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Evaluation of the treatment response of lung cancer with positron emission tomography and L-[methyl-^{11}C]methionine: a preliminary study

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Abstract. We carried out a study to evaluate treatment response and residual mass in lung cancer with positron emission tomography (PET), using L-[methyl-^{11}C]methionine (MET). MET tumour uptake and tumour volume measured by computed tomography (CT) before and within 2 weeks after radiotherapy or chemo-radiotherapy were compared in 43 studies of 21 patients. Ten patients with local control (no recurrence) of tumour showed a larger decrease in MET uptake ($65.2\% \pm 12.2\%$) than in tumour volume ($50.8\% \pm 9.6\%$, $P < 0.01$). Five patients with early recurrence (from 1 to 4 months) showed smaller decreases in both MET uptake ($22.2\% \pm 13.5\%$) and tumour volume ($28.6\% \pm 20.0\%$) than those in the no-recurrence group ($P < 0.01$). Four patients with late recurrence (after 11 months or more) showed a similar decrease to the no-recurrence group in MET uptake ($72.8\% \pm 14.8\%$) but little change in tumour volume ($18.5\% \pm 19.0\%$), the latter result corresponding to that in the early-recurrence group. Using tumour volume only, the no-recurrence group was differentiated from both the early- and the late-recurrence group ($P < 0.01$), but the early-recurrence group was not differentiated from the late-recurrence group. Using the MET uptake data, the early-recurrence group was clearly distinguished from the late-recurrence group ($P < 0.01$), but the late-recurrence group was indistinguishable from the no-recurrence group. CT was useful in distinguishing the no-recurrence group from the groups in which there was ultimate recurrence, whether early or late. When a residual mass is seen on CT, PET seems to be helpful in evaluating tumour viability.

Key words: Positron emission tomography – Lung cancer – Computed tomography – Carbon-11 methionine

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Introduction

Tumour size measurement by X-ray or computed tomography (CT) has long been the standard method of treatment evaluation in lung cancer. However, since tumour volume reflects the balance of cell loss and the growth fraction [1], and also the balance of necrosis absorption and replacement of fibrosis after chemo-radiotherapy, the value of this measurement in treatment evaluation seems to depend on the cell kinetics of the individual tumour and its interaction with the host tissue. This produces the diagnostic problem that the residual mass after treatment is not always indicative of the residual disease. There is an emerging need for an oncological evaluation method which can monitor disease directly. Monitoring the viability of the tumour together with evaluation of the residual mass would be beneficial for non-invasive treatment evaluation.

Positron emission tomography (PET) has made possible tumour imaging based on tumour metabolism. Preliminary studies have shown the possibility of monitoring treatment response with PET and fluorine-18-fluorodeoxyglucose (FDG) in head and neck cancer [2], breast cancer [3], lung cancer [4], liver tumours [5, 6], colon cancer [7, 8] and miscellaneous cancers [9]. These studies showed various levels of reduction in FDG uptake after radio- or chemotherapy, most of which were well correlated with the clinical evaluation of treatment responses. However, a few false-positive cases were reported. The possible role of PET, compared to conventional imaging modalities such as CT, for monitoring treatment needs further evaluation.

PET studies of pituitary tumours [10] and gliomas [11] have shown sensitive responses of L-[methyl-^{11}C]methionine (MET) uptake to chemo- or radiotherapy. However, the use of MET for treatment evaluation of non-CNS tumours has not yet been reported, except

in case reports [12, 13]. To study the possible role of PET using MET in the evaluation of treatment response and residual lung cancer mass, we compared the changes in MET tumour uptake as assessed by PET and the tumour volume as assessed by CT with the clinical evaluation of treatment results.

Materials and methods

Patients. Twenty-one lung cancer patients were studied (Table 1). None had received any previous anti-neoplastic treatment. Histological diagnoses were obtained by transbronchial or needle biopsy. TNM staging, based on the 1987 edition of the UICC guidelines [14], was performed using chest radiography and CT, bone scan, brain CT and abdominal ultrasonography or CT. Two stage 1 patients refused operation, and other patients with stage 3a or 3b disease received conventional radiotherapy with cobalt-60. A total tumour dose of 50–70 Gy (2 Gy/fraction, 10 Gy/week) was given depending on the tumour size, location and the patient's physical condition. Six patients received simultaneous chemotherapy (cisplatin 80 mg/m^2 day 1, vindesine 3 mg/m^2 days 1 and 8) which was completed in the second or third week of radiotherapy. No patients had active radiation pneumonitis after radiotherapy at the time of the PET and CT studies. Prognostic data were obtained for all patients, either from the clinical records in our hospital or by inquiries to other hospitals. The interval from the end of radiotherapy to local recurrence detected by chest X-ray or CT was recorded. The cause of death and the survival time from the beginning of treatment were also obtained.

The investigation was approved by the clinical research committee of our university and informed consent was obtained from each patient.

PET and CT. Eighteen patients were studied with PET and CT. Examinations were carried out twice, before and after completion of radiotherapy or chemo-radiotherapy. One patient (no. 6) had three PET and CT studies, before, during (42 Gy) and after radiotherapy. Post-treatment studies were performed within 2 weeks after completion of the radiotherapy. Two patients were studied twice, before and during radiotherapy (dose 10 Gy). A total of 43 PET and CT studies were performed.

MET was synthesized using an automated synthesis system, and quality assurance tests were performed as described previously [15]. The mean injection dose of MET for PET study was 14.2±

Table 1. Patient characteristics and treatment evaluation data

Pt. No.	Age/Sex	Histology	Stage	RT dose (Gy)	MET uptake (T/M)			Tumour volume (cm^3)			Local recurrence (mo)	Cause of death	Survival (mo)
					Pre-treatment	Post-treatment	% Reduction	Pre-treatment	Post-treatment	% Reduction			
Group A													
1	60/M	Large cell	3b	50+C	5.8	2.7	53	100	56	44	–	A	7
2	69/M	Large cell	3b	60	5.0	2.0	60	102	61	40	–	B	5
3	74/F	Adeno	1	64	3.4	1.6	53	2.1	1.1	48	–	PL	27
4	69/M	Adeno	3b	66+C	5.2	1.6	70	2.1	1.2	43	–	L	20
5	66/M	Squamous	3b	50+C	7.4	1.4	81	67	33.5	50	–	B	15.5
6	39/M	Adeno	3b	69	6.4	1.6	75	68	35	49	–	A	12
7	50/M	Adeno	3b	60+C	6.5	1.4	78	88.5	35.3	60	–	B	7
8	64/M	Squamous	3b	50	5.7	1.9	67	270	74	73	–	L	7
9	76/M	Squamous	3a	50	3.4	1.9	44	30.1	15.7	48	–	–	12+
10	63/M	Squamous	3a	50	8.7	2.5	71	104.2	49.5	53	–	L	6
Group B													
11	49/F	MFH	3b	68	7.7	4.9	36	215	173	20	1.0	A	3
12	64/M	Squamous	3a	40+C	4.5	4.4	2	44	43	2	2.5	RG	13.5
13	55/M	Adeno	3a	51	6.2	4.6	26	45	34	24	2.5	RG	4.5
14	64/M	Large cell	3a	70	7.5	6.3	16	121	59	51	4	B	19
15	57/M	Squamous	3a	48	6.7	4.6	31	50	27	46	2	–	3+
Group C													
16	61/F	Small cell	3b	60+C	7.8	2.6	67	41	30	27	16	B	17.5
17	71/M	Squamous	3a	59	4.8	2.0	58	46	36	22	18	RG	30
18	52/M	Large cell	3b	64	4.8	1.3	73	41	44.5	−9	11	H	12
19	63/M	Adeno	3b	62	3.9	0.34	91	410	271	34	–	RP	7.5
Others													
20	76/M	Adeno	3a	10	8.6	5.0	42	28	25	11	–	P	3.5
21	82/M	Large cell	1	10	6.7	5.7	15	4.5	4.46	0.9	18	–	40+

RT, Radiotherapy; +C, chemotherapy; T/M; tumour/muscle radioactivity ratio; MFH, malignant fibrous histiocytoma; Survival +, living; % Reduction = (1 − post-treatment/pre-treatment) × 100; A, abdominal metastasis; B, brain metastasis; H, haemoptysis; L, lung metastasis; P, pneumonia; PL, pleuritis; RG, regrowth; RP, radiation pneumonitis

6.7 mCi (525.4±247.9 MBq). A PT931/04 PET scanner (CTI, Knoxville, Tenn., USA; seven 7.15-mm-width slices, simultaneous acquisition, 50 mm axial field of view, FWHM 7.1 mm) was used for 29 studies. When it was out of service or was occupied by other patients, an ECAT2 PET scanner (EG &G Ortec, Oak Ridge, Tenn., USA; single-slice acquisition with 18 mm width, FWHM 14 mm) was used; this was done for 14 studies.

After the transmission scan, MET was injected intravenously as a bolus and serial 5- or 10-min frames were obtained as described previously [16]. The PET images were reconstructed using a measured attenuation correction and were corrected for decay. CT was performed on the day before every PET study to evaluate the tumour volume and to determine the image level of the greatest tumour diameter for the PET study; the positioning supports were identical to those used with PET.

Evaluation. All images were formally examined on films and compared to CT scans by three or four observers. Evaluation of tumour activity, using the region of interest (ROI) technique, was then performed, as described below, by one or two observers who did not know the fate of the treated tumour.

Because of low blood-pool activity and constant tumour and muscle activity, PET images obtained 35–40 min or 30–40 min after injection were used for evaluation [16]. The tumour area, including the highest radioactivity point, was used for the tumour ROI, and the mean ROI size was 4.4±1.1 cm^2. The mean radioactivity per pixel within the tumour ROI was used for the study. To avoid contamination of the non-tumour area, tumour ROIs were superimposed on both the transmission image and on early postinjection images which showed the vascular structure, and were checked carefully.

Eight muscle ROIs were placed in the bilateral paravertebral, lateral chest wall, shoulder, and anterior chest muscles in the same slice as the tumour. Muscle ROIs were placed in the transmission image first and were then superimposed on the corresponding emission image with the same dimension in the display. Mean muscle radioactivity per pixel was obtained by averaging the six ROIs, neglecting the maximum and minimum ROIs. The tumour muscle radioactivity (T/M) ratio was then obtained.

The tumour area on the hard copy of the sequential CT images was measured with a planimeter, multiplied by the scan interval (5–10 mm), and calibrated by the matrix size for volumetry. Total tumour volume was obtained by the summation of all tumour slices.

Results

Details of patient characteristics and treatment evaluation data are shown in Table 1. Nineteen patients were studied before and after completion of radiotherapy. They had residual tumours at the end of radiotherapy and were classified according to the fate of the residual primary tumour.

Ten patients (nos. 1–10, group A) showed no local regrowth of the residual tumour. Nine of these (nos. 1–8, and 10) died of metastasis to the abdomen, brain, lung, or pleura, with a survival time of 5–27 months (mean 11.8 months). Patient no. 9 is alive at 12 months and was disease-free at the time of manuscript preparation. The MET tumour uptake in this group showed significant reductions after treatment (Fig. 1, left panel),

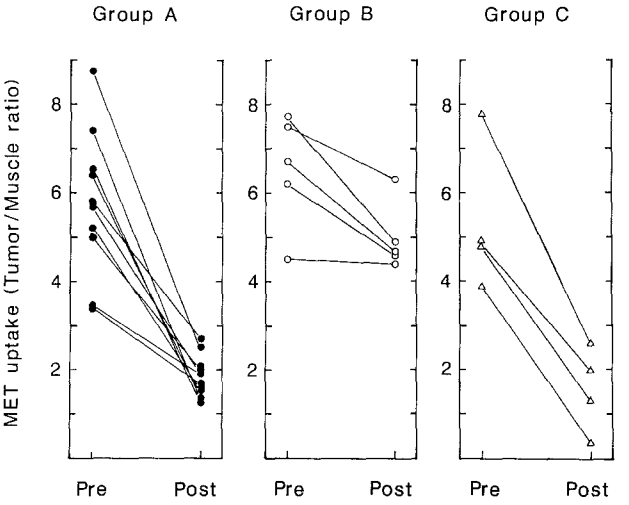

Fig. 1. Changes in MET uptake by tumours pre- and post-treatment. *Left panel:* group A, no recurrence, $n=10$; *middle panel:* group B, early recurrence, $n=5$; *right panel:* group C, late recurrence, $n=4$. For details of each category, see the text. The *ordinate* shows MET uptake by the tumour as the tumour/muscle radioactivity ratio

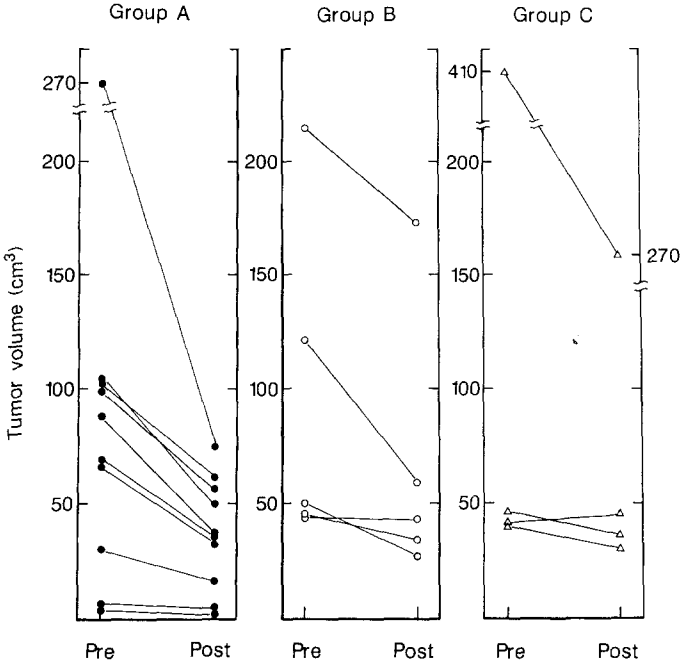

Fig. 2. Changes in tumour volume studied by CT pre- and post-treatment. *Left panel:* group A, no recurrence, $n=10$; *middle panel:* group B, early recurrence, $n=5$; *right panel:* group C, late recurrence, $n=4$. The *ordinate* shows tumour volume as assessed by CT

and the tumour volume after treatment exhibited a large decrease (Fig. 2). The reduction in MET uptake was significantly larger than the reduction in tumour volume (Table 2). Patient no. 6, who was studied three times, before, during (42 Gy) and after radiotherapy (69 Gy), showed a rapid decrease early and a slow decrease late both in MET uptake and in tumour volume (T/M ratio

Table 2. PET and CT before and after lung cancer radiotherapy

Group	RT dose (Gy)	MET uptake (T/M)			Tumour volume (cm^3) % reduction	Survival (mo)
		Pre-treatment	Post-treatment	% reduction		
A ($n=10$)	56.9±7.7	5.75±1.64	1.86±0.44	65.2±12.2	50.8±9.6**	11.8±7.6
B ($n=5$)	55.4±13.0	6.52±1.28	4.96±0.77*	22.2±13.5*	28.6±20.0	10.0±7.6
C ($n=4$)	61.2±2.2	5.33±1.70	1.56±0.97	72.8±14.8	18.5±19.0	16.8±9.7

* $P<0.001$ vs groups A and C by one-way analysis of variance test
** $P<0.01$ vs groups B and C by one-way analysis of variance test
RT, Radiotherapy

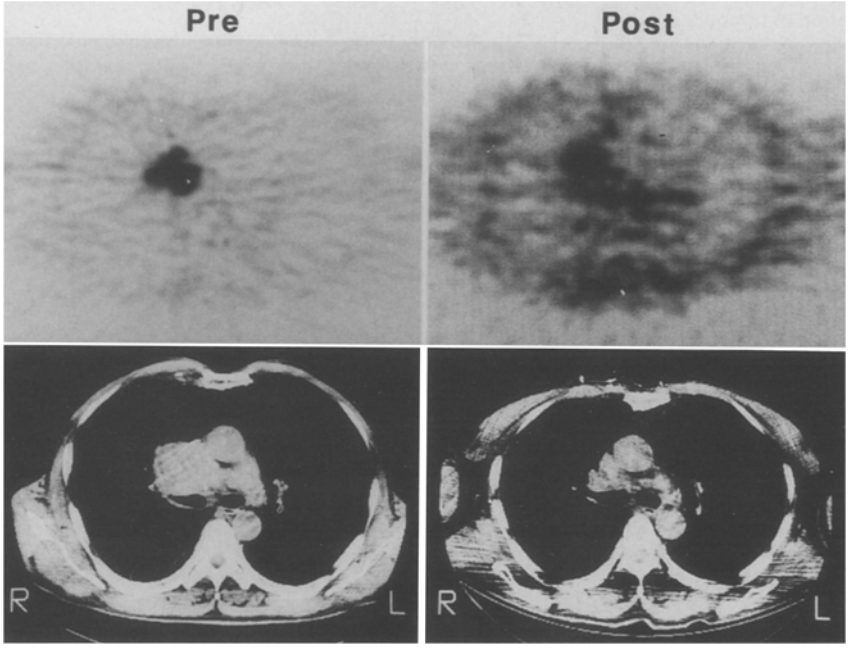

Fig. 3. PET and CT images of a typical group A patient, local control (no. 1); large cell carcinoma stage 3b. *Lower panel:* chest CT pre- and post-chemo-radiotherapy (50 Gy). Tumour volume was reduced by 44%. *Upper panel:* MET-PET image pre- and post-chemo-radiotherapy. MET uptake decreased from 5.8 to 2.7 (T/M ratio), a 53% reduciton

of MET uptake: 6.4, 3.0 and 1.6, respectively; tumour volume: 68, 41 and 35 cm^3 respectively). PET and CT images of a typical case (Patient no. 1) are shown in Fig. 3.

Five patients (nos. 11–15, group B) had local recurrence of tumour from 1 to 4 months after the radiotherapy (mean and SD: 2.4±1.1 months). Two of these patients died of metastasis, and two of local tumour extensions in the lung. MET uptake after treatment exhibited a small reduction, as shown the middle panel of Fig. 1; this pattern was clearly different from that in Group A. Tumour volume showed small reductions in patients no. 11–13, but patients no. 14 and 15 showed reductions as large as those in group A (Fig. 2). The mean value showed that both the reduction in MET uptake and the reduction in the tumour volume in group B were significantly smaller than in group A (Table 2).

Three patients (nos. 16–18, group C) had tumour recurrence at 11–18 months after radiotherapy. They showed a slight decrease in tumour volume (Fig. 2) but a large decrease in MET uptake at the end of radiotherapy. Patient no. 19, who showed the same pattern of changes in both parameters but died of radiation pneumonitis at 7.5 months, was included in this group. The reduction in MET uptake in group C was equal to that in group A and was significantly larger than that in group B (Fig. 1). The volume reduction in group C was significantly less than that in group A ($P<0.01$, Table 2) and was equal to that in group B. All three groups, A, B and C, had equivalent MET uptake before radiotherapy (Fig. 1).

Two patients (nos. 20 and 21) were studied before and after the first 10 Gy of irradiation. The findings were used only to consider the early effect of irradiation; tumour uptake of MET began to decrease within the first week of radiotherapy.

When the reduction in MET uptake was combined with the reduction in tumour volume, the differentiation

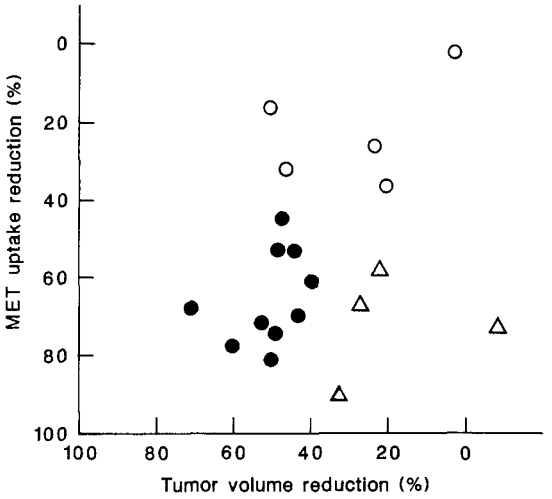

Fig. 4. Individual correlations between reduction in MET tumour uptake (%) and reduction in tumour volume (%) in the comparison of pre- and post-treatment PET and CT studies. % Reduction = (1 − post/pre) × 100. Patients in group A, no recurrence (●), group B, early recurrence (○), and group C, late recurrence (△) are plotted. For details of each category, see the text

of each group became easier than when a single parameter was used (Fig. 4). This differentiation was supported by the statistics of the mean and SD of each parameter (Table 2).

Group C, the late-recurrence group, showed longer survival and group B, the early-recurrence group, shorter survival than group A, the no-recurrence group. However, there were no statistically significant differences since the number of patients was small.

Discussion

In this study, since there was no complete response in these patients, they were classified according to the fate of the primary tumour, i.e., no recurrence, early recurrence and late recurrence, rather than being classified by the standard system of complete response, partial response and progressive disease. When we used tumour volume only, we were able to differentiate the no-recurrence group from both the early- and the late-recurrence group. However, we could not differentiate the early- from the late-recurrence group. Using the MET uptake data, the early-recurrence group B was clearly distinguished from the late-recurrence group C. However, the late-recurrence group was indistinguishable from the no-recurrence group. By combining PET and CT, it became possible to differentiate each of the three groups.

MET tumour uptake, representing amino acid metabolism, is strongly correlated with protein synthesis [17] and appears to indicate the metabolic activity of viable tumour cells. The higher MET uptake in group B after treatment seems to represent a larger number of residual viable cells in the tumour, and the lower MET uptake in group C, a smaller number of such cells. However, reductions in the tumour volume in both groups were the same. The number of residual viable cells appears to determine the time of recurrence, i.e. whether it is early or late. When a residual mass is seen on CT, PET seems to be helpful for evaluating the viability of the tumour.

In studies using FDG, false-positive FDG uptake after radiotherapy has been observed in some cases [7–9]. An inflammatory reaction at the site of necrosis induction and absorption after radiotherapy [18] and high FDG uptake by macrophages and granulation tissue within the tumour [19] seem to explain this phenomnon. In our previous MET study, we experienced false-positive cases of benign abscess lesions, similar to those experienced with FDG [16]. In this study, however, we had no false-positive residual high tumour uptake after treatment. In a comparative experimental study, we found differences in amino acid metabolism and glucose utilization in response to radiotherapy [20]. Differences between MET and FDG in the PET treatment evaluation studies cited may be due to the nature of the tracers. However, the patient populations were different, and further studies are thus necessary before conclusions can be drawn.

In this study, in two patients studied at 10 Gy, the MET tumour uptake began to decrease within the first week of radiotherapy. Patient no. 6, who was studied three times, showed a rapid decrease early and a slow decrease late. In group A, the reduction in MET uptake was significantly larger than the reduction in tumour volume. These results are consistent with the results of our experimental studies [21, 22]. Rapid response to radiotherapy may be an advantage of treatment evaluation with PET using MET. In radiation biology, in vitro cell survival curves with fractionation radiotherapy showed a linear decrease on a long-normal plot [23]. In the normal scale, this is consistent with a rapid decrease early and slow decrease late, as in MET uptake with PET. In vitro studies have reported that the survival fraction at 2 Gy correlated with the intrinsic cellular radiosensitivity, and the importance of the initial slope of the survival curve has been emphasized [24]. The initial decrease in tumour uptake of MET in radiotherapy seems to be important, but further evaluation is necessary.

Six patients received chemotherapy in this study. However, the effects of chemotherapy on methionine uptake, whether direct or indirect through metabolic disturbance, seemed to be negligible since the chemotherapy was completed in the early course of radiotherapy and patients had completely recovered from its side-effects at the second PET study. There is also the possibility of differential responses by the various histological types of lung cancer. However, since the three histological types, squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, were scattered in groups showing different responses, this possibility appears to be remote.

No significant difference in survival time was found among the three groups in this study. Most of the patients had advanced disease, the major cause of death being metastatic disease. There have been reports that thoracic radiotherapy does not prolong survival in patients with advanced non-small cell lung cancer [25] and that the high incidence of distant metastases is the cause of radiotherapy failure in advanced lung cancer [26]. Although control of the primary lesion is very important in lung cancer treatment, it alone is not sufficient to achieve long-term survival. This factor seems to be a limitation in the evaluation of treatment for lung cancer. PET studies using MET have been reported in the diagnosis of lymphoma, breast cancer, head and neck cancer [27–29] and brain tumours [11]. Treatment evaluation studies of these tumours are awaited.

Using CT, we were able to differentiate the no-recurrence group from those with ultimate recurrence, which is most important in practice. When we consider the timing of additional treatment directed against the residual mass, prediction of the recurrence as early or late could be helpful. Whether or not the residual tumour mass detected by CT contains a large number of viable tumour cells may be evaluated by metabolic imaging with PET and MET. Although PET seems to be valuable in this regard, it appears to play a supplementary role to CT in treatment evaluation.

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