gy/30 fr. and patient no. 22 received 40 Gy/20 fr. instead. All patients had resections of the rectal cancer after the radiotherapy. Twenty-two patients underwent Miles' operations, while the remaining 18 patients were given LAR. Their resected specimens were analyzed histopathologically following the guideline by the Japanese Society of Surgical Oncology,[10] including the degree of the differentiation and infiltration of the vessels and lymphatic channels. Local microscopic residual and lymph node metastases were also examined. The degree of shrinkage of the tumor during the radiotherapy was evaluated with a set of CT scans performed immediately before the PET studies described below.

FDG-PET

All patients underwent two series of FDG-PET: one before pre-operative radiotherapy and the other three to five weeks after the treatment (days after radiotherapy ranged from 21 to 35; mean days after radiotherapy 29.6 ± 4.3 days). ^{18}F was synthesized using the Cypris Model 370 Cyclotron (Sumitomo Heavy Industries, Japan), and FDG was generated with an automated FDG synthesis based on the method reported by Ehrenkaufer et al.[11] Radiochemical purity was greater than 95%. PET scanning was performed with a Headtome IV dedicated PET scanner (Shimadzu Corp., Kyoto) with seven imaging planes at 13-mm intervals, each 10 mm thick. The in-plane resolution was 4.5 mm full-width at half maximum (FWHM). The axial resolution was 9.5 mm FWHM and the overall sensitivity was 144 kcps/(micro Ci/m*l*). The physical characteristics of this machine were described in detail in a previous study.[12] Patients fasted for at least 4 1/2 hours before PET scanning so that serum glucose levels were between 80 and 110 mg/m*l*. Bladder catheterization was not performed. Transmission scans were performed for 8 minutes each. Three-hundred and thirty-three to 444 MBq of FDG was injected 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 using a filtered back-projection algorithm with a Hanning filter using a cut-off frequency of 0.3 and a 128 by 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. A pixel is a square measuring 2 mm by 2 mm. FDG accumulation was measured using the SUV given by the following equation.[13,14]

$$\text{SUV} = (\text{decay corrected PET value})/((\text{injected dose})/(\text{body weight}))$$

The SUV on the basis of ideal body weight (SUV-ibw) was calculated using the following equations[15]:

$$\text{SUV-ibw} = (\text{decay corrected PET value})/((\text{injected dose})/\text{ibw}),$$

where ibw represents the ideal body weight, calculated as $45.5 + 0.91 \times$ (patient height in centimeters minus 152) for women and $48.0 + 1.06 \times$ (patient height in centimeters minus 152) for men. In addition, the SUV on the basis of the lean body mass was calculated using the following formula:

$$\text{SUV-lbm} = (\text{decay corrected PET value})/((\text{injected dose})/\text{lbm})$$

where lbm represents lean body mass, given as $1.07 \times (\text{weight}) - 148 \times (\text{weight/height})^2$ for women and $1.10 \times (\text{weight}) - 120 \times (\text{weight/height})^2$ for men.

Statistical Analysis

Results are presented as mean ± 1 SD. For statistical analysis, comparisons between two groups were made using an unpaired Student t-test with computer-based statistical software (STATVIEW, version 5.0, SAS institute, NC, USA). $P < 0.05$ was considered to be statistically significant. To determine the best indicator of the prognosis, SUV1, SUV2 and the ratio SUV2/SUV1 were accounted for in this process of analysis. Estimation of the sensitivity, specificity, likelihood ratio and accuracy were performed with respect to various thresholds for SUV, as

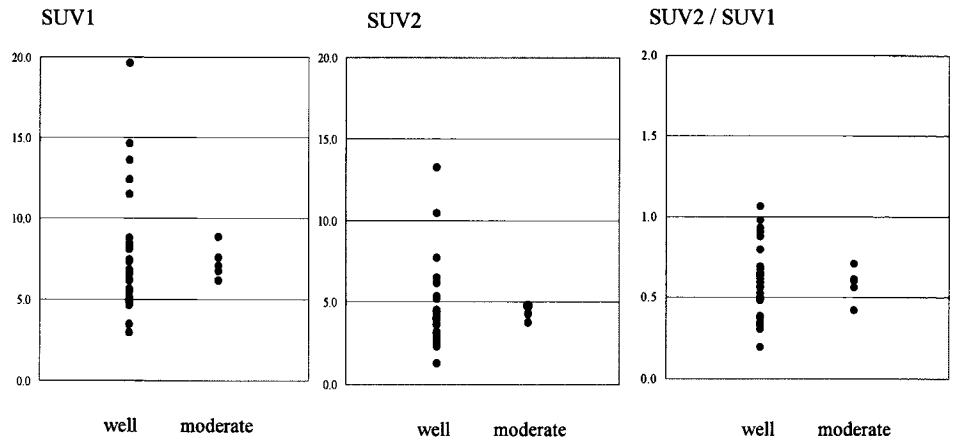

Fig. 1 Correlation between SUV1, SUV2, and SUV2/SUV1 with the degree of histological differentiation. A statistically significant correlation was not demonstrated.

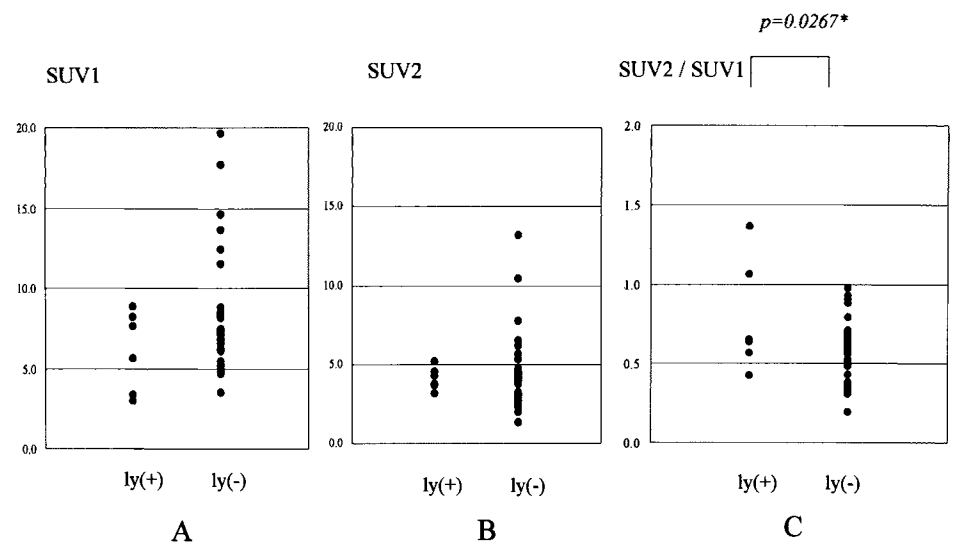

Fig. 2 Correlation between SUV1, SUV2, and SUV2/SUV1 with the absence/presence of lymphatic infiltration. SUV2/SUV1 demonstrated statistically significant correlation (C), whereas SUV1 and SUV2 demonstrated no statistically significant correlation (A and B).

well as the receiver operator characteristics (ROC) analysis in order to decide the cut-off value for SUV.[16,17]

Tumor Response

Calculation of the ratio of shrinkage of lesions with radiotherapy was performed with measurements based on two-dimensional measurements with the CT images performed immediately prior to the PET studies using the following formula:

(ratio of shrinkage) = D2/D1,

where D1 and D2 are the bigger values between axial and in-plane tumor size before and after radiotherapy respectively.

RESULTS

The median follow-up period for the patients was 3.33 years (ranging from 1.38 to 5.88 years). Of the 40 patients, 4 had local recurrence during the observation period, 13 showed distant metastases, and the rest displayed no recurrence or metastases. All 40 patients had high FDG uptake before radiotherapy. Their mean and SD of SUV1 were 7.6 ± 3.6 (n = 40, ranging from 3.0 to 19.6). Following radiotherapy, SUV decreased for 38 of the 40 patients and was 4.2 ± 2.2 (n = 40, 1.2 to 13.2). The p-values of unpaired t-tests for SUV1, SUV2, and SUV2/SUV1 between the well differentiated and moderately differentiated cases were p = 0.794, p = 0.691, and p = 0.643, respectively. There was no statistically significant difference in SUV1, SUV2, nor SUV2/SUV1 between histological subcategories of well differentiated, moderately differentiated (Fig. 1), as well as among these and those of poorly differentiated or others. The patients with positive lymphatic infiltration in the postoperative histo-

pathological diagnosis of the resected specimen displayed a milder decrease in SUV through radiotherapy than patients with negative lymphatic, with SUV2/SUV1 = 0.55 ± 0.19 and 0.78 ± 0.35, respectively (p = 0.0267). The differences in SUV1 and SUV2 for these two groups of patients were not statistically different (p = 0.256 and p = 0.875) (Fig. 2). There were no statistically significant differences in SUV1, SUV2, or SUV2/SUV1 between groups with presence/ absence of micro residual, infiltration of the vessels and lymph node metastasis. Related p-values have been summarized in Table 2. There were also no statistically significant differences of the incidence of positive histopathological findings, i.e., local microscopic residual, infiltration of the vessels, lymphatic infiltration or lymph node metastases, and the incidence of recurrence. Their p-values were 0.202, 0.204, 0.115 and 0.723 respectively. CEA before radiotherapy (CEA1), after radiotherapy (CEA2), and their ratio between them displayed no statistically significant difference between the groups with or without recurrence. CEA2/CEA1 and SUV2/SUV1 had no correlation (p = 0.580). SUV2 had a weak negative correlation with the shrinkage rate (r = −0.406, p = 0.0108), as well as with SUV2/SUV1 (r = −0.383, p = 0.0140). SUV1 did not show any correlation with the shrinkage rate (r = −0.160, p = 0.326) (Fig. 3). SUV2 displayed a statistical difference in the group with or without recurrence (p = 0.0466). On the other hand, SUV1 nor SUV2/SUV1 displayed no statistically significant difference with the incidence (p = 0.599 and p = 0.287, respectively) (Fig. 4). For SUV2, the ROC analysis was performed and revealed that the cut-off level should be around the range between 3.11 to 3.16. (Fig. 5) The positive likelihood ratio and accuracy with the thresholds between 2.8 and 3.5 (with 0.1 gaps) were evaluated, and with a threshold = 3.2, the positive likelihood and accuracy were the highest (1.60 and 62.5%, respectively). There was no correlation between body weight and SUV-bw. Patient no. 14, who displayed high SUV1 and prominent decrease of SUV2, had no recurrence, whereas the other patient, no. 16, who showed relatively high SUV2 had a metastasis to the lung (Fig. 6A and 6B).

Table 2 Statistical outcome of SUV1, SUV2 and SUV2/SUV1 with histopathological analyses

variance	category	p-value	statisitical significance
SUV1	mr (+)/mr (−)	0.937	n.s.
SUV2	mr (+)/mr (−)	0.984	n.s.
SUV1/SUV2	mr (+)/mr (−)	0.507	n.s
SUV1	v (+)/v (−)	0.522	n.s.
SUV2	v (+)/v (−)	0.724	n.s.
SUV1/SUV2	v (+)/v (−)	0.214	n.s.
SUV1	LNM (+)/LNM (−)	0.400	n.s.
SUV2	LNM (+)/LNM (−)	0.927	n.s.
SUV1/SUV2	LNM (+)/LNM (−)	0.293	n.s.

mr, local micrscopic residual; v, infiltration of the vessels; LNM, lymph node metastasis; n.s., not statistically significant

DISCUSSION

The data suggest that SUV2, i.e. the SUV after the preoperative radiotherapy, is a better indicator of prognosis than SUV1 and SUV2/SUV1. The fact that FDG uptake before surgery has some correlation with prognosis has been already discussed,[18–20] to a certain extent, but none of the published literature described long-term survival for specific types of cancer like esophageal or head and neck. Furthermore, the authors made comparisons between various SUV-related parameters: SUV1, SUV2, and SUV2/SUV1. Thus, guidelines for appropriate timing of PET have been established in order to predict prognosis.

In early PET studies, the first implication of the usefulness of SUV as a prognostic indicator appeared in an article published in 1991 in which they stated that patients

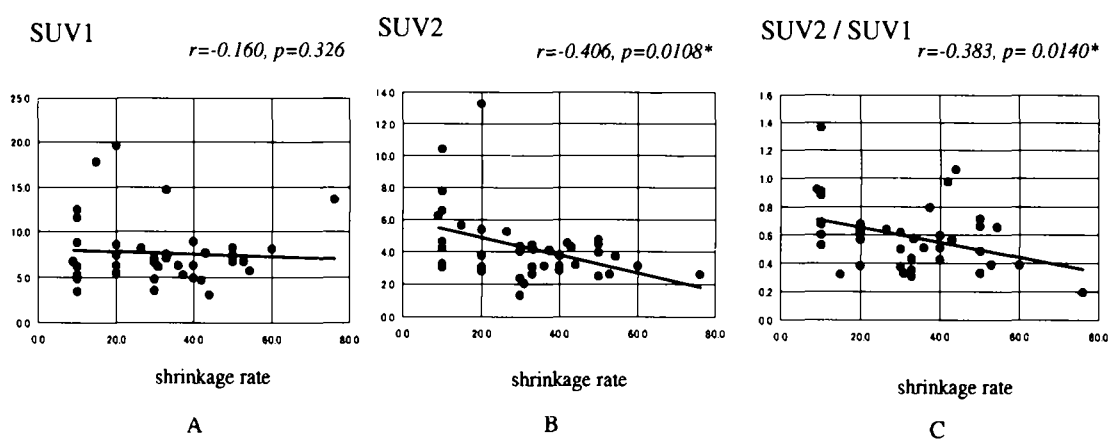

Fig. 3 Correlation between SUV1, SUV2, and SUV2/SUV1 with the radiographical shrinkage rate. SUV2 had a weak negative correlation with the shrinkage rate as well as with SUV2/SUV1 (B and C), whereas SUV1 did not demonstrate any correlation with the shrinkage rate (A).

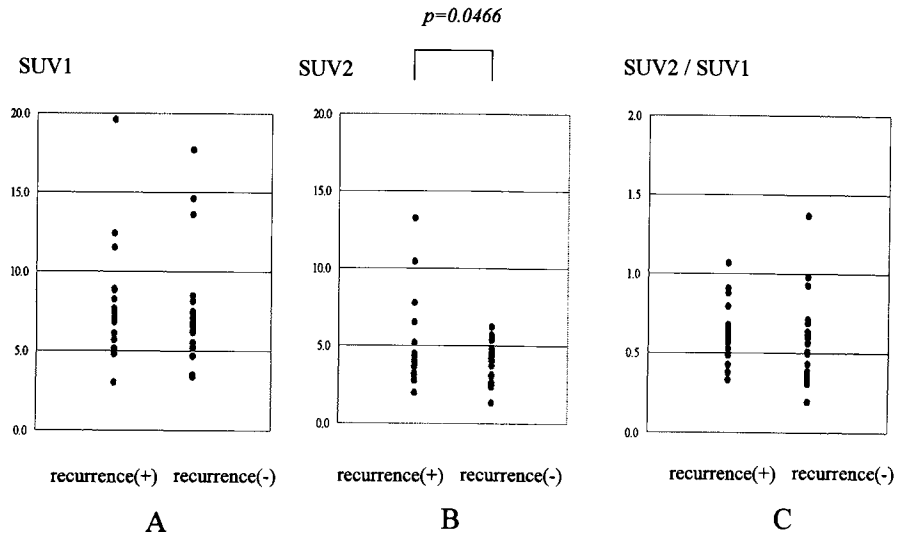

Fig. 4 Correlation between SUV1, SUV2, and SUV2/SUV1 with the absence/presence of recurrence. SUV2 demonstrated statistically significant correlation (B), whereas SUV1 and SUV2/SUV1 demonstrated no statistically significant correlation (A and C).

with higher SUV before chemotherapy had less incidence of relapse than those with lower SUV.[21] As their patient population included miscellaneous cancers, the statistical results are easily criticized. Moreover, their "prognosis" was evaluated 6 months after the treatment, so they are more likely to have estimated initial therapeutic effect rather than long-term survival. Another group insisted in their article about esophageal cancer that SUV1 serves as a prognostic factor: patients with SUV1 below 7.0 have a better survival rate than those with SUV1 above 7.0.[19] In addition, Minn et al. stated in a recent article that SUV-lean below 9.0 indicates a better chance of survival in head and neck cancer and they recommended an aggressive treatment regimen for a high SUV.[20] These results explained one of the two aspects of the current research results; the risk factor of recurrence, a high SUV2, can be considered to be a combination of a high SUV1 and a small value for its consequent decrease (presented as SUV2/SUV1).

Another difference is that Minn et al. used the survival rate, but not the incidence of recurrence, mainly because esophageal cancer or head and neck cancer have, in general, poorer prognosis than rectal cancer. In their study models, they performed only one PET study as they went directly to radical resection without prior adjuvant therapy; thus, measurement like the current SUV2 did not exist. This point also increases the significance of the current study that compared SUV1 and SUV2 as monitoring tools for long-term survival.

Intuitional consideration seems to rather favor SUV1 or SUV2/SUV1, as the former directly reflects the activity of an untreated tumor and the latter represents the effect of adjuvant radiotherapy. The current results, on the contrary, suggest that SUV2 is more closely related to the incidence of recurrence than these factors, and that a patient with an SUV2 above a certain threshold must be followed up carefully as he/she has a high risk of local recurrence or metastases. The ROC analysis and the estimation of the likelihood ratio and accuracy revealed that 3.2 as the threshold could well separate the groups with bigger/smaller risk of metastasis/recurrence. The authors would underscore the fact that a high SUV2 includes the following two factors: (1) SUV before radiotherapy is high, and (2) SUV did not decrease with therapy. These factors are represented by SUV1 and the ratio SUV2/SUV1, respectively. As shown in Figure 6, neither of these factors was an indicator of the incidence of recurrence. Moreover, SUV2 can serve as a good prognostic indicator, as it reflects both of these factors adequately.

The variation in SUVs has been compared in terms of SUV-ibw and SUV-lbm, as well as SUV-bw. The statistical results with these variances produced quasi-identical results to those of SUV-bw. Zasadney et al. pointed out a positive correlation between SUV and body weight for breast cancer patients ($r = 0.207$, $p = 0.33$).[13,15] In the current data, however, no correlation between SUV-bw and body weight was demonstrated. The deviation in body weight in Japan is much smaller than that in the United States and the study involved a relatively small number of cases. Therefore, the superiority of SUV-ibw or SUV-lbm was not evident.

In this article, other candidates as a prognostic indicator, i.e., CEA and histopathological parameters, were evaluated in relation to SUVs. CEA itself did not show any statistical significance with the absence/presence of recurrence and there was no correlation between CEA change and SUV change. Among the histopathological parameters, the absence/presence of lymphatic infiltration alone displayed statistically significant correlation

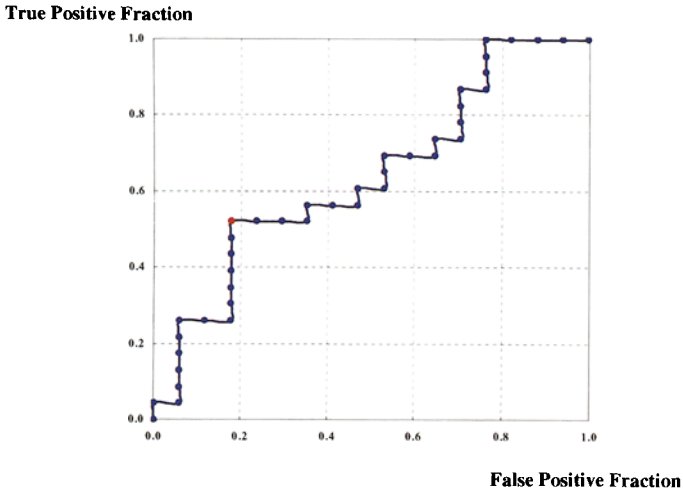

Fig. 5 ROC analysis of SUV2 cut-off value. Red circle corresponds to 3.11–3.16 SUV2 range.

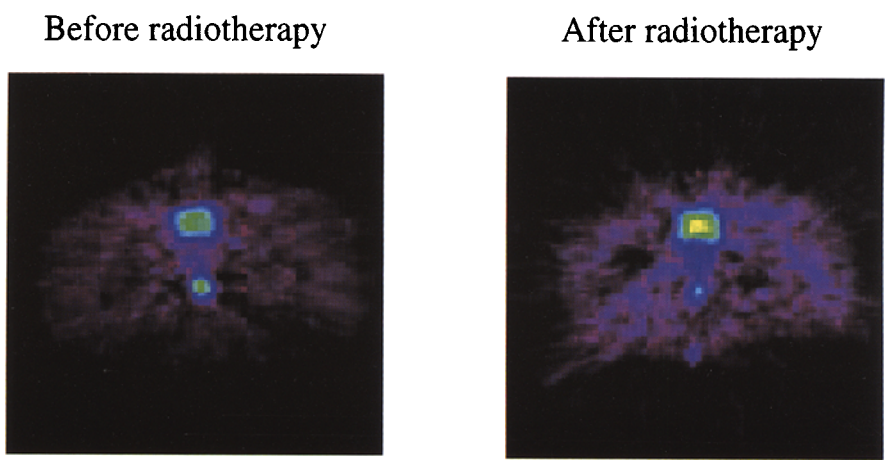

Fig. 6A FDG-PET images of the patient no. 14. Before the radiotherapy, a high accumulation of the tumor was shown (SUV1 = 13.6) (*left*), whereas after the radiotherapy, the accumulation decreased substantially (SUV2 = 2.6) (*right*). High accumulation in the ventral side was the bladder. This patient showed no recurrence.

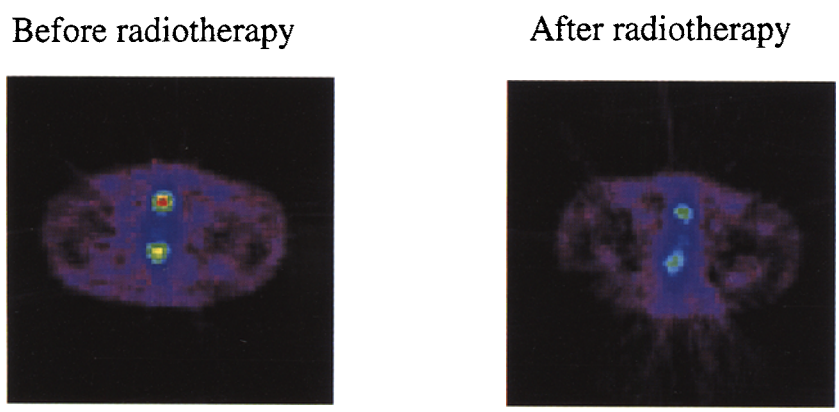

Fig. 6B FDG-PET images of the patient no. 16. Before the radiotherapy, a high accumulation was shown (SUV1 = 12.4) (*left*). After the radiotherapy, the accumulation decreased but remained high (SUV2 = 6.5) (*right*). High accumulation in the ventral side was the bladder. This patient presented with a metastasis of the lung.

with SUV2/SUV1, but not with SUV1 or SUV2. The clinical usefulness of this parameter should be studied further.

In conclusion, the current study demonstrated the usefulness of semi-quantification parameters over a long period of time after adjuvant radiotherapy. These data are preferable to those from other research to the point that a well established factor to predict prognosis has been proposed. The second point is that this article revealed that SUV after radiotherapy better indicates the prognosis after the curative combination therapy of radiotherapy and surgery.

Further evaluation with other tumors can enhance its utility.

CONCLUSION

The relationship between SUVs and long-term prognosis was studied in rectal cancer patients. The data showed that SUV semi-quantification displayed a good prognostic value. There was a significant difference in SUV2 between the groups with and without recurrence ($p < 0.05$), thus not SUV1 but SUV after radiotherapy was proved to be a better prognostic indicator. Subsets of patients with SUV2 greater than 3.2 should be observed closely.

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